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Medicinrådet

Bilag til Medicinrådets anbefaling vedrørende oral azacitidin til behandling af akut myeloid leukæmi

Vers. 1.0

Bilagsoversigt

1. Ansøgers notat til Rådet vedr. oral azacitidin
    1.1. Ansøgers svar på Rådets spørgsmål i forbindelse med rådsmøde den 18. maj 2022
2. Forhandlingsnotat fra Amgros vedr. oral azacitidin
3. Ansøgers endelige ansøgning vedr. oral azacitidin

Bristol Myers Squibb
Hummeltoftevej 49
2830 Virum
Denmark
Phone: +45 4593 0506
www.bms.com/dk

Virum, 21. april 2022.

Til Medicinrådet

Bristol Myers Squibbs tilbagemelding på udkast til vurderingsrapport for Onureg (oral azacitidin) til vedligeholdelsesbehandling af patienter med akut myeloid leukæmi

Bristol Myers Squibb (BMS) imødeser Medicinrådets anbefaling vedr. behandling med Onureg til vedligeholdelsesbehandling af patienter med akut myeloid leukæmi (AML). BMS takker hermed for muligheden for at give en tilbagemelding på vurderingsrapporten, og benytter lejligheden til at gøre opmærksom på to faktorer, som, hvis ignoreret, kan lede til en fejlagtig anbefaling.

For det første er det problematisk, at Medicinrådet vælger en yderst konservativ tilgang til modelleringen af overlevelse. Dette fører til en kraftig reduktion i den forventede sundhedsmæssige gevinst og en stigning i den inkrementelle cost-effectiveness ratio (ICER). Dette er potentielt særligt problematisk givet at Medicinrådet er gået væk fra at præsentere resultatet af ansøgers analyse i sin vurderingsrapport. Det er umuligt at spå om fremtiden og ingen kan vide, hvordan den bliver. Usikkerhed er dermed et vilkår og derfor er det vigtigt, at Rådet præsenteres for ansøgers analyse, så Rådet informeres tilstrækkeligt om usikkerheden forbundet med Medicinrådssekretariatets analyse.

I dette konkrete tilfælde estimerer BMS en inkrementel gevinst i leveår på 0,94 år og Medicinrådet en gevinst på 0,57 år. Forskellen i median OS i QUAZAR-AML-001 studiet var på 9,9 måneder (Wei et al. 2020). Ift. QALYs estimerer BMS en forskel på 0,76 QALYs og Medicinrådet en forskel på 0,45 QALYs. Til sammenligning kan nævnes, at den canadiske HTA-myndighed CADTH estimerer en forskel på 0,91 QALYs (CADTH 2022) og Medicinrådet er dermed på et estimat som er under halvdelen af, hvad en tilsvarende myndighed er kommet frem til. Denne forskel indikerer også, at estimatet i BMS' ansøgning måske ikke er helt så optimistisk, som det fremgår af Medicinrådets afrapportering.

Ovennævnte forskel er markant og sammen med forskelle i estimater af omkostninger betyder det, at ICER'en i BMS' analyse er 2,4 mio. kr. pr. QALY mod Medicinrådets 4,1 mio. kr. pr. QALY, svarende til en stigning på 68 %. Til sammenligning medførte CADTH's justeringer af BMS' hovedanalyse i Canada en stigning i ICER'en på 2 % (CADTH 2022).

Medicinrådet skal have ros for at understrege, at deres antagelser er konservative, men BMS opfordrer til, at man i stedet for en konservativ tilgang vælger en mere realistisk tilgang i sine analyser fremadrettet, samt at man proaktivt præsenterer Rådet for resultaterne af ansøgers analyse så usikkerheden belyses mere fyldestgørende.

Og hvorfor så denne forskel? Der er flere årsager til, at Medicinrådets valg af ekstrapolation er et yderst konservativt estimat.

Som sit primære argument fremfører Medicinrådet, at der ikke kan forventes at være forskel i andelen af langtidsoverlevere, hvorfor man vælger en ekstrapolationskurve som får de to overlevelseskurver til hurtigt at nærme sig hinanden. Det er dog afgørende at holde sig for øje, som Medicinrådet også bemærker, at overlevelsesdata i dette studie er modne og med median opfølgning på 51,7 måneder har relativt lang opfølgning.

I dansk klinisk praksis beskrives 5-års OS rate for AML-patienter >60 år i remissionsinducerende behandling som et vigtigt parameter som indikation for, at patienterne er langtidsoverlevende og derfor kan betragtes som helbredte (Danish Acute Leukemia Group 2021). Dette understøttes af danske data der antyder, at risikoen for tilbagefald hos patienter, der opnåede komplet remission efter intensiv kemoterapi (og hermed, risikoen for at dø af AML) var høj inden for de 5 første år før de fladede ud (Østgård et al. 2018). Der er dermed gode argumenter for, hvorfor den separation af OS kurverne som observeres imod slutningen af opfølgningen i QUAZAR AML-001 kan vare ved længere end i Medicinrådets ekstrapolationer.

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Dette underbygges yderligere af, at ved en median opfølgningstid på 51,7 måneder (sept 2020 cutoff), viser halen af den opdaterede Kaplan Meier OS-kurve en større adskillelse sammenlignet med den primære analyse (juli 2019 cutoff, median opfølgning på 41,2 måneder). Dette antyder en OS-fordel ved Onureg versus placebo ved 5 år, hvor patienter kan betragtes som potentielt helbredte og dermed langsigts-overlevende (Wei et al. 2020; Wei et al. 2021).

Ovenstående understreger vigtigheden af at vælge den ekstrapolationsmodel, der mest præcist afspejler fordelene ved en AML-behandling inden for de 5 første år, og for hvilken OS-data fra QUAZAR AML-001 studiet er tilgængelige (Wei et al. 2021). Ved at bruge individuel generaliseret gamma funktion til at modellere OS antager Medicinrådet en øget dødelighed for Onureg efter 2.5 år sammenlignet med placebo, hvilket modsiges af QUAZAR AML-001 data og derved ikke bør kunne betragtes som den mest klinisk plausible (Wei et al. 2020; Wei et al. 2021; Medicinrådet 2022).

Derudover nævner Medicinrådet at mange patienter (ca. 80 %) oplever sygdomstilbagefald, hyppigst inden for de første år efter komplet remission (Medicinrådet 2022). Tidligere studier, der har undersøgt hypomethylerende midler som vedligeholdelsesbehandling efter intensiv kemoterapi, har vist en forlængelse af sygdomsfri overlevelse eller RFS men ingen vist signifikant effekt på OS (Wei et al. 2020; Burnett et al. 2015; Boumber et al. 2012; Huls et al. 2019). Disse tidligere studiers resultater sætter således spørgsmål ved korrelation mellem RFS og OS hos patienter, der opnår komplet remission efter intensiv kemoterapi, og antyder, at vægten af RFS-langsigtede data til ekstrapolering af langsigtede OS-fordele bør anvendes med større forsigtighed end hvad Medicinrådet gør.

For det andet er det vigtigt at understrege, at AML er en meget alvorlig sygdom selv for patienter der ikke har målbar restsygdom (er MRD-negative). Som tidligere nævnt, oplever de fleste AML patienter sygdomstilbagefald og hyppigst inden for de første år efter komplet remission og kun HSCT er en kurativ intenderet behandling (Medicinrådet 2022). Behandling med Onureg var associeret med OS- og RFS-gevinst versus placebo uafhængigt af baseline MRD-status (Roboz et al. 2022). Dog bemærkes, at QUAZAR AML-001 studiet ikke var designet til at undersøge en eventuel forskel i effekt baseret på MRD-status ved baseline og MRD analyser er inkluderet som et eksplorativt endepunkt (Roboz et al. 2022; Wei et al. 2020).

For MRD-negative patienter ved baseline (<0.1%), var den mediane varighed af MRD-negativitet forlænget med 16 måneder hos patienter behandlet med Onureg (26,4 måneder) sammenlignet med placebo (10,4 måneder). For patienter, som var MRD-positive ved baseline og opnåede MRD negativitet i studiet (37% af patienter behandlet med Onureg versus 19% med placebo), var den mediane varighed af MRD-negativitet ikke opnået for Onureg sammenlignet med 12,9 måneder for placebo.

En multivariate analyse bekræftede den markante og uafhængige behandlingseffekt på OS og RFS for Onureg sammenlignet med placebo, når det var korrigeret for MRD status ved baseline. MRD status er en stærk prognostisk indikator for OS og RFS men de forskellige analyser efter MRD-status tyder på, at Onureg er associeret med en klinisk relevant overlevelsesgevinst uanset MRD-status ved baseline, selv i den NPM1-muterede subgruppe, der typisk er forbundet med en relativt favorabel prognose (Roboz et al. 2022). Medicinrådet bemærker, at risikoen for overbehandling er større for MRD-negative patienter men i den kontekst bemærkes det, at der ikke sås betydende forskelle i livskvalitet mellem Onureg og placebo målt ved 3 forskellige spørgeskemaer (EQ-5D-3L, EQ-5D VAS og FACIT-fatigue score)(Roboz et al. 2021).

Samlet set betyder Medicinrådets valg af ekstrapolationsfunktion, at effekten af Onureg undervurderes betragteligt og Medicinrådets hovedanalyse giver derfor et misvisende billede af forventet QALY-gevinst og deraf en overestimering af ICER. For patienter med AML, som ikke er kandidater til HSCT, er der behov for effektive vedligeholdelsesbehandlinger som kan reducere risikoen for tilbagefald og øge overlevelsen samtidig med at patienternes livskvalitet bevares. Vi mener Onureg er en sådan behandling.

Med venlig hilsen,

Anders Thelborg
Adm. direktør
Bristol Myers Squibb, Denmark

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Bristol Myers Squibb
Hummeltoftevej 49
2830 Virum
Denmark
Phone: +45 4593 0506
www.bms.com/dk

Medicinrådet har foretaget clock-stop i vurderingen af Onureg fordi der dels mangler en række oplysninger fra ansøger og dels en bearbejdning heraf hos rådets sekretariat. Det drejer sig om følgende punkter:
Spørgsmål 1: Vi har noteret os, at BMS påpeger, at CADTH estimerer en forskel på 0,91 QALY medens BMS selv opgør forskellen til 0,76 QALY – hvilket skal sammenholdes med Medicinrådets opgørelse af en forskel på 0,45 QALY. Da BMS fremdrager disse forhold bedes BMS redegøre nærmere herfor. A. Det ønskes bl.a. forklaret hvad der begrunder denne store forskel. Er der tale om forskellige datagrundlag eller forskellige antagelser? B. CADTH fremhæver selv at der er usikkerhed i antagelser – hvad drejer det sig om – og er det relevant i forhold til en dansk beslutning? C. Kan BMS gøre rede for hvorfor Medicinrådets antagelser ikke er brugbare og underbygge det med data?
Svar:

A. Der er en række forhold som fører til de forskelle i estimaterne, eksempelvis forskellige diskonteringsrenter der betyder, at fremtidige sundhedsgevinster og omkostninger bliver vægtet forskelligt imellem Danmark og Canada. Ligeledes kan der være forskelle i eksempelvis baggrundsmortaliteten. Det primære grundlag for begge analyser QUAZAR AML-001-studiet og der er dermed et substantielt overlap i den mest betydende del af datagrundlaget. Dog er ekstrapolationerne i den canadiske analyse baseret på det tidlige data-cut (juli 2019).

   Den største forskel på den danske og den canadiske analyse går på hvilken ekstrapolationsmetode, der er valgt. I Canada har man estimeret Onureg og ingen aktiv behandling samlet med en log-normal fordeling i stedet for i den danske model, hvor behandlingerne er estimeret hver for sig. Anvendes samme ekstrapolationsmetode i den danske model fås en QALY-gevinst på 0,84 QALY. At BMS i Danmark har indsendt en analyse, som giver en gevinst på 0,76 QALY har været for at lave et mere konservativt skøn for den fremtidige overlevelse end det som er accepteret af CADTH i Canada.

B. Der vil altid være usikkerhed forbundet med antagelser om fremtiden, hvilket er et grundvilkår ved vurderingen af alle nye lægemidler. Netop derfor er det afgørende at belyse usikkerheden ved antagelserne. Dette understreger også det kritisable ved, at Medicinrådets sekretariat er holdt op med at præsentere Rådet for resultaterne, af ansøgers sundhedsøkonomiske analyser. Det er endvidere afgørende, at Rådet præsenteres for scenarier, som med udgangspunkt i tilgængelige studiedata og dansk klinisk praksis er realistiske, om end disse ikke nødvendigvis repræsenterer de mest konservative scenarier. Man bør overveje at vægte de forskellige scenarier med sandsynligheder for, hvor realistiske de vurderes, og så præsentere Rådet for et vægtet gennemsnit. Alt vil i hvert fald være bedre end blot at lægge langt størstedelen af vægten på de mest konservative antagelser.

Den primære kilde til usikkerhed ligger i valg af antagelsen til ekstrapolation af OS og RFS.

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Medicinrådet forventer, at oral azacitidin vil udskyde tidspunktet for relaps, men at der ikke kan forventes yderligere gevinst ved brugen af oral azacitidin, udover den tid behandlingen pågår. Denne vurdering understøttes af, at kurverne for RFS næsten konvergerer inden for den observerede tidsperiode. Derfor vurderer Medicinrådet, at kurverne for azacitidin og placebo vil konvergere, så andelen af langtids-relapsfri patienter vil være ens mellem de to behandlinger. Medicinrådet vælger derfor ikke at justere RFS-kurven

C. Som sit primære argument fremfører Medicinrådet, at der ikke kan forventes at være forskel i andelen af langtidsoverlevere, hvorfor man vælger en ekstrapolationskurve som får de to overlevelseskurver til hurtigt at nærme sig hinanden. Det er dog afgørende at holde sig for øje, som Medicinrådet også bemærker, at overlevelsesdata i dette studie er modne og med median opfølgning på 51,7 måneder har relativt lang opfølgning. Medicinrådets antagelser og argumentet om langtidsoverlevelse modsiges af studiedata, de kliniske retningslinjer og tidligere anbefalinger fra Medicinrådet, hvor der så sent som på mødet den 18.5.2022 var et andet lægemiddel til behandling af AML på agendaen - se nærmere i punkt 2 nedenfor.

Spørgsmål 2: Er det korrekt, at det er almindelig klinisk praksis, at en god indikation for langtidsoverlevelse er 5-års OS-rate efter ophørt behandling eller ubehandlet? Gælder denne antagelse også i dette tilfælde?

Svar: BMS opfordrer Medicinrådet til også at vende dette spørgsmål med fagudvalgets kliniske eksperter. Når det er sagt, er det BMS' opfattelse at overlevelse efter tre eller fem år er beskrevet i dansk klinisk praksis som en indikator for patientens sandsynlighed for at opnå langsigtsoverlevelse.
Udgangspunktet i dansk klinisk praksis er at bruge ofte blot 3-års overlevelse som indikator for langtidsoverlevelse.
En mere konservativ tilgang er at bruge den mest stringente antagelse mht. langtidsoverlevere, dvs. 5-års overlevelse, beskrevet i de 3 nedenstående hovedkilder:

- Årsrapporten 2020 fra den Danske Akut Leukæmi Database, i sektionen "Vurdering af indikatorens anvendelighed" for indikator 8c, dvs. 5-års overlevelse for AML-patienter >60 år i remissionsinducerende behandling, er indikatoren beskrevet som vigtig, da den indikerer at patienterne er langtidsoverlevere og dermed kan betragtes som helbredte (Danish Acute Leukemia Group 2021).
- Opfølgningsprogrammet for akut leukæmi fra Sundhedsstyrelsen (Februar 2015), hvor der anbefales blodprøvekontrol hver 1-3. måned i de første 2 år og derefter hver 3-6. måned i op til 5 år i sektion, 4.2 Opsporing af resttumor og recidiv (Sundhedsstyrelsen. 2015)
- Danske data, der antyder, at risikoen for tilbagefald hos patienter, der opnåede komplet remission efter intensiv kemoterapi (og hermed, risikoen for at dø af AML) var tilsted inden for ca. de 5 første år (Østgård et al. 2018)

Derudover er det dokumenteret, at sygdomstilbagefald optræder indenfor de første 1-4 år efter afsluttet behandling (Sundhedsstyrelsen. 2015)(indsigt fra danske kliniske eksperter). Derfor er i Danmark 3-års overlevelse betragtet som den første vurdering om patienterne bliver langtidsoverlevere (og dermed helbredte) og kontrolforløbet forventes at afsluttes for flest af danske patienter uden tilbagefald efter 3 år (Danish Acute Leukemia Group 2021, 2020)(indsigt fra danske kliniske eksperter).

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I tidligere anbefalinger har Fagudvalget ønsket overlevelsen opgjort efter 3 år. Begrundelsen er, at kliniske erfaringer understøtter, at recidiv vil have vist sig indenfor 3-års opfølgning samt at 3-års overlevelse er udtryk for andelen af patienter, der har længere overlevelse. Denne begrundelse er brugt ved tidligere vurderinger af både CPX-351 (Vyxeos), gemtucumab ozgamicin og gilteritinib, mens der for midostaurin sås på 5-års overlevelsen. Dette understøttes af følgende citater fra tidligere rapporter publiceret på Medicinrådets hjemmeside.

Udklip fra CPX-351 - anbefaling 10. april 2019

Overlevelsesrate ved 2 år
Fagudvalget har i protokollen ønsket overlevelsesraten opgjort efter 3 år. Dette valg er truffet efter et klinisk rationale om, at man, baseret på erfaring fra behandling med kemoterapi, efter 3 års opfølgning kan forvente, at evt. recidiv vil have vist sig. Man har også kendskab til, hvorvidt en stamcelletransplantation har været succesfuld. 3-årsoverlevelsen bliver derfor et mål for langtidsoverlevelse. Fagudvalget vurderer også, at såfremt 3-års opfølgningstid ikke forefindes, vil 2-års opfølgningstid kunne anvendes, idet den sygdomsrelaterede mortalitet for akut leukæmi ses tidligt efter sygdomsdebut eller stamcelletransplantation. Derfor vil forskellene i effekten efter 2-års opfølgningstid i praksis være en stærk prædiktor for 3-års overlevelse. Der sker kun få tilfælde af relaps efter 2 år, og derfor vil der ikke forventes væsentlige forskelle.

Udklip fra gemtucumab ozgamicin 30. januar 2019

Overlevelse (kritisk)
Fagudvalget har i protokollen vurderet, at det er relevant at se på overlevelse udtrykt både som medianoverlevelse og som overlevelse efter 3 år. Tidshorisonten på 3 år er valgt, da man kan forvente, at evt. relaps vil have vist sig indenfor dette tidsrum, samt at man indenfor dette tidsrum ved, om en evt. stamcelletransplantation har været succesfuld. HR præsenteret i nedenstående er for længst mulig opfølgningstid i studiet og ikke tidsafgrænset til et specifikt opfølgningstidspunkt, jf. 6.1.1.

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Udklip fra gilteritinib - anbefaling 18.maj 2022:

Kritiske effektmål

Overlevelse (overall survival)
Overlevelse er guldstandard for at demonstrere klinisk effekt i cancerstudier, herunder akut myeloid leukæmi. Det er et patientrelevant effektmål, der belyser patienternes levetid efter en fast opfølgningstid. Overlevelse defineres som tiden fra randomisering eller opstart af behandling til død uanset årsag.

Fagudvalget ønsker at se på andelen af patienter, som er i live efter 3 år som et udtryk for andelen af patienter, der har en længere overlevelse. Tidshorisonten på 3 år er valgt, da man kan forvente, at evt. recidiv vil have vist sig indenfor dette tidsrum, samt at man indenfor dette tidsrum ved, om en evt. stamcelletransplantation har været succesfuld. Fagudvalget vurderer ikke, at en længere opfølgningstid vil bidrage med yderligere information. Såfremt data for 3 år ikke forefindes, kan ansøger indlevere data med længst mulig opfølgning, dog minimum 2 år. Ved nuværende standardbehandling forventes det, at maks. 10 % af patientgruppen, AML med FLT3-mutationer som er refraktære eller i relaps, vil være langtidsoverlevere, dvs. som overlever i 3 år eller mere. Dette svarer til 0-2 patienter pr. år. Fagudvalget vurderer, at en forskel på 7 procentpoint er en klinisk relevant forskel i andelen af patienter, der opnår 3-årsoverlevelse. Den samme mindste klinisk relevante forskel er gældende for 2-årsoverlevelse.

Yderligere finder fagudvalget det relevant at se på overlevelse udtrykt som medianoverlevelse. Den forventede mediane overlevelse for patientgruppen, AML med FLT3-mutatione, som er refraktære eller i relaps, er med nuværende dansk standardbehandling 4-6 måneder. Fagudvalget vurderer, at 4 måneder er en klinisk relevant forskel i medianoverlevelse for denne patientgruppe.

Udklip fra midostaurin - anbefaling 30. januar 2018

Kritiske effektmål

Overlevelse (overall survival) er guldstandard for at demonstrere klinisk effekt i cancerstudier, herunder akut myeloid leukæmi. Det er et patientrelevant effektmål, der belyser patienternes levetid efter en fast opfølgningstid. Overlevelse defineres som tiden fra randomisering eller opstart af behandling til død uanset årsag. Fagudvalget finder det relevant at se på overlevelse udtrykt både som median overlevelse og som overlevelse efter 5 år. Efter 5 år anses patienten for at være kureret. Recidiv opstår sjældent 3 år efter endt behandling, og da midostaurin administreres som vedligeholdelsesterapi i 1 år efter endt kemoterapi vurderer fagudvalget, at 5 år vil være mest retvisende for vurdering af langtidsoverlevelse. Fagudvalget vurderer, at en forskel på 10 procentpoint er en klinisk relevant forskel i andelen af patienter, der opnår 5-årsoverlevelse, mens 4 måneder er en klinisk relevant forskel i median overlevelse for denne patientgruppe.

På trods af, at Medicinrådet har taget en ny metode i brug, bør det ikke ændrer på, hvordan Medicinrådet i praksis definerer langtidsoverlevelsen i samme sygdomsområde. Det vil derfor ikke være urimeligt at forvente, at samme antagelse også gør sig gældende for Onureg
Ovenstående understreger vigtigheden af at vælge den ekstrapolationsmodel, der mest præcist afspejler fordelene ved en AML-behandling inden for mindst de 3 første år, og for hvilken OS-data fra QUAZAR AML-001 studiet er modne. BMS har nævnt 5-års overlevelsen for at inddrage OS data med tilstrækkelig opfølgningstiden (sept 2020 data cutoff) til at belyse relevante effektforskelle, som fortrukket af Medicinrådet. Disse data, hvor mest censurering sker efter 3 år, angiver modne 3-års OS rate, som er betragtet som den mest almindelige antagelse for langtidsoverlevere, hhv. 37,4% for Onureg versus 27,9% for placebo. Givet ovennævnte kilder er det ikke urimeligt at antage, at en del af disse 9,5% af patienterne vil være langsigtsoverlevere som dermed vil opnå en langsigtet effekt af behandlingen med Onureg.
Der er dermed gode argumenter for, hvorfor den separation af OS kurverne som observeres imod slutningen af opfølgningen i QUAZAR AML-001 kan vare ved længere end i Medicinrådets ekstrapolationer, som antager en øget dødelighed for Onureg efter 2.5 år sammenlignet med

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placebo.

Spørgsmål 3: BMS påpeger, at halen af Kaplan Meier OS-kurven viser en større adskillelse ved 51,7 måneder end ved 41,2 måneder – er det korrekt? Og hvilken betydning har det i givet fald?
Ja, det er korrekt at ved en median opfølgningstid på 51,7 måneder (sept 2020 cutoff) (figur 2), viser halen af den opdaterede Kaplan Meier OS-kurve en større adskillelse sammenlignet med den primære analyse (juli 2019 cutoff, median opfølgning på 41,2 måneder) (figur 1).

Figur 1. Kaplan-Meier OS kurve for Onureg versus placebo for juli 2019 cutoff. Median opfølgning på 41,2 måneder. (Wei et al. 2020; European Medicines Agency 2021)

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En tolkning af den øgede separation er, at man med længere opfølgning og mindre censurering bedre kan se den langsigtede effekt af Onureg at den tyder på en øget overlevelse.
Som Medicinrådet skriver på side 23 i udkastet til anbefalingen og som nævnt ovenfor, har andelen af langtidsoverlevere stor betydning for den estimerede gennemsnitlige overlevelse, og derfor også den forventede QALY gevinst.
Som vist ovenfor er dansk klinisk praksis, at flertallet af patienter følges op til 3 år, hvor efter de vurderes som langtidsoverlevere. Som vist ovenfor er den modne 3-års OS rate højere i Onureg-arm (37,4%) versus placebo (27,9%) og dermed tyder på, at en højere antal patienter i Onureg-arm vil være langsigtsoverlevere versus i placebo-arm. Yderligere tyder den større adskillelse af kurverne også på en OS-fordel ved Onureg versus placebo ved 5 år, hvor patienter kan betragtes som potentielt helbredte. Dette er en modsætning til Medicinrådets argument om, at der ikke kan forventes at være forskel på langtidsoverlevelse mellem Onureg og placebo.

Spørgsmål 4: BMS påpeger at Medicinrådets modellering bygger på en antagelse om øget dødelighed i forhold til placebo efter 2.5 år. BMS oplyser at dette modsiges af data. Kan vi ikke se denne datadokumentation?
Svar: Figur 3 nedenfor viser smooth OS hazard kurver (altså sandsynligheden for at dø over tid) for patienter behandlet med hhv. Onureg og ingen aktiv behandling i QUAZAR AML-001 studiet. Det fremgår, at for patienter behandlet med Onureg, er risikoen stigende i starten, toppende omkring [redacted] måneder, hvorefter risikoen er faldende. For patienter med ingen aktiv behandling er risikoen endnu højere i starten af perioden hvorefter den falder.

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De to kurver krydses omkring [redacted] måneder, men separeres ikke voldsomt. Der er en svag indikation af, at kurverne krydser igen ved [redacted] måneder, men det er baseret på meget få observationer, og man skal være varsom med at tolke på kurveforløb i enden af halen.
Den faldende risiko for død understøtter ligeledes, at patienter som overlever til et vist tidspunkt vil kunne formodes at opnå langsigtsoverlevelse, hvilket synes klinisk plausibelt jf. ovenfor.
Kurverne i figur 3 skal holdes op imod de modellerede hazards i de sundhedsøkonomiske analyser. Figur 5 i Medicinrådets vurderingsrapport viser kurverne for BMS' hovedanalyse og figur 7 viser tilsvarende for Medicinrådets hovedanalyse.
I BMS' analyse antages ens hazards fra ca. [redacted] måneder, hvilket frem til 40 måneder undervurderer gevinsten af Onureg og derefter potentielt overvurderer den (i det omfang at man tolker, at kurverne separeres). I Medicinrådets analyse antages højere hazard for Onureg fra ca. 30 måneder og frem til ca. 120 måneder.

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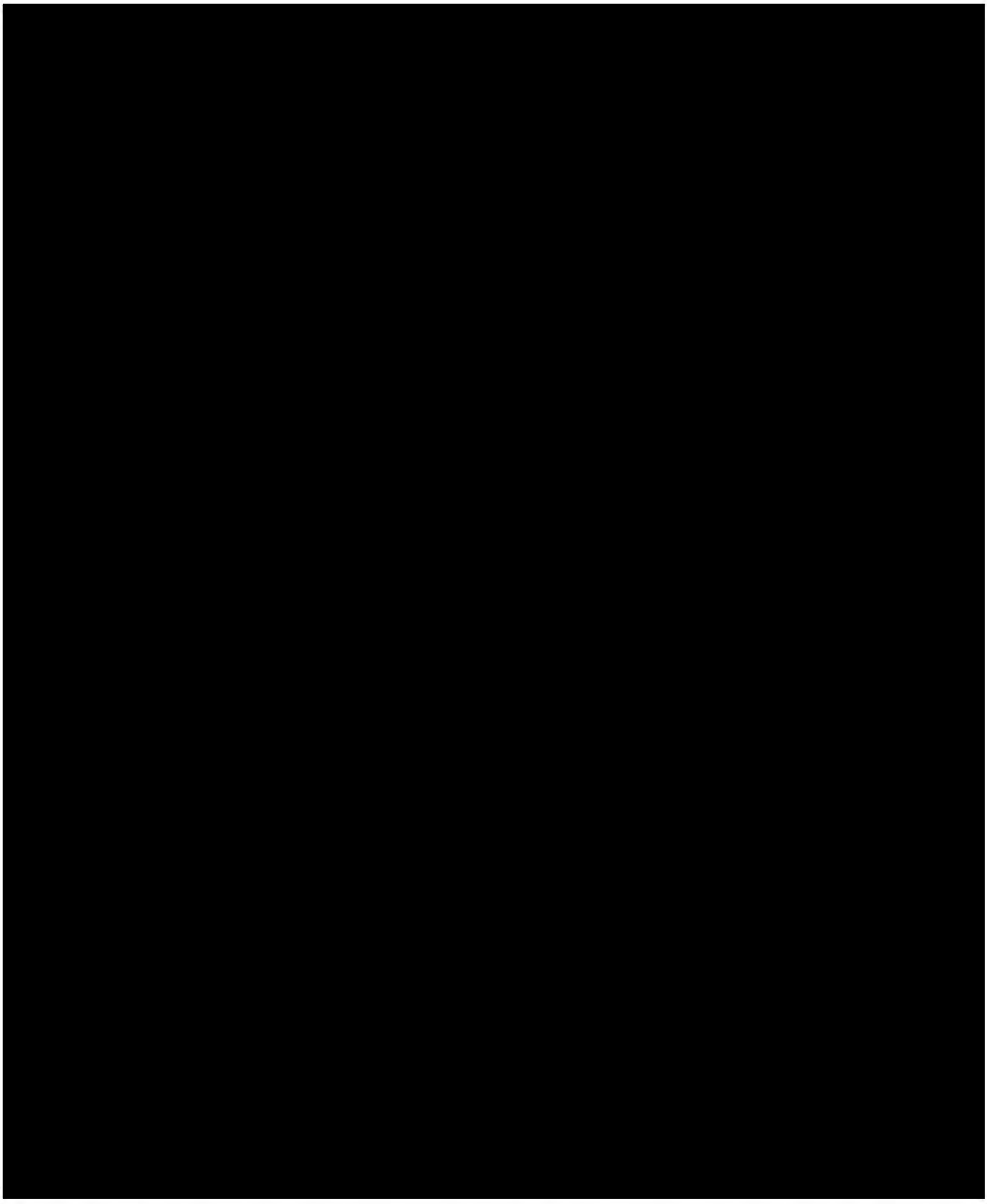

Spørgsmål 5: Der rejses tvivl om validiteten af de livskvalitetsmålinger der indgår i QALY-beregningerne. Er der data der understøtter denne tvivl eller som alternativt kan understøtte den foreliggende opgørelse.

Svar: BMS er ikke bekendte med, at der foreligger data, som understøtter den tvivl om validiteten af de livskvalitetsmålinger som Medicinrådet rejser. Tværtimod er det et relativt solidt datagrundlag med en besvarelses procent på 95 % i begge behandlingsarmer ved *baseline* og som forblev høj (> 85 %) på tværs af postbaseline-besøg undtagen ved behandlingsafslutning (~65%),

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hvilket tyder på, at HRQoL-endepunkter sandsynligvis ikke blev forvekslet af manglende data, hvilket også understreges af Medicinrådet på side 32:

Medicinrådets vurdering

Livskvaliteten er målt i hver cyklus, og der er en høj andel af patienter, der har besvaret de anvendte spørgeskemaer. Medicinrådet vurderer derfor, at data er relativt robust, og at manglende data ikke udgør et betydende problem.

I QUAZAR AML-001-studiet blev både FACIT-Fatigue og EQ-5D-3L indsamlet på dag 1 i hver cyklus og afslutning af behandlingen (Roboz et al. 2021). Dette svarer til mindst 2 andre nylige kliniske fase 3 studier i AML, der har inkluderet vurdering af livskvalitet såsom Viale-A studiet, der undersøgte Venetoclax i kombination med azacitidin versus azacitidin i behandlingsnaive AML patienter, der ikke var egnet til induktionsterapi (NCT02993523) og Viale-C studiet, der undersøgte Venetoclax i kombination med lavdosis cytarabin versus lavdosis cytarabin alene i behandlingsnaive AML patienter, der ikke var egnet til intensiv kemoterapi (NCT03069352). I disse 2 studier er alle spørgeskemaer for patientrapporterede oplysninger (PRO) blev indsamlet på cyklus 1 dag 1 og derefter på dag 1 i hver anden cyklus gennem begge studier og ved sidst besøg (Pratz et al. 2022). Kombinationen af venetoclax med et hypomethylerende stof er p.t. under vurdering i Medicinrådet.

Medicinrådet nævner, at nytteværdierne synes høje. BMS noterer sig, at de dog er lavere end de nytteværdier som er fundet i den danske befolkning i aldersgruppen på over 70 år (Jensen et al. 2021).

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Amgros I/S
Dampfærgevej 22
2100 København Ø
Danmark

T +45 88713000
F +45 88713008

Medicin@amgros.dk
www.amgros.dk

25.05.2022
MGK/CAF

Forhandlingsnotat

Dato for behandling i Medicinrådet	18.05.2022
Leverandør	Bristol Myers Squibb
Lægemiddel	Onureg (azacitidin)
Ansøgt indikation	Vedligeholdelsesbehandling til voksne patienter med akut myeloid leukæmi (AML) som har opnået komplet remission efter induktionsbehandling og som ikke kandiderer til hæmatopoietisk stamcelletransplantation.

Forhandlingsresultat

Amgros har opnået følgende priser på Onureg (azacitidin):

[redacted]

Tabel 1a: Forhandlingsresultat betinget af en anbefaling til hele populationen

Lægemiddel	Styrke/dosis	Pakningsstørrelse	AIP (DKK)	Forhandlet SAIP (DKK)	Rabatprocent ift. AIP
Onureg (azacitidin)	300mg/ 300 mg oral behandling én gang dagligt i 14 dage efterfulgt af 14 dages pause.	7 stk.	48.204,87	[redacted]	[redacted]

Prisen er **betinget** af en anbefaling [redacted]

Tabel 2b: [redacted]

Lægemiddel	Styrke/dosis	Pakningsstørrelse	AIP (DKK)	Forhandlet SAIP (DKK)	Rabatprocent ift. AIP
Onureg (azacitidin)	300mg/ 300 mg oral behandling én gang dagligt i 14 dage efterfulgt af 14 dages pause.	7 stk.	48.204,87	[redacted]	[redacted]

[redacted]

Informationer fra forhandlingen

[redacted]

Konkurrencesituationen

Der er på nuværende tidspunkt ingen lægemidler i direkte konkurrence, og Amgros har heller ingen oplysninger om, at nye lægemidler er på vej til samme indikation.
[redacted]

Tabel 2 nedenfor viser lægemiddelprisen for et års behandling med Onureg (azacitidin).

Tabel 3: Årlig lægemiddelpris for Onureg (azacitidin)

Lægemiddel	Styrke/dosis	Pakningsstørrelse	Pakningspris SAIP (DKK)	Antal pakninger/år	Årlig lægemiddelpris SAIP pr. år (DKK)
Onureg (azacitidin)	300mg / 300 mg oral behandling én gang dagligt i 14 dage efterfulgt af 14 dages pause.	7 stk.	[redacted]	26	[redacted]
Onureg (azacitidin)	300mg / 300 mg oral behandling én gang dagligt i 14 dage efterfulgt af 14 dages pause.	7 stk.	[redacted]	26	[redacted]

[redacted]

Status fra andre lande

Norge: Under vurdering.
Sverige: Vurderer ikke tabletbehandlinger.
England: Under vurdering
Canada: Anbefalet[1] med start/stop kriterier.

Konklusion

[redacted]

[1] https://cadth.ca/sites/default/files/DRR/2021/PC0245%20Onureg%20-%20CADTH%20Final%20Rec.pdf

Medicinrådet

Application for the assessment of oral azacitidine (Onureg®) as maintenance therapy for patients with acute myeloid leukaemia

Medicinrådet Dampfærgevej 27-29, 3. th. DK-2100 København Ø +45 70 10 36 00 medicinraadet@medicinraadet.dk www.medicinraadet.dk

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1 Basic information

Contact information	
Name	Lasse Lund Gundtoft
Title	Market Access Manager
Phone number	+45 20454797
Email	Lasse.Gundtoft@bms.com
Name	Morten Størling Hedegaard
Title	HTA Manager
Phone number	+45 53659819
Email	Morten.Hedegaard@bms.com

Overview of the pharmaceutical	
Proprietary name	Onureg®
Generic name	CC-486; azacitidine tablets
Marketing authorisation holder in Denmark	Celgene ApS (Denmark) C/O Bristol Myers Squibb Denmark Hummeltoftevej 49 2830 Virum
ATC code	L01BC07
Pharmacotherapeutic group	Pyrimidine analogues
Active substance(s)	Azacitidine
Pharmaceutical form(s)	Film-coated tablet
Mechanism of action	Onureg is an orally administered formulation of the hypomethylating agent azacitidine, a cytidine nucleoside analogue that incorporates into DNA and RNA. Azacitidine exerts its clinical efficacy through reduction of DNA hypermethylation and induction of cytotoxicity in abnormal haematopoietic cells.[1] Re-expression of aberrantly hypermethylated genes involved in normal cell-cycle regulation, differentiation, and apoptotic pathways is believed to improve haematopoiesis and suppress malignant cells in haematopoietic disorders such as AML. The cytotoxic effects of azacitidine may be associated with inhibition of protein synthesis and activation of DNA damage pathways through incorporation into RNA and DNA, respectively.[2,3]
Dosage regimen	The recommended dosage is 300 mg Onureg once daily. Each repeated cycle consists of a treatment period of 14 days followed by a treatment-free period of 14 days (28-day treatment cycle). In the case of disease relapse, with 5%-15% blasts in peripheral blood or bone marrow, in conjunction with a clinical assessment, an extension of the dosing schedule from 14 to 21 days of repeated 28-day cycles should be considered.
Therapeutic indication relevant for assessment (as defined by the EMA)	Onureg is indicated as maintenance therapy in adult patients with AML who achieved CR or CRi following induction therapy with or without consolidation treatment and who are not candidates for, including those who choose not to proceed to, HSCT.
Other approved therapeutic indications	Not applicable
Will dispensing be restricted to hospitals?	Yes.

Overview of the pharmaceutical	
Combination therapy and/or co-medication	Patients are to be treated with an antiemetic 30 minutes prior to each dose of Onureg for the first 2 treatment cycles. Antiemetic prophylaxis may be omitted after 2 cycles if there has been no nausea and vomiting. Diarrhoea should be treated promptly at the onset of symptoms.
Packaging – types, sizes/number of units, and concentrations	Onureg film-coated tablets are packaged in aluminium foil blister packs. Each pack contains either 7 or 14 tablets of either 200 mg or 300 mg Onureg.
Orphan drug designation	Not applicable.

AML = acute myeloid leukaemia; ATC = Anatomical Therapeutic Chemical Classification System; CR = complete remission; CRi = complete remission with incomplete blood count recovery; EMA = European Medicines Agency; HSCT = haematopoietic stem cell transplantation.

Source: Onureg SmPC (2020)[4]

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2 Abbreviations

Abbreviation	Expansion
AE	adverse event
AIC	Akaike's information criterion
AML	acute myeloid leukaemia
ANC	absolute neutrophil count
APL	acute promyelocytic leukaemia
ATC	Anatomical Therapeutic Chemical Classification System
AZA	azacitidine
BIC	Bayesian information criterion
BM	bone marrow
BSA	body surface area
BSC	best supportive care
CBC	complete blood count
CEAC	cost-effectiveness acceptability curve
CHMP	Committee for Medicinal Products for Human Use
CI	confidence interval
CML	chronic myeloid leukaemia
CMML	chronic myelomonocytic leukaemia
CR	complete remission
CRi	complete remission with incomplete blood count recovery
CSR	clinical study report
DKK	Danish krone
DNMT	deoxyribonucleic acid methyltransferase
DNMT3A	deoxyribonucleic acid methyltransferase 3A
DP	diphosphate
ECOG PS	Eastern Cooperative Oncology Group performance status
EMA	European Medicines Agency
EORTC QLQ-C30	European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire–Core Module
EQ-5D-3L	3-level EQ-5D
EQ-5D-5L	5-level EQ-5D
EU	European Union
FAB	French-American-British
FACIT-Fatigue	Functional Assessment of Chronic Illness Therapy–Fatigue
FLT3	fms-like tyrosine kinase 3
HMA	hypomethylating agent
HR	hazard ratio
HRQoL	health-related quality of life
HSCT	haematopoietic stem cell transplantation

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HSUV	health state utility value
HTA	health technology assessment
IC	induction chemotherapy
ICER	incremental cost-effectiveness ratio
ITD	internal tandem duplication
ITT	intent to treat
IV	intravenous(ly)
IVRS	interactive voice response system
IWG	International Working Group
KM	Kaplan-Meier
MDS	myelodysplastic syndrome
MedDRA	Medical Dictionary for Regulatory Activities
MID	minimally important difference
mITT	modified intent to treat
MP	monophosphate
MPN	myeloproliferative neoplasm
MRD	measurable residual disease
N/A	not applicable
NA	not available
NCCN	National Comprehensive Cancer Network
NCT	National Clinical Trial
OS	overall survival
PBO	placebo
PINR	Physical Impairment Numeric Rating
PPP	purchasing power parity
QALY	quality-adjusted life-year
QD	once daily
RBC	red blood cell
RFS	relapse-free survival
SAE	serious adverse event
SC	subcutaneous
SCT	stem cell transplantation
SD	standard deviation
SE	standard error
SLR	systematic literature review
SmPC	summary of product characteristics
TEAE	treatment-emergent adverse event
TET2	ten-eleven translocation-2
TP	triphosphate
UK	United Kingdom

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US	United States
VAS	visual analogue scale
WHO	World Health Organization

3 Tables and Figures

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4 Summary

4.1 Indication

Onureg (CC-486, oral azacitidine) is indicated as maintenance therapy in adult patients with acute myeloid leukaemia (AML) who achieved complete remission (CR) or CR with incomplete blood count recovery (CRi) following induction therapy with or without consolidation treatment and who are not candidates for, including those who choose not to proceed to, haematopoietic stem cell transplantation (HSCT).

This indication received a positive Committee for Medicinal Products for Human Use (CHMP) opinion on 22 April 2021 and marketing authorisation on 17 June 2021.

4.2 Disease overview

AML is an aggressive haematologic cancer that originates in the myeloid line of haematopoietic precursor cells, commonly as the result of a genetic aberration.[5,6]

The signs and symptoms associated with AML are often non-specific and secondary to the development of other conditions. Flu-like symptoms are commonly observed for a period of 4 to 6 weeks before diagnosis.[7] Patients may have anaemia, neutropenia, and/or thrombocytopenia as a result of impaired haematopoiesis.[5,7] In some cases, leukaemic cells can spread to the organs. Symptoms associated with leukaemic cell infiltration in the brain and spinal cord include headaches, weakness, seizures, vomiting, issues with balance, and blurred vision.[7,8]

Acute myeloid leukaemia is a rare cancer, despite being the most common acute leukaemia among adults.[9-11] Approximately 250 cases of AML are diagnosed in Denmark per year.[12] The median age for newly diagnosed patients with AML in 2019 in Denmark was 73 years.[13]

4.3 Current management and unmet need

Despite the achievement of CR with standard induction chemotherapy in 40% to 60% of AML patients > 60 years, most patients (80%-90%) eventually have a relapse.[14-16] It is expected that Onureg will be positioned as a maintenance treatment in adults with AML who achieved CR or CRi following induction therapy with or without consolidation treatment and who are not candidates for HSCT, including those who choose not to proceed to HSCT. Currently, in Denmark, almost all of these patients will be closely monitored after intensive chemotherapy and will receive no further active therapy until recurrence.

4.4 Onureg

Onureg is an orally administered formulation of the hypomethylating agent (HMA) azacitidine, a cytidine nucleoside analogue that incorporates into DNA and RNA.[1,2,17] The recommended dosage of Onureg is 300 mg once daily. Each repeated cycle consists of a treatment period of 14 days followed by a treatment-free period of 14 days (28-day treatment cycle). In the case of disease relapse, with 5% to 15% blasts in peripheral blood or bone marrow, in conjunction with a clinical assessment, an extension of the dosing schedule from 14 to 21 days of repeated 28-day cycles should be considered.

Onureg is the first approved treatment option given as maintenance therapy post-standard intensive chemotherapy for patients with AML in CR/CRi, regardless of the mutation status.

4.4.1 Clinical evidence

The safety and efficacy of Onureg as a maintenance therapy for patients with AML has been demonstrated in the pivotal randomised phase 3 QUAZAR AML-001 trial.[18,19] In QUAZAR AML-001, Onureg demonstrated a clinically and statistically significant improvement in overall survival (OS, primary endpoint) compared with placebo. At a median follow-up of 41.2 months (based on a July 2019 database lock), the median OS was 24.7 months (95% confidence interval [CI], 18.7-30.5 months) for patients treated with Onureg versus 14.8 months (95% CI, 11.7-17.6 months) for those treated with placebo (hazard ratio [HR], 0.69; 95% CI, 0.55-0.86; $P < 0.001$).[18,19] [redacted]

The efficacy benefit observed with Onureg versus placebo was further supported by the key secondary endpoint of relapse-free survival (RFS), (10.2 months vs. 4.8 months, HR, 0.65 [95% CI, 0.52-0.81], $P = 0.0001$),[18,19] while the noninferiority of Onureg relative to placebo for health-related quality of life (HRQoL), as assessed by the Functional Assessment of Chronic Illness Therapy–Fatigue (FACIT-Fatigue) and the 3-level EQ-5D (EQ-5D-3L), was demonstrated.

In QUAZAR AML-001, Onureg was well tolerated, with a low rate of discontinuation due to treatment-emergent adverse events (TEAEs); Onureg, 13.1%; placebo, 4.3%) and no reported treatment-related deaths. Rates of serious adverse events (SAEs) and grade 3 or 4 TEAEs were relatively similar between treatment groups (33.5% vs. 25.3% and 71.6% vs. 63.1%; Onureg vs. placebo, respectively).[18]

Because the standard of care comparator in Denmark for this patient group is careful monitoring, the head-to-head comparison in the QUAZAR AML-001 trial of Onureg versus placebo provides the most robust comparison, and no indirect treatment comparison has been performed.

4.4.2 Economic evidence

This economic evaluation considered the cost-effectiveness of Onureg plus best supportive care (BSC) compared with no active therapy plus BSC in the maintenance treatment of adult patients with AML who have achieved CR/CRi and are ineligible for HSCT in Denmark. Compared with no active therapy, treatment with Onureg was more costly (Danish krone [DKK] 1,843,881) and more effective (0.76 quality-adjusted life-years [QALYs]), with an incremental cost-effectiveness ratio (ICER) of DKK 2,419,302 per QALY gained. The probabilistic results were aligned with the deterministic results. Overall, Onureg is estimated to result in more life-years and QALYs and to increase the time patients spend in the RFS state.

4.5 Conclusion

Onureg is the first therapy to show a significant improvement in OS in the maintenance setting in patients with AML in CR following induction chemotherapy, while maintaining HRQoL compared with placebo. Further, as an orally administered maintenance therapy, Onureg provides prolonged, low-level exposure to azacitidine with a manageable safety profile and low rate of discontinuation due to adverse events (AEs). The results of the economic evaluation presented in this document are based on list prices and must be interpreted with caution. Once the analysis is made with net prices, the use of Onureg on top of current standard of care is expected to be a cost-effective treatment in Denmark.

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5 The patient population, the intervention and choice of comparator(s)

5.1 The medical condition and patient population

5.1.1 Disease background

Acute myeloid leukaemia is a rare and aggressive haematologic cancer that originates in the myeloid line of haematopoietic precursor cells, commonly as the result of a genetic aberration.[5,6] The disease may arise secondary to an antecedent haematologic disorder as the result of exposure to prior chemotherapy, after radiation therapy, or in the absence of prior therapy or disease (primary or de novo AML).[5] Regardless of the underlying cause, the pathophysiology of AML involves dysfunctional differentiation of myeloblasts and suppression of normal bone marrow haematopoiesis, leading to excessive proliferation of immature blasts and accumulation of leukaemic cells in the bone marrow.[5,6,21] Most of the clinical manifestations of the disease result from the infiltration and accumulation of these malignant, undifferentiated myeloid cells in the bone marrow, peripheral blood, and other tissues, contributing to impaired blood cell production and bone marrow failure.[5,6,21]

AML commonly results from chromosomal abnormalities or single-gene mutations: approximately 97% of patients have at least 1 genetic mutation and approximately 48% have at least 2.[22] These mutations result in activation of pro-proliferative pathways (e.g., FLT3), dysfunctional haematopoietic differentiation (e.g., nucleophosmin-1), or altered epigenetic regulation (e.g., the DNA methylation-related genes DNMT3A,[i] TET2,[ii] isocitrate dehydrogenase 2, and isocitrate dehydrogenase 1). Notably, mutations in the third group of genes result in DNA hypermethylation, leading to downstream effects on both cellular proliferation and differentiation.[5]

AML is diagnosed based on the presence of 20% or more blasts in the bone marrow or peripheral blood in combination with immunohistochemistry, cytogenetics, and molecular analyses.[5,14,23-27] Subtypes of AML were first introduced by the French-American-British (FAB) classification system, which included 8 subtypes (M0 through M7) based on the morphological and cytochemical characteristics of the leukaemia cells.[5,28] More recently, the World Health Organization (WHO) described a classification system for AML and related neoplasms that incorporates genetic information, immunophenotype, morphology, and clinical presentation information to define 6 AML categories: AML with recurrent genetic abnormalities, AML with myelodysplasia-related changes, therapy-related myeloid neoplasms, AML not otherwise specified, myeloid sarcoma, and myeloid proliferations related to Down syndrome.[26] These categories are used to help define risk categories and to select appropriate treatment strategies.[5]

The signs and symptoms associated with AML are often non-specific and secondary to the development of other conditions. Flu-like symptoms are commonly observed for a period of 4 to 6 weeks before diagnosis.[7] Patients may have anaemia, neutropenia, and/or thrombocytopenia as a result of impaired haematopoiesis.[5,7] In some cases, leukaemic cells can spread to the organs. Symptoms associated with leukaemic cell infiltration in the brain and spinal cord include headaches, weakness, seizures, vomiting, issues with balance, and blurred vision.[7,8]

AML is a serious and rapidly progressing disease with a very poor prognosis.[6,11,29] Although most patients who are fit for intensive chemotherapy are able to achieve CR, most of these patients will eventually relapse,[16,30,31] many within the first year after achieving CR.[32,33] Relapse is associated with significantly reduced OS[14,31,34,35] and impaired HRQoL.[36-39]

[i] Deoxyribonucleic acid methyltransferase 3A.

[ii] Ten-eleven translocation-2.

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The HRQoL of patients with AML is substantially impaired by the debilitating symptoms of the disease and the inconvenience, discomfort, and side effects associated with certain therapies.[39,40] Patients with AML consistently report functional domain and global health status scores on the European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire–Core Module (EORTC QLQ-C30), that are substantially lower than scores for the general healthy population.[41-45]

5.1.2 Epidemiology of acute myeloid leukaemia in Denmark

5.1.2.1 Incidence and prevalence

Acute myeloid leukaemia is a rare cancer, despite being the most common acute leukaemia among adults.[9-11] The incidence of the disease increases with age,[9-11,46] and the median age at diagnosis is between 63 and 71 years in the United States (US), United Kingdom (UK), Canada, Australia, and Sweden.[11] Men are 1.2 to 1.6 times more likely than women to develop AML during their lifetime, as evidenced by population-based studies conducted in the US, UK, Canada, Denmark, Australia, and Algeria.[11] In the European Union (EU), approximately 1 in 10,000 residents had AML in 2016, equivalent to more than 51,000 people.[47] The overall estimated prevalence of the disease was 11.0 cases per 100,000 from 1995 to 2002, and the overall incidence rate was 3.6 to 3.7 cases per 100,000 from 2000 to 2002.[9,10] Given its low prevalence, AML has been designated as an orphan condition in the EU.[iii,47,48]

Approximately 250 cases of AML are diagnosed in Denmark per year.[12] The median age for newly diagnosed patients with AML in Denmark is 73 years.[13] Table 1 reports the incidence and prevalence of AML in Denmark.

Table 1. Incidence and prevalence of AML in Denmark (2016-2020)

	2016	2017	2018	2019
Incidence	251	261	275	267
Prevalence	996	1,025	1,045	NA

NA = not available.

Sources: Dansk Akut Leukæmi Database & Myelodysplastisk Syndrom Database (2020)[13,49]

5.1.2.2 Mortality and survival rates

Acute myeloid leukaemia is associated with the lowest survival rate across all types of leukaemia.[6,11,29] Data from Europe indicate that 5-year relative survival rates of the disease are the lowest among all myeloid leukaemias (Figure 1).[10,50-52] Furthermore, 5-year OS rates for AML are the fifth and seventh lowest across all types of cancer in the US (24.0%) and the EU (~17%[iv]), respectively.[11,53] Among patients diagnosed at 65 years of age or older, AML has the lowest median OS (2.7 months) and 1-year survival rate (21.8%) across all cancer types in the US.[11]

[iii] In the EU, an orphan condition is defined as one that affects fewer than 1 in 2,000 individuals.[48]

[iv] Value estimated from a bar chart in De Angelis et al. (2014)[53]

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The Dansk Akut Leukæmi Database & Myelodysplastisk Syndrom Database report also presents survival data for patients with AML aged 60 years and older who have received intensive chemotherapy, with an increasing proportion of those undergoing allogeneic transplantation (Figure 3).[13] In contrast, patients in the QUAZAR AML-001 trial were not candidates for transplantation at enrolment. Among this subpopulation of Danish patients with AML, the KM estimated 1-year survival is 67.2% (95% CI, 57.8%-74.9%) and the 5-year survival rate is 25.5% (95% CI, 19.6%-31.7%) for the most recent 6-year period.[13]

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5.1.3 Patient populations relevant for this application

It is expected that Onureg will be positioned as a maintenance treatment in adults with AML who achieved CR or CRi following induction therapy with or without consolidation treatment and who are not candidates for HSCT, including those who choose not to proceed to HSCT. Currently, in Denmark, most of these patients will be closely monitored without receiving further antileukemic therapy, one exception being the FLT3-ITD–positive AML patients who have not undergone a transplant and are eligible for maintenance therapy with midostaurin.

FLT3-positive AML patients (20%-30% at diagnosis) are eligible for targeted therapy with midostaurin in combination with standard induction and consolidation chemotherapy, followed by single agent maintenance therapy for patients in complete response who have not undergone a transplant.[54,55] FLT3-ITD mutations are associated with a poor prognosis.[56] However, treatment with FLT3 tyrosine kinase inhibitor (TKI) in combination with intensive therapy and routine use of allogeneic stem cell transplant as consolidative therapy has significantly improved outcomes and is the standard of care for FLT3-positive AML patients in Denmark.[57] Indeed, according to a Danish clinical expert, only a handful of Danish patients (approximately 5) have received midostaurin maintenance since the approval by the DMC in January 2018.[57] Consequently, close monitoring without further antileukemic therapy is considered the only relevant comparator for Onureg in the current application.

There were 267 newly diagnosed patients with AMLs in Denmark in 2019.[13] Thus, it is anticipated that approximately 44 patients would be eligible for maintenance treatment with Onureg (Table 2).

Table 2. Eligible patient calculations

Population	No. of patients	Calculation	Source
Number of patients newly diagnosed with AML in Denmark in 2019	267	52 patients were 60 years of age or less; 215 patients were over 60 years of age	Dansk Akut Leukæmi Database & Myelodysplastisk Syndrom Database (2020)[13]
Number of patients receiving remission-inducing chemotherapy	96	96 patients received remission-inducing therapy	Dansk Akut Leukæmi Database & Myelodysplastisk Syndrom Database (2020)[13]
Number of patients who achieve CR	81	84.4%	Dansk Akut Leukæmi Database & Myelodysplastisk Syndrom Database (2020)[13]
Number of patients who do not proceed to SCT (receiving close monitoring and BSC)	59	In 2010-2014, 26.6% of patients with AML in first CR underwent HSCT; therefore, 73.4% had close monitoring	Ostgard et al. (2018)[58]
Number of patients eligible for Onureg treatment	44	Approximately 75% of patients receiving close monitoring / or BSC are ≥ 55 years of age	Dansk Akut Leukæmi Database & Myelodysplastisk Syndrom Database (2020)[13] BMS estimate based on input from a Danish expert

AML = acute myeloid leukaemia; BSC = best supportive care; CR = complete remission; HSCT = haematopoietic stem cell transplantation; SCT = stem cell transplantation.

Table 3. Estimated number of patients eligible for treatment in Denmark

	2021	2022	2023	2024	2025
Number of patients in Denmark who are expected to use Onureg in the coming years[a]	44	69	85	98	108

[a] Calculated based on 44 incident patients in 2021 and overall survival of BAT arm in the economic model.

5.1.4 Age group of the population affected and patient group currently eligible for treatment in Denmark

The incidence of AML increases with age,[9-11,46] and the median age at diagnosis is between 63 and 71 years in the US, UK, Canada, Australia, and Sweden.[11] The median age for newly diagnosed patients with AML in Denmark in 2019 was 73 years.[13]

The median age in the overall QUAZAR AML-001 trial population was 68 years (range, 55-86 years).[18] The median age of patients enrolled in QUAZAR AML-001 is expected to be relatively close to the median age of Danish patients eligible for intensive chemotherapy and who are not candidates for HSCT. The other baseline characteristics are expected to be relatively similar to the Danish AML population achieving CR/CRi after intensive chemotherapy.

5.1.5 Subgroup of patients that is expected to have a different efficacy and safety than anticipated for the entire population

Allogeneic HSCT provides the best chance of cure for patients with AML;[59,60] however, many patients are not considered candidates for HSCT, especially older patients (aged ≥ 70 years) and those with significant comorbidities.

Although enrolment in QUAZAR AML-001 was limited to patients who were not considered candidates for HSCT at screening, 10% of randomised patients ultimately received HSCT after discontinuing study treatment.[18,61] Enrolment began in 2013. Recent developments, including alternative donor sources, high-resolution HLA-typing, lower-intensity conditioning regimens, and improvements in supportive care,[62] may have allowed some patients who were not originally considered candidates for HSCT to undergo transplant after discontinuing treatment in QUAZAR AML-001. Nevertheless, the focus of the submission is Onureg in transplant-ineligible patients in accordance with the design of QUAZAR AML-001 and current Onureg indication.

5.1.6 Current treatment options

The first-line treatment approach for patients with newly diagnosed AML is highly dependent on a patient's fitness for intensive therapy, which is determined based on factors such as age, performance status, and comorbidities as well as cytogenetic risk status and molecular risk factors.[5,14,27] For patients who are fit for intensive therapy, the standard of care is induction chemotherapy (typically with cytarabine and an anthracycline), with the goal of achieving CR.[63-65] After induction chemotherapy, patients will often receive 1 to 2 subsequent cycles of consolidation chemotherapy or allogeneic HSCT.[14,16,27,65] The goal of consolidation therapy is to sustain the CR that was achieved with induction chemotherapy using a limited number of treatment cycles to reduce the potential for cumulative toxicity.[66-68] Allogeneic HSCT provides the best chance of cure for patients with AML.[59,60] Across Denmark,[13] 26.6% of patients with AML in first CR underwent HSCT during the years 2010 to 2014.[58] This patient group would not be eligible to receive Onureg.

Despite the achievement of CR with standard induction chemotherapy in 40% to 60% of patients with AML > 60 years, most patients (80%-90%) eventually have a relapse.[14-16] Aside from Onureg, only midostaurin is approved by the European Medicines Agency (EMA) for maintenance therapy in newly diagnosed FLT3 mutation–positive patients in CR after treatment with midostaurin in combination with standard intensive and consolidation therapy.[54]

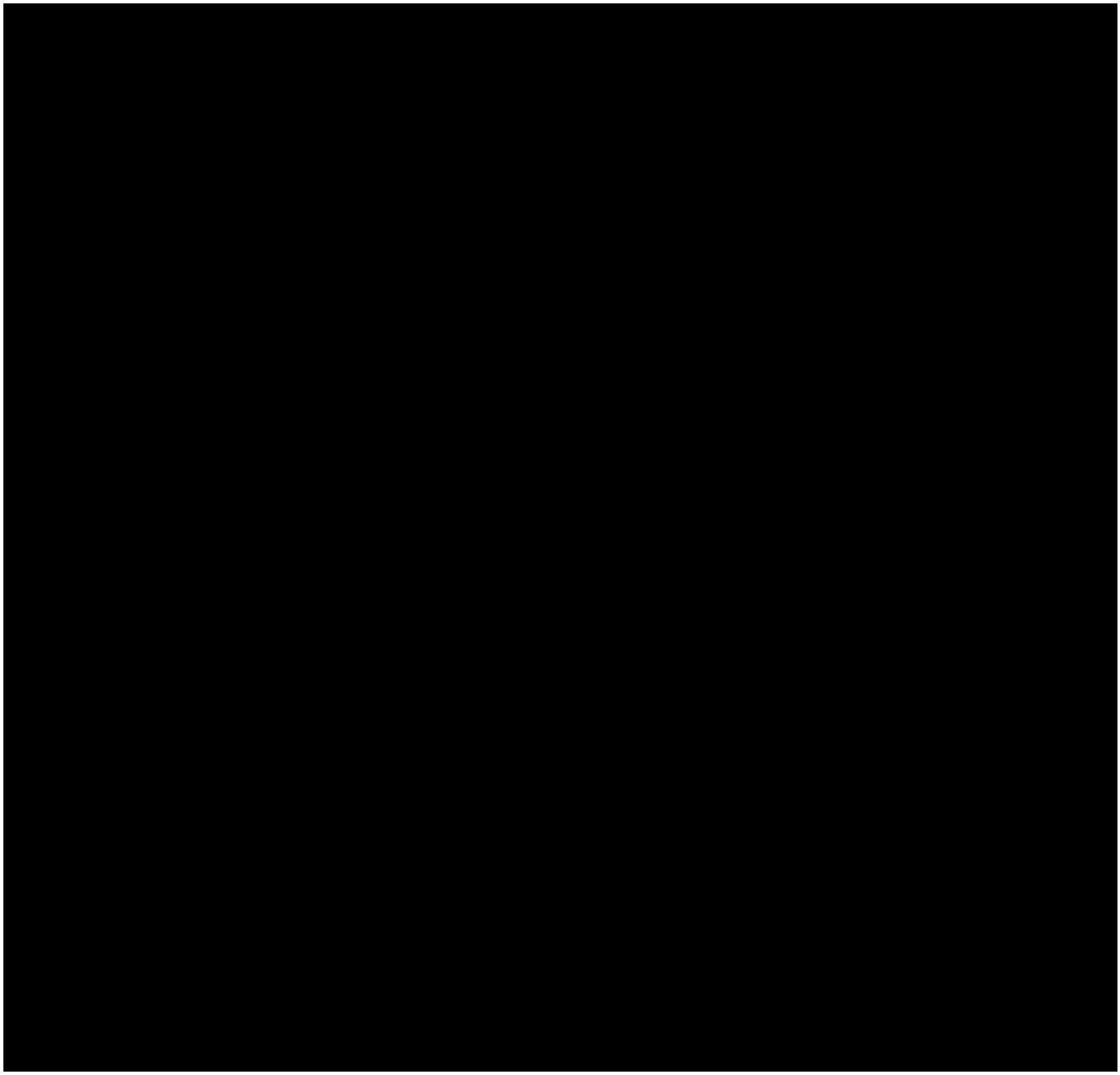
The Danish AML treatment guideline from December 2020 recommends the following induction regimen, which consists of 2 cycles of intensive chemotherapy as follows: the first cycle consists of ("3 + 10") cytarabine intravenously (IV) 100 mg/m^2 twice daily for 10 days; daunorubicin IV 60 mg/m^2 for 3 days.[65] Three to 4 weeks after, the second cycle of induction is given as follows ("3 + 8"), cytarabine IV 100 mg/m^2 twice daily for 8 days; daunorubicin IV 50 mg/m^2 for 3 days. Danish physicians consider that the induction regimens recommended in Denmark (3 + 10 or 3 + 8 [65]) and 3 + 7 described in the Onureg clinical study report (CSR) are equivalent.

For patients younger than 60 years, 2 consolidation regimens are recommended: cytarabine IV 3 g/m^2 administered 6 times over 6 days, with 12 hours between doses 1 and 2 and doses 3, 4, 5, and 6; and 24 hours between doses 2, 3, 4 and 5.[65] In patients over 60 years of age, a consolidation regimen of cytarabine IV 2 g/m^2 administered 6 times over 6 days, with 12 hours between doses 1 and 2 and doses 3, 4, 5, and 6; and 24 hours between doses 2, 3, 4, and 5 is recommended. In the QUAZAR AML-001 study, 80% of patients received ≥ 1 cycle of consolidation therapy,[18] which is expected to be relatively similar to Danish clinical practice, based on the above recommendations.

A potential addition of gemtuzumab ozogamicin 3 mg/m^2 (max. 5 mg) to curative chemotherapy either according to the French ALFA regimen or the English Medical Research Council regimen can be considered for CD33-positive patients with AML with favourable or intermediate cytogenetic risk profile.[69]

The Danish guideline includes a recommendation for addition of midostaurin 50 mg twice daily for 14 days from 2 days after completion of induction/consolidation therapy and for a further 12 months after completion of therapy in

the small subgroup of patients with FLT3-ITD–positive AML.[65] This should not be given after allogeneic HSCT or in patients who have received gemtuzumab ozogamicin. Most of the patients with FLT3-ITD– positive AML are offered allogeneic HSCT. Therefore, few FLT3-positive patients will receive midostaurin as maintenance therapy (input from Danish experts). Figure 4 presents the treatment pathway in Denmark.



5.1.7 Choice of comparator(s)

In Denmark, no antileukemic treatment is used as standard of care in AML maintenance for HSCT-ineligible patients who achieved a CR/CRi after intensive chemotherapy; therefore, close monitoring is the predominant strategy in these patients and the appropriate comparator for Onureg. Here, midostaurin is not considered as a relevant comparator for Onureg for several reasons. First, the current Danish standard of care for FLT3-positive AML patients includes allogeneic transplantation after standard intensive chemotherapy given in combination with midostaurin.[65] Supporting this, very few Danish FLT3-positive AML patients have apparently received midostaurin maintenance since

the approval by the DMC (~1-2 patients per year). Further, the patient population enrolled in the pivotal phase 3 RATIFY trial, which is supporting the current approval of midostaurin in patients with AML, greatly differs from the population enrolled in the QUAZAR AML-001 trial. In contrast to QUAZAR AML-001, patients eligible for transplantation were allowed in RATIFY, and patients aged 18 to 59 years were enrolled, whereas patients aged 55 years or older were enrolled in QUAZAR AML-001. A total of 205 patients who attained CR/CRi and were not transplanted received maintenance (120 on the midostaurin arm and 85 on placebo), with a median age of 49 years (range, 19-60), which is 9 years below the median age in the QUAZAR AML-001 study (68 years; range, 55-86).[70] Further, 10 patients had started maintenance therapy (7 on the midostaurin arm and 3 on the placebo arm) prior to receiving allo-HCT while still in first CR. To our knowledge, information about subsequent therapy after discontinuation of maintenance for this subgroup of patients in the RATIFY study is not available, and the proportion of patients who were subsequently transplanted is unknown. In addition, the RATIFY trial was not designed to specifically investigate the efficacy of midostaurin maintenance, which remains unclear based on currently evaluable data. In contrast, the QUAZAR AML-001 study randomised transplant-ineligible patients with AML who have achieved CR/CRi after intensive chemotherapy (regardless of mutation status) and showed that Onureg maintenance was associated with a significant OS benefit compared with placebo, with a manageable safety profile and maintained HRQoL throughout treatment.

5.1.8 Description of the comparator(s)

5.2 The intervention

Onureg is as maintenance therapy in adult patients with AML who achieved CR or CRi following induction therapy with or without consolidation treatment and who are not candidates for HSCT, including those who choose not to proceed to HSCT. Table 4 summarises the use of Onureg as indicated. Full details of the prescribing information for Onureg are available from the summary of product characteristics (SmPC).

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Table 4. Description of Onureg

Generic name(s) (ATC code)	L01BC07
Mode of action	Onureg is an orally administered formulation of the hypomethylating agent azacitidine, a cytidine nucleoside analogue that incorporates into DNA and RNA. Azacitidine exerts its clinical efficacy through reduction of DNA hypermethylation and induction of cytotoxicity in abnormal haematopoietic cells.[1] Re-expression of aberrantly hypermethylated genes involved in normal cell-cycle regulation, differentiation, and apoptotic pathways is believed to improve haematopoiesis and suppress malignant cells in haematopoietic disorders such as AML. The cytotoxic effects of azacitidine may be associated with inhibition of protein synthesis and activation of DNA damage pathways through incorporation into RNA and DNA, respectively. [2,3]
Pharmaceutical form	Film-coated tablets
Posology	The recommended dosage is Onureg 300 mg once daily.
Method of administration	Oral
Dosing	The recommended dosage is 300 mg Onureg once daily. Each repeated cycle consists of a treatment period of 14 days followed by a treatment-free period of 14 days (28-day treatment cycle). In the case of disease relapse, with 5%-15% blasts in peripheral blood or bone marrow, in conjunction with a clinical assessment, an extension of the dosing schedule from 14 to 21 days of repeated 28-day cycles should be considered.
Should the pharmaceutical be administered with other medicines?	Patients are to be treated with an antiemetic 30 minutes prior to each dose of Onureg for the first 2 treatment cycles. Antiemetic prophylaxis may be omitted after 2 cycles if there has been no nausea and vomiting. Diarrhoea should be treated promptly at the onset of symptoms.
Treatment duration	Onureg treatment should be continued until no more than 15% blasts are observed in peripheral blood or bone marrow or until unacceptable toxicity.
Necessary monitoring, both during administration and during the treatment period	A complete blood count should be performed prior to initiation of Onureg and is also recommended every other week for the first 2 cycles (56 days), every other week for the 2 cycles after dose adjustment (if necessary), and monthly thereafter prior to the start of subsequent treatment cycles.
Additional tests or investigations	Not applicable.
Packaging	Onureg film-coated tablets are packaged in aluminium foil blister packs. Each pack contains either 7 or 14 tablets of either 200 mg or 300 mg Onureg.

AML = acute myeloid leukaemia; ATC = Anatomical Therapeutic Chemical Classification System.
Source: Onureg SmPC (2020)[4]

5.2.1 Onureg: mode of action

Onureg (CC-486) is an orally administered formulation of the HMA azacitidine, a cytidine nucleoside analogue that incorporates into DNA and RNA.[1,2,17] Azacitidine exerts its clinical efficacy through reduction of DNA hypermethylation and induction of cytotoxicity in abnormal haematopoietic cells.[1] Re-expression of aberrantly hypermethylated genes involved in normal cell-cycle regulation, differentiation, and apoptotic pathways is believed to improve haematopoiesis and suppress malignant cells in haematopoietic disorders such as AML. The cytotoxic effects of azacitidine may be associated with inhibition of protein synthesis and activation of DNA damage pathways through incorporation into RNA and DNA, respectively.[2,3]

Incorporation of azacitidine into DNA inactivates DNA methyltransferases.[1] When DNA replication occurs in cells with suppressed activity of these enzymes, DNA methylation is reduced. However, the incorporation of azacitidine into DNA is S phase restricted, and the drug has a short plasma half-life.[1,2,71] Therefore, optimal activity of azacitidine may

require longer exposure of diseased cells to the drug, increasing the opportunity for incorporation into DNA at the necessary stage of the cell cycle.[71]

[redacted]

5.2.2 Comparison between Onureg and injectable azacitidine

Although Onureg and injectable azacitidine contain the same active pharmaceutical ingredient, they are different formulations and are not bioequivalent. Indeed, Onureg should not be used interchangeably with injectable azacitidine due to differences in the exposure, dose, and schedule of treatment[73] As an orally administered therapy, Onureg provides the opportunity to deliver azacitidine at low systemic doses over a prolonged period (14 days or 21 days of each 28-day cycle). In contrast, injectable azacitidine requires a shorter duration of drug exposure (administered subcutaneously or IV for up to 7 days of each 28-day cycle).[1,71] The lower levels of azacitidine exposure with Onureg over a longer period may increase the chances that diseased cells will be in the required cell-cycle stage (i.e., S phase) for DNA incorporation of the drug. Further, low, prolonged exposure may decrease the risk of toxicity (e.g., exacerbation of existing cytopenias) compared with exposure to higher levels over a shorter duration.

Quality of life is an important aspect for older patients with AML, and oral formulation has a clear advantage compared with injectable azacitadine.[74,75] More crucially, because no OS benefit has been demonstrated with injectable azacitidine, it is neither approved nor used in Denmark. The HOVON97 trial demonstrated a significant improvement in DFS after maintenance with injectable azacitidine versus observation/no maintenance (64% vs. 42% at 1 year; $P = 0.04$). However, this study did not show a significant OS benefit. Also, due to slow accrual and early termination of the study, fewer patients were enrolled than planned.[76]

Further, oral administration eliminates the discomfort of repeated injections/infusions and the recurrence of injection site reactions,[1] which may be especially important for use in the maintenance setting.[77]

5.2.3 Onureg: position in the treatment pathway

Currently, no single-agent maintenance therapies are approved for use in Denmark. The Danish guidelines include a recommendation for addition of midostaurin 50 mg twice daily for 14 days from 2 days after completion of induction/consolidation therapy and for a further 12 months after completion of therapy in the small subgroup of patients with FLT3-ITD–positive AML.[65] However, this should not be given after allogeneic HSCT or in patients who have received gemtuzumab ozogamicin. Most of the patients with FLT3-ITD–positive AML are offered allogeneic HSCT, and few patients receive midostaurin as maintenance therapy (input from Danish experts). If recommended, Onureg will be the single agent mainly used as maintenance therapy for AML in Denmark.

Onureg is indicated as maintenance therapy in adult patients with AML who achieved CR or CRi following induction therapy with or without consolidation treatment and who are not candidates for HSCT, including those who choose not to proceed to HSCT. As an orally administered therapy, Onureg provides low-level exposure to azacitidine during a prolonged period of time, resulting in sustained antileukaemic activity. Furthermore, it may decrease the inconvenience and discomfort associated with subcutaneous/IV administration of other HMAs.[54,78,79]

The current clinical treatment pathway for patients with AML in Denmark is shown in Figure 4 and includes the proposed place of Onureg in the pathway as confirmed by clinical input.

6 Literature search and identification of efficacy and safety studies

6.1 Identification and selection of relevant studies

A systematic literature review (SLR) of clinical evidence to identify efficacy and safety data for maintenance treatments for patients with AML who have achieved CR or CRi after intensive induction therapy, with or without consolidation, and are ineligible for (or choose not to have) stem cell transplantation was conducted.

Appendix A provides an overview of the SLR methodology and search results. In summary, a protocol was developed that included the PICOS (Population, Intervention, Comparators, Outcomes, Study design) criteria and methodology. Search strategies (see Appendix A.2) for the electronic database searches were developed to ensure all relevant RCTs were identified to answer the question: What is the clinical trial evidence for the efficacy and safety of AML maintenance treatments? Electronic database searches of Embase, Medline and the Cochrane library were conducted on 18 January 2020 and updated on 19 February 2021. In addition, supplementary searches of clinical trial registries and conference abstracts were conducted. Two reviewers assessed the identified titles and abstracts using predefined inclusion and exclusion criteria (Appendix A, Table A-6). Citations considered to describe potentially eligible articles were independently reviewed in full-text form for formal inclusion in the final review. Disagreements between reviewers were resolved during a consensus meeting.

As detailed in Appendix A.3, 6,411 unique references were identified in the original literature search and 801 in the updated search. Following screening, 22 studies (25 publications) were identified in the original search, after the update a total of 24 studies (33 publications) were included in the original review.

Of the 24 studies identified in the SLR,1 key study that included the intervention and comparator in the population relevant to the scope of this submission was identified:

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- QUAZAR AML-001 (CC-486-AML-001) was a phase 3, international, multicentre, randomised, double-blind, placebo-controlled study that compared the efficacy and safety of Onureg versus placebo as maintenance therapy among patients with AML who were in CR/CRi after intensive chemotherapy.[18,19]

Because the standard of care comparator in Denmark is close monitoring and this is represented by the placebo arm in the QUAZAR AML-001 trial, no other studies identified in the SLR are relevant to this submission, and the head-to-head trial provides the most robust comparison. The 23 studies excluded at this stage of the review due to non-relevant setting or intervention are listed in Table 5.

Table 5. Studies included in the systematic literature review and excluded from this assessment due to inappropriate intervention or setting.

Author, year	Trial name	Trial number	Maintenance treatment
Main analysis is maintenance therapy			
Baer et al. (2008)[80]	CALGB 9720	NCT00003190	Recombinant IL-2 (rIL-2)
Foran et al. (2019)[81]	E-A E2906	NCT02085408	Decitabine
Huls et al. (2019)[76]	HOVON97	EUCTR2008-001290-15	Azacitidine (SC)
Hunault-Berger et al. (2017)[82]	LAMSA-maintenance Rev-5Aza	NCT01301820	Azacitidine (SC)/lenalidomide
Löwenberg et al. (2010)[83]	HOVON43	ISRCTN77039377	Gemtuzumab ozogamicin (GO)
Oliva et al. (2018)[84]; Oliva et al. (2019)[85]	QoLESS AZA-AMLE	EUCTR2010-019710-24	Azacitidine (SC/IV)
Pautas et al. (2010)[86]	ALFA-9801	NCT00931138	Recombinant IL-2 (rhIL-2)
Pigneux et al. (2017)[87]	LAM SA 2002	NCT00700544	Idarubicin, cytarabine, lomustine/ methotrexate + 6-mercaptopurine, norethandrolone
Usuki et al. (2007)[88]	NR	NR	Recombinant human IL-11 (rhIL-11)
Yamaguchi et al. (2018)[89]	NR	NCT01961882	OCV-501 (WT1 peptide vaccine)
Clinicaltrials.gov NCT01687387 (2012)[90]	EFFIKIR	NCT01687387	Lirilumab
Clinicaltrials.gov NCT00398983 (2006)[91]	NR	NCT00398983	Decitabine
Main analysis is consolidation therapy			
Hengeveld et al. (2012)[92]	AML 8B	NR	Daunorubicin, cytarabine
Schlenk et al. (2006)[93]	AML HD98-B	NR	Idarubicin, etoposide
Main analysis is induction therapy			
Burnett et al. (2017)[94]	AML 16	NCT00454480	Azacitidine (SC)
Latagliata et al. (2008)[95]	GSI 103-AMLE	NCT00589082	Cytarabine, ATRA
Petersdorf et al. (2013)[96]	S0106	NCT00085709	Gemtuzumab ozogamicin (GO)
Pigneux et al. (2007)[97]	BGMT95	NCT00480064	Idarubicin/cytarabine + methotrexate/6-mercaptopurine
Röllig et al. (2015)[98]; Rollig et al. (2017)[99]	SORAML	NCT00893373	Sorafenib
Schlenk et al. (2019)[100]	AMLSG 12-09	NCT01180322	Azacitidine (SC)

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Author, year	Trial name	Trial number	Maintenance treatment
Stone et al. (2017)[55]; Voso et al. (2018)[101]; Voso et al. (2020)[102]	RATIFY	NCT00651261	Midostaurin
Pardee et al. (2020)[103]	NR	NR	Selinexor
Wei et al. (2020)[104]	ALLG AML M16	ACTRN12611001112954	Sorafenib

6.2 List of relevant studies

The relevant studies included in this assessment is presented in Table 6. For detailed information about included studies, refer to Appendix B.

Table 6. Relevant studies included in the assessment

Reference (title, author, journal, year)	Trial name	NCT number	Dates of study (start and expected completion date)	Used in comparison of
Wei AH, Döhner H, Pocock C, Montesinos P, Afanasyev B, Dombret H, et al. Oral azacitidine maintenance therapy for acute myeloid leukemia in first remission. N Engl J Med. 2020 Dec 24;383(26):2526-37. doi:http://dx.doi.org/10.1056/NEJMoa2004444. [18]	QUAZAR AML-001	NCT01757535	April 2013 to December 2021 (primary completion was July 2019)	Onureg vs. placebo (no active antileukemic treatment or close monitoring) after induction chemotherapy

NCT = National Clinical Trial.

In addition, as detailed in Appendix A3, two onging studies of Onureg in the AML maintenance population were identified in clinical trial registries (Table 7). Neither are considered further in this submission,Study 2016-000069-22 is an open-labvel trial to assess the use of Onureg long-term after the QAZAR study, results are not yet avaiuable. Study 2018-001012-30 assesses the use of Onureg after allogenic haematopoietic stem cell transplantation and is not therefore relevant to ths submission.

Table 7. Active Onureg trials in the AML maintenance population identified in ClinicalTrials.gov and EU Clinical Trials Register

Study/ID	Study title
2016-000069-22 https://www.clinicaltrialsregister.eu/ctr-search/trial/2016-000069-22/FR	A phase 2, open-label, single-arm rollover study to evaluate long-term safety in subjects who participated in other Celgene sponsored CC-486 (oral azacitidine) clinical trials in solid tumors and hematological disorders
2018-001012-30 https://www.clinicaltrialsregister.eu/ctr-search/trial/2018-001012-30/GB	A double-blind, phase III, randomised study to compare the efficacy and safety of oral azacitidine (CC-486) versus placebo in subjects with acute myeloid leukaemia or myelodysplastic syndromes as maintenance after allogeneic haematopoietic stem cell transplantation

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7 Efficacy and safety

7.1 Efficacy and safety of Onureg compared with placebo for patients with AML in first complete remission

The safety and efficacy of Onureg as a maintenance therapy for patients with AML is currently supported by evidence from the QUAZAR AML-001 trial (ONUREG-AML-001; Clinicaltrials.gov identifier: NCT01757535; EudraCT number: 2012-003457-28). QUAZAR AML-001 was a phase 3, international, multicentre, randomised, double-blind, placebo-controlled study that compared the efficacy and safety of Onureg versus placebo as maintenance therapy among patients with AML who were in CR/CRi after intensive chemotherapy.[18,19] This section describes the study and the results available at the end of the follow-up phase primary database cutoff of 15 July 2019; these results have been published and are the basis of the current European Commission approval.[4,17,18,75,105-108] [redacted]

7.1.1 Relevant studies: QUAZAR AML-001

The QUAZAR AML-001 trial is the pivotal phase 3 randomised controlled trial providing key efficacy and safety data relevant to this application.[18,19] Summary of the trial methodology is presented in Table 8. The study design is briefly described in Section 7.1.1.1, with further details about characteristics provided in Appendix B, and baseline characteristics of patients included in the study are provided in Appendix C.

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Table 8. QUAZAR AML-001: summary of trial methodology

Key publication	Wei AH, Döhner H, Pocock C, Montesinos P, Afanasyev B, Dombret H, et al. Oral azacitidine maintenance therapy for acute myeloid leukemia in first remission. N Engl J Med. 2020 Dec 24;383(26):2526-37. doi:http://dx.doi.org/10.1056/NEJMoa2004444.
Sample size (n)	472 patients
Study design	International, multicentre, placebo-controlled, phase 3 double-blind, randomised, parallel-group design
Location	Europe, including Austria, Belgium, Czech Republic, Finland, France, Germany, Ireland, Israel, Italy, Lithuania, Poland, Portugal, the Russian Federation, Spain, and Turkey; North America, including Canada, Mexico, and the United States; Asia, including South Korea and Taiwan; Australia; South America, including Brazil
Patient population	Adults aged ≥ 55 years with AML in first CR
Randomisation	Within 4 months (± 7 days) of CR/CRi Stratified by: ▪ Age (55-64 or ≥ 65 years) ▪ Prior MDS/CMML (yes/no) ▪ Cytogenetic risk (intermediate/poor) ▪ Consolidation (yes/no) After randomisation, crossover between the arms was not permitted at any point during the study
Intervention(s)	Onureg (n = 238): 300 mg once daily for the first 14 days of each 28-day cycle, with the possibility of an escalated 21-day dosing schedule
Comparator(s)	Placebo (n = 234): placebo for the first 14 days of each 28-days cycle
Follow-up period	Median follow-up was 41.2 months for 15 July 2019 database cutoff and 51.7 months for 8 September 2020 database cutoff
Primary endpoints reported	OS
Other outcomes reported include results	**Secondary endpoints:** ▪ RFS ▪ Time to relapse from CR/CRi ▪ Time to discontinuation from treatment ▪ Safety/tolerability ▪ HRQoL as measured by FACIT-Fatigue Scale and EQ-5D-3L **Exploratory endpoints:** ▪ MRD assessed centrally by flow cytometry (≥ 0.1% MRD-positive threshold) ▪ Exploratory HRQoL analysis
Subgroups	Analyses were performed for the OS and RFS endpoints for the following key subgroups: ▪ Age at induction therapy (< 65, ≥ 65, ≥ 75 years) ▪ Sex (male, female) ▪ CR/CRi status at: randomisation, first achieving response, randomisation and use of consolidation ▪ Prior history of MDS or CMML (yes, no) ▪ Cytogenetic risk category at induction therapy (intermediate, poor) ▪ MRD status at screening (prior to randomisation) (positive, negative) ▪ Consolidation therapy following induction (yes, no; 1 or 2 cycles, 3 or 4 cycles) ▪ ECOG PS (0 or 1, 2 or 3) ▪ WHO AML classification ▪ Types of first-line subsequent therapy

AML = acute myeloid leukaemia; CMML = chronic myelomonocytic leukaemia; CR = complete remission; CRi = complete remission with incomplete blood count recovery; ECOG PS = Eastern Cooperative Oncology Group performance status; EQ-5D-3L = 3-level EQ-5D; FACIT-Fatigue = Functional Assessment of Chronic Illness Therapy–Fatigue; HRQoL = health-related quality of life; MDS = myelodysplastic syndrome; MRD = measurable residual disease; OS = overall survival; RFS = relapse-free survival; WHO = World Health Organization.

Sources: Wei et al. (2020)[18]; Wei et al. (2019)[19]

7.1.1.1 QUAZAR AML-001: study design

The QUAZAR AML-001 trial was an international, multicentre, placebo-controlled, phase 3 study with a double-blind, randomised, parallel-group design that compares Onureg versus placebo as maintenance treatment in adults with AML in first CR who were not candidates for HSCT. The planned enrolment was approximately 460 patients across approximately 150 clinical sites worldwide; actual enrolment was 472 patients across 148 sites in 23 countries (including 14 countries in Europe).[18,19]

The trial consisted of 3 phases: prerandomisation (screening phase), treatment, and follow-up (Figure 6).

The study protocol was amended to include an extension phase, in which patients receiving Onureg and demonstrating clinical benefit as assessed by the investigators, were able to continue treatment after unblinding until study discontinuation or until Onureg became commercially available and reimbursed. Patients who discontinued treatment but remained in the study were (or are being) followed for survival. After randomisation, no crossover between treatment groups was allowed.[18,19]

Patients were randomised 1:1 within 4 months (± 7 days) of CR/CRi to receive 300 mg Onureg once daily or placebo for the first 14 days of each 28-day cycle. Randomisation was stratified by the following key prognostic factors:

- Age at the time of induction therapy (55-64 years or ≥ 65 years)
- Prior history of myelodysplastic syndrome (MDS) or chronic myelomonocytic leukaemia (CMML) (yes or no)
- Cytogenetic risk status at the time of induction therapy (intermediate or poor risk)
- Receipt of consolidation therapy (yes or no)

The dose and schedule of Onureg (300 mg once daily for 14 days) were based on cumulative safety, efficacy, tolerability, and biologic data from phase 1/2 studies.[2,109,110] Throughout the treatment period of the QUAZAR AML-001 trial, patients in both the placebo and Onureg treatment groups were permitted to receive BSC,

which may have included red blood cell and platelet transfusions; use of an erythropoiesis-stimulating agent; antibiotic, antiviral, and/or antifungal therapy; nutritional support; and/or granulocyte colony-stimulating factor for patients experiencing neutropenic infections.[18,111] The inclusion of BSC in the study design minimised the risk of providing patients with inadequate care and is consistent with current practice for many patients with AML who are in CR after induction/consolidation therapy.[27,111]

Many assessments were conducted during the treatment phase, including monitoring for AEs and maintenance of CR/CRi or relapse, completion of patient-reported outcomes for HRQoL, utilisation of healthcare resources, and evaluation of physical/clinical status.[18,86] A central review of all bone marrow aspirates, bone marrow biopsies, and peripheral blood smears was conducted by an independent pathologist blinded to treatment to confirm CR/CRi status at screening and during treatment. Status assessments for maintenance of CR/CRi occurred every 3 cycles up to cycle 24, every 6 cycles from cycles 24 to 36 (at the investigator's discretion thereafter), and at the treatment discontinuation visit (regardless of the number of cycles completed).[18]

Patients on study who had subsequent evidence of AML relapse with blasts ≥ 5% and ≤ 15% in either the peripheral blood or bone marrow were eligible for an extension of the dosing schedule of Onureg. The schedule could be extended from 300 mg once daily for 14 days to 300 mg once daily for 21 days of each 28-day cycle, provided it was in the patient's best interest as judged by the investigator.[105,112] Treatment was discontinued when patients had > 15% blasts in either the peripheral blood or bone marrow.[18]

During the follow-up phase, all patients who discontinued study treatment underwent discontinuation visit procedures at the time they left the study. Patients had a follow-up visit for collection of AEs up to 28 days after the last dose of study treatment or up to the treatment discontinuation visit, whichever was longer. Patients were subsequently followed for survival every month for the first year and then every 3 months until death, withdrawal of consent for further follow-up, study end, or loss to follow-up.[18,111]

7.1.1.2 QUAZAR AML-001: patient eligibility

Patients who were aged ≥ 55 years with de novo AML or AML secondary to MDS or CMML and who had achieved CR/CRi after induction with or without consolidation chemotherapy within 4 months (+/-7 days) before randomisation were eligible for the trial.[19,111] Patients who previously achieved a CR/CRi after therapy with an HMA were excluded from the study, as were those with favourable-risk cytogenetics. Patients who were candidates for allogeneic bone marrow transplant or HSCT at screening (within 28 days prior to randomisation) were also excluded. Eligibility for transplant was determined by the physician/investigator using patient- and disease-related factors.[111]

Appendix B describes the main inclusion and exclusion criteria.

7.1.1.3 QUAZAR AML-001: endpoints

Study endpoints are described below, and Appendix B provides full study details.

The primary efficacy endpoint in the QUAZAR AML-001 was OS, which was evaluated from the time of randomisation to death from any cause.[18]

Secondary endpoints were RFS, time from randomisation to relapse or death,[v] time to discontinuation from treatment, and HRQoL as measured by the FACIT-Fatigue and EQ-5D-3L. Although no AML/MDS-validated HRQoL instruments were available for use in this study, the included instruments provide valuable information about patients' health status, the burden of AML, and AML's impact on their quality of life.[18]

Safety assessments were a secondary objective and included evaluation of AEs and SAEs. Treatment-emergent AEs included AEs that started between the first dose date and up to 28 days after the last dose date of study treatment.[18]

Exploratory endpoint in the QUAZAR AML-001 trial included MRD assessed centrally by flow cytometry (≥ 0.1% MRD-positive threshold) and exploratory HRQoL analysis.[18]

Exploratory subgroup analyses were conducted for OS and RFS, provided that an adequate number of patients was available in each subgroup to allow for meaningful interpretation of results. Key demographic and disease-related subgroups that were analysed included age at induction therapy (≥ 55 years to < 65 years, ≥ 65 years), sex (male, female), CR/CRi status at randomisation, cytogenetic risk category (intermediate, poor), receipt of consolidation therapy after induction (yes, no), Eastern Cooperative Oncology Group performance status (ECOG PS) score (0 or 1, 2 or 3), prior MDS or CMML (yes, no), and MRD status at screening (positive, negative).[18,19]

7.1.1.4 QUAZAR AML-001 Statistical testing

Methods of statistical testing in QUAZAR AML-001 are described here briefly; see Appendix B for more details.

The primary, key secondary efficacy and HRQoL endpoints were analysed using the intent-to-treat (ITT) population (Table 9). Overall survival and RFS were estimated with the use of the KM method. Treatment comparison between the groups was conducted by using a stratified log-rank test (stratified by age at induction, prior history of MDS, whether consolidation therapy was administered, and cytogenetic risk category at time of induction therapy, at a two-sided alpha level of 0.05).[111] A sequential gatekeeping approach was used to test OS and RFS.[111] The assumption of proportional hazards was tested with a time-dependent Cox model with interaction terms of treatment and time and with a *P* value of 0.006. The proportional hazards assumption appeared to be violated, as indicated by the significant treatment-by-time interaction; thus, HRs are not provided. Confidence intervals for survival estimates at 6 months, 1 year, and 2 years were calculated with Greenwood's variance estimate.[18] The HRQoL endpoints were evaluated for the HRQoL-evaluable population, which was defined as all randomised patients who had a valid (i.e., non-missing) assessment at baseline (i.e., cycle 1 Day 1) and at least 1 valid postbaseline assessment. This population was derived for each HRQoL measure (FACIT-Fatigue Scale and EQ-5D-3L).[18,111]

Sensitivity analyses

Sensitivity analyses were conducted for both OS and RFS, repeating the analysis using the modified ITT (mITT) population (see Table 9 for definition). Additional sensitivity analyses for OS assessed the confounding effects of subsequent therapy after discontinuation of study treatment. These analyses included (1) censoring for all subsequent therapy for AML (including posttreatment transplant), (2) censoring for subsequent disease-modifying therapy for AML (i.e., all subsequent therapy for AML except for hydroxycarbamide), and (3) censoring for posttreatment

[v] In AML trials, RFS is traditionally measured from the date of CR/CRi,[113] whereas in QUAZAR AML-001, RFS was measured from the date of randomisation, which occurred at a median of 85 days after CR/CRi.[18] Therefore, RFS should not be compared between QUAZAR AML-001 and other trials in AML.

transplant only. Additional sensitivity analyses for RFS included using EMA censoring rules and using documented relapse based on investigator-assessed response instead of programmatically derived documented relapse from the central pathology laboratory.[18,111]

Sample size calculation

Sample size calculations were based on a one-sided alpha of 0.025. It was assumed that with a median OS of 16.0 months in the placebo group and 22.9 months in the Onureg group, a trial duration of 60 months, a 5% dropout rate, and 330 deaths, enrolment of approximately 460 patients (230 per group) would provide 90% power to detect an HR of 0.70 and to show a significant difference in OS between the treatment groups.[18]

Analysis population

Analysis sets in the QUAZAR AML-001 trial included the ITT population, the safety population, and the mITT population.[18,19]

Table 9. QUAZAR AML-001: analysis population

Analysis population	Onureg (n = 238), n (%)	Placebo (n = 234), n (%)	Total (N = 472), n (%)	Definition
ITT population	238 (100.0)	234 (100.0)	472 (100.0)	The ITT population included all randomised patients, regardless of whether they received study treatment; this population was used for analyses of the primary and secondary efficacy endpoints (other than HRQoL endpoints). Patients were analysed based on randomised treatment group as assigned by the IVRS.
Safety population	236 (99.2)	233 (99.6)	469 (99.4)	The safety population included all randomised patients who received at least 1 dose of study treatment; this population was used for drug exposure and all safety analyses unless otherwise specified. Patients were analysed based on the initial treatment received.
mITT population	[redacted]	[redacted]	[redacted]	The mITT population included all patients who met the inclusion/exclusion criteria, experienced no protocol violations during the study, and received a minimum of 1 cycle of treatment. This population was used for sensitivity analyses of primary and secondary efficacy endpoints. Patients were analysed based on randomised treatment group.

HRQoL = health-related quality of life; ITT = intent to treat; IVRS = interactive voice response system; mITT = modified intent to treat.
Sources: Wei et al. (2020)[111], Celgene data on file (2020)[114], Wei et al. (2020)[18], EMA (2021)[115]

7.1.2 Efficacy and safety: QUAZAR AML-001

The results of efficacy and safety analyses in the QUAZAR AML-001 trial presented here are for the database cutoff of 15 July 2019 (median follow-up, 41.2 months)[18,19] [redacted] Appendix D provides a detailed description of endpoints, measurements, validity, and clinical relevance.

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7.1.2.1 Primary endpoint: overall survival—15 July 2019 database cutoff

At the database cutoff of 15 July 2019 (median follow-up, 41.2 months), Onureg demonstrated a significant improvement in OS compared with placebo. The primary efficacy endpoint analysis showed that Onureg was associated with significantly and clinically meaningful difference in median OS of 9.9 months amounting to a 31% reduction in mortality risk (median OS: 24.7 months [95% CI, 18.7-30.5] vs. 14.8 months [95% CI, 11.7-17.6]; $P < 0.001$) (Figure 7).[18,19] A lower death rate was observed in the Onureg group than in the placebo group as early as 90 days after randomisation (1.7% vs. 8.5%).[115] Survival rates (as estimated using the reverse KM method) were higher in the Onureg group than in the placebo group at 1 year (72.8% vs. 55.8%) and 2 years (50.6% vs. 37.1%) after randomisation (Table 10).[18]

Table 10. **QUAZAR AML-001: summary of overall survival for the ITT population (July 2019 database cutoff; median follow-up, 41.2 months)**

Parameter	Onureg (n = 238)	Placebo (n = 234)	Difference (95% CI)
Patients with event (death), n (%)	158 (66.4)	171 (73.1)	—
Patients censored, n (%)	80 (33.6)	63 (26.9)	—
Median OS, months (95% CI)[a]	24.7 (18.7-30.5)	14.8 (11.7-17.6)	9.9 (4.6-15.3)
Hazard ratio (Onureg:placebo) (95% CI)[b]	0.69 (0.55-0.86)		—
Stratified log-rank test: *P* value[c]	0.0009		—
1-year survival estimate (95% CI)[d]	0.73 (0.67-0.78)	0.56 (0.49-0.62)	0.17 (0.1-0.26)
2-year survival estimate (95% CI)[d]	0.51 (0.44-0.57)	0.37 (0.31-0.43)	0.14 (0.05-0.23)

CI = confidence interval; ITT = intent to treat; OS = overall survival.

Note: Percentages are based on the number of patients in each treatment group, unless otherwise specified.

[a] Median estimate of OS was derived using the Kaplan-Meier method. Difference was calculated as Onureg minus placebo. The CI for the difference was derived using Kosorok's method.

[b] The hazard ratio is from a Cox proportional hazards model stratified by age, cytogenetic risk category, and receipt of consolidation therapy or not.

[c] The *P* value is two-sided from a log-rank test stratified by age, cytogenetic risk category, and receipt of consolidation therapy or not.

[d] Kaplan-Meier methods were used to estimate the 1-year and 2-year survival probabilities. The CIs for the difference in the 1-year and 2-year survival probabilities were derived using Greenwood's variance estimate.

Sources: Wei et al. (2020)[18]

At the database cutoff date (15 July 2019), 71 patients remained on study and receiving treatment (Onureg: n = 45 [19%]; placebo: n = 26 [11%]). Although the number of events that occurred to this point allowed for a fully powered OS analysis, the OS outcomes of these 71 patients were censored at the database cutoff.[18]

Sensitivity analyses

[redacted] Notably, the outcome for the sensitivity analysis that censored for posttreatment transplant was highly consistent with that of the primary analysis, showing a significant OS benefit for Onureg compared with placebo (HR, 0.67 [95% CI, 0.53-0.84]; *P* = 0.0006). This is especially important because transplant is known to impact OS, and more patients in the placebo group underwent posttreatment transplant than in the Onureg group. Despite this, Onureg was associated with a significant improvement in OS compared with placebo.[61]

Subgroup analyses

The analyses of OS in subgroups defined on the basis of clinically relevant characteristics are presented in Figure 8. The OS findings in the full study population were consistent across prespecified subgroups with Onureg showing clinical benefit regardless of patients' clinical characteristics. Across the subgroups, the 2-year OS rates were generally higher with Onureg than with placebo.[18] Notably, several subgroups (i.e., age ≥ 55 years to < 65 years, CRi status at randomisation, poor cytogenetic risk status, no consolidation therapy after induction, ECOG PS score of 2 or 3, and

prior MDS or CMML) had small sample sizes; therefore, the analyses may not have been sufficiently powered to detect statistically significant difference between groups, and the overall result may have been influenced by the outcome for individual patients. A favourable treatment effect was observed for Onureg compared with placebo regardless of MRD status. Onureg was associated with a higher rate of MRD response (baseline MRD+, became MRD- on-study) vs. placebo: 37% vs. 19%, respectively. The direction of the point estimate suggests that Onureg may provide a survival benefit independent of baseline MRD status.[108]

Overall survival is especially poor among older patients with AML.[11] Therefore, an additional subgroup analysis was conducted to evaluate the impact of treatment with Onureg on OS among patients aged ≥ 75 years.[107,117] Despite the small sample size of these patients in the ITT population (n = 28 for Onureg; n = 23 for placebo), Onureg was associated with an OS benefit compared with placebo (median OS: 24.8 months vs. 9.9 months; HR, 0.48 [95% CI, 0.25-0.94]; *P* = 0.0281).[107,117]

As mentioned in section 5.1.3, although QUAZAR AML-001 study included patients who were not considered candidates for HSCT at screening, 47 (10%) of randomised patients ultimately received HSCT after discontinuing study

treatment.[18,61] Out of the 15 patients transplanted after Onureg discontinuation, 6 were in CR1 at the time of HSCT and 9 had relapsed before HSCT, whereas for placebo, all 32 patients had relapsed. An analysis of OS outcomes in the QUAZAR AML-001 study has shown that the significant OS improvement with Onureg maintenance therapy versus placebo persisted when patients who received HSCT were censored at transplant (HR, 0.67; 95% CI, 0.53-0.84; $P = 0.0006$).[61]

[redacted]

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[redacted]

Parameter	[redacted]	[redacted]	[redacted]
Patients with event (death), n (%)	[redacted]	[redacted]	[redacted]
Patients censored, n (%)	[redacted]	[redacted]	[redacted]
Median OS, months (95% CI)[a]	[redacted]	[redacted]	[redacted]
Hazard ratio (Onureg:placebo) (95% CI)[b]		[redacted]	[redacted]
Stratified log-rank test: *P* value[c]		[redacted]	[redacted]
OS estimates, rate (95% CI)[d]			
1-year	[redacted]	[redacted]	[redacted]
2-year	[redacted]	[redacted]	[redacted]
3-year	[redacted]	[redacted]	[redacted]

CI = confidence interval; ITT = intent to treat; OS = overall survival.

[a] Median estimate of OS was derived using the Kaplan-Meier method. Difference was calculated as Onureg minus placebo. The CI for the difference was derived using Kosorok's method.

[b] The hazard ratio is from a Cox proportional hazards model stratified by age, cytogenetic risk category, and receipt of consolidation therapy or not.

[c] The *P* value is 2-sided from a log-rank test stratified by age, cytogenetic risk category, and receipt of consolidation therapy or not.

[d] Kaplan-Meier methods were used to estimate the 1-year and 2-year survival probabilities. The CIs for the difference in the 1-year and 2-year survival probabilities were derived using Greenwood's variance estimate.

Note: Percentages are based on the number of patients in each treatment group, unless otherwise specified.

Sources: Bristol Myers Squibb data on file (2021)[20]

7.1.2.2 Key secondary endpoint: relapse-free survival

The analysis of the key secondary endpoint at the database cutoff of 15 July 2019 (median follow-up, 41.2 months), showed that Onureg was associated with significantly improved RFS compared with placebo, with a clinically meaningful difference in median RFS of 5.3 months and a 35% reduction in risk of relapse or death (median RFS: 10.2 months vs. 4.8 months; HR, 0.65 [95% CI, 0.52-0.81]; *P* = 0.0001) (Figure 10).[18,19] Higher RFS rates were observed in the Onureg group than in the placebo group at 6 months (67.4% vs. 45.2%), 1 year (44.9% vs. 27.4%), and 2 years (26.6% vs. 17.4%) (Table 12).[18] It is important to note that, in clinical trials of AML, RFS is traditionally measured from the date of CR/CRi,[113] whereas in QUAZAR AML-001, RFS was measured from the date of randomisation, which occurred at a median of 85 days after CR/CRi.[18] Therefore, the definition of RFS in QUAZAR AML-001 differs from other AML studies and potential cross-trial comparisons should be made with caution.

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Table 12. QUAZAR AML-001: summary of relapse-free survival for the ITT population (median follow-up, 41.2 months)

Parameter	Onureg (n = 238)	Placebo (n = 234)	Difference (95% CI)
Patients with event (relapse or death), n (%)	164 (68.9)	181 (77.4)	—
Patients censored, n (%)	74 (31.1)	53 (22.6)	—
Median RFS, months (95% CI)[a]	10.2 (7.9-12.9)	4.8 (4.6-6.4)	5.3 (3.1-7.5)
Hazard ratio (Onureg:placebo) (95% CI)[b]	0.65 (0.52-0.81)		—
Stratified log-rank test: *P* value[c]	0.0001		—
6-month RFS estimate (95% CI)[d]	0.67 (0.61-0.73)	0.45 (0.39-0.52)	0.22 (0.13-0.31)
1-year RFS estimate (95% CI)[d]	0.45 (0.38-0.51)	0.27 (0.22-0.34)	0.18 (0.09-0.26)
2-year RFS estimate (95% CI)[d]	0.27 (0.21-0.33)	0.17 (0.13-0.23)	0.09 (0.01-0.17)

CI = confidence interval; ITT = intent to treat; RFS = relapse-free survival.

Note: Percentages are based on the number of patients in each treatment group, unless otherwise specified.

[a] Median estimate of RFS was derived using the Kaplan-Meier method. Difference was calculated as Onureg minus placebo. The CI for the difference was derived using Kosorok's method.

[b] The hazard ratio is from a Cox proportional hazards model stratified by age, cytogenetic risk category, and receipt of consolidation therapy or not.

[c] The *P* value is 2-sided from a log-rank test stratified by age, cytogenetic risk category, and receipt of consolidation therapy or not.

[d] Kaplan-Meier methods were used to estimate the 6-month, 1-year, and 2-year RFS probabilities. The CIs for the difference in these RFS probabilities were derived using Greenwood's variance estimate.

Sources: Wei et al. (2020)[18]; EMA (2021)[115]

Subgroup Analyses

Figure 11 presents the result of the subgroup analyses for the secondary endpoint of RFS. The RFS benefit observed with Onureg compared with placebo in the overall population was also observed in the predefined clinically relevant subgroups.[18,19] Although several subgroups had small sample sizes, all subgroup analyses favoured Onureg over placebo with all except 1 upper CI limit not crossing 1 (i.e., subgroup of patients with poor cytogenetic risk status; n = 35 for Onureg; n = 31 for placebo; HR, 0.61 [95% CI, 0.35-1.04]).[19]

The risk of relapse is particularly high among older patients with AML who achieve CR/CRi with intensive chemotherapy.[16,30] Therefore, an additional subgroup analysis was conducted to evaluate the impact of maintenance treatment with Onureg on RFS among elderly patients aged ≥ 75 years. Despite the small sample size of this subgroup of patients in the ITT population (n = 28 for Onureg; n = 24 for placebo), Onureg was associated with a longer duration of RFS compared with placebo, with the 95% CI upper limit of estimated HR not crossing 1 (median RFS: 10.2 months vs. 2.3 months; HR, 0.40 [95% CI, 0.20-0.79]; *P* = 0.0061).[107,117]

7.1.2.3 Secondary endpoint: time to relapse

At the database cutoff of 15 July 2019 for the primary analysis (median follow-up, 41.2 months), 154 patients (64.7%) in the Onureg group and 179 (76.5%) in the placebo group had a programmatically derived documented relapse.[18] Ten patients (4.2%) in the Onureg group and 2 (0.9%) in the placebo group died without documented relapse. The median time to relapse was 10.2 months in the Onureg group and 4.9 months in the placebo group. Lower relapse rates were observed in the Onureg group than in the placebo group at 6 months (31.3% vs. 54.4%), 1 year (52.8% vs. 71.7%), and 2 years (69.1% vs. 81.7%) (Table 13).[18]

Table 13. QUAZAR AML-001: summary of time to relapse (ITT population; median follow-up, 41.2 months)

Parameter	Onureg (n = 238)	Placebo (n = 234)
Patients relapsed, n (%)	154 (64.7)	179 (76.5)
Patients died without reported relapse, n (%)	10 (4.2)	2 (0.9)
Patients censored, n (%)	74 (31.1)	53 (22.6)
Median time to relapse, months (95% CI)[a]	10.2 (8.3-13.4)	4.9 (4.6-6.4)
6-month relapse rate estimate (95% CI)[b]	0.31 (0.25-0.37)	0.54 (0.48-0.61)
1-year relapse rate estimate (95% CI)[b]	0.53 (0.46-0.59)	0.72 (0.65-0.77)
2-year relapse rate estimate (95% CI)[b]	0.69 (0.62-0.75)	0.82 (0.76-0.86)

CI = confidence interval; CR = complete remission; CRi = complete remission with incomplete blood count recovery; ITT = intent to treat.

Note: Percentages are based on the number of patients in each treatment group, unless otherwise specified. Time to relapse is defined as the interval from the date of randomisation to the date of documented relapse.

[a] Unstratified Kaplan-Meier analysis.

[b] Estimates of relapse rates are based on the cumulative incidence function from a competing risk analysis with death as a competing risk of relapse from CR/CRi.

Source: Wei et al. (2020)[18]

7.1.2.4 Secondary endpoint: time to discontinuation from treatment

As of the database cutoff of 15 July 2019 for the primary analysis (median follow-up, 41.2 months), most patients in both the Onureg group (81.1%) and the placebo group (88.9%) had discontinued from study treatment. However, patients in the Onureg group remained on study treatment for longer than patients in the placebo group: the median time to discontinuation for any reason was 11.4 months in the Onureg group and 6.1 months in the placebo group. Lower treatment discontinuation rates were observed in the Onureg group than in the placebo group at 6 months (29.8% vs. 49.6%), 1 year (52.1% vs. 71.4%), and 2 years (70.6% vs. 85.9%) (Table 14).[18]

Table 14. QUAZAR AML-001: summary of time to discontinuation from treatment (ITT population; median follow-up, 41.2 months)

Parameter	Onureg, (n = 238)	Placebo, (n = 234)	Difference, (95% CI)
Patients with treatment discontinuation, n (%)	193 (81.1)	208 (88.9)	—
Patients censored, n (%)	45 (18.9)	26 (11.1)	—
Median time to treatment discontinuation, months (95% CI)[a]	11.4 (9.8-13.6)	6.1 (5.1-7.4)	5.4 (3.1-7.8)
6-month treatment discontinuation rate estimate (95% CI)[b]	0.30 (0.24-0.36)	0.50 (0.43-0.56)	−0.2 (−0.29 to −0.11)
1-year treatment discontinuation rate estimate (95% CI)[b]	0.52 (0.46-0.58)	0.71 (0.65-0.77)	−0.19 (−0.28 to −0.11)
2-year treatment discontinuation rate estimate (95% CI)[b]	0.71 (0.64-0.76)	0.86 (0.81-0.90)	−0.15 (−0.23 to −0.08)
Time to treatment discontinuation due to relapse, months, median (95% CI)	14.6 (11.3-20.1)	6.9 (5.3-7.9)	-

CI = confidence interval; ITT = intent to treat.

Note: Percentages are based on the number of patients in each treatment group, unless otherwise specified.

[a] Median estimate of time to discontinuation is from an unstratified Kaplan-Meier analysis. Differences were calculated as Onureg minus placebo. The CIs for the differences were derived using Kosorok's method.

[b] Kaplan-Meier methods were used to estimate the treatment discontinuation rate. Differences were calculated as Onureg minus placebo. The CIs for the difference were derived using Greenwood's variance estimate.

Source: Wei et al. (2020)[18]

The analysis was further refined by evaluating time to treatment discontinuation because of disease relapse using a competing risk method. Overall, 143 patients (60.1%) in the Onureg group and 180 (76.9%) in the placebo group had discontinued treatment because of disease relapse. The median time to discontinuation because of disease relapse was 14.6 months in the Onureg group and 6.9 months in the placebo group.[18]

7.1.2.5 Secondary endpoint: health-related quality of life

In the QUAZAR AML-001 trial, HRQoL was assessed using the FACIT-Fatigue scale and the EQ-5D-3L health utility index. In the ITT population, 225 patients (94.5%) in the Onureg group and 219 (93.6%) in the placebo group were included in the HRQoL-evaluable population for the FACIT-Fatigue scale. Similarly, 225 patients (94.5%) in the Onureg group and 217 (92.7%) in the placebo group were included in the HRQoL-evaluable population for the EQ-5D-3L health utility index.[18,118] Assessment of HRQoL using the EQ-5D-3L health utility index was conducted from baseline until treatment discontinuation; thus, no HRQoL data are available after disease progression when treatment stopped.[18]

There were no marked differences in baseline demographic and disease characteristics between treatment groups for the HRQoL-evaluable population. At baseline, mean scores on both the FACIT-Fatigue scale and the EQ-5D-3L health utility index were similar across the Onureg and placebo groups[18,118] and were comparable to average scores for an age-matched general population (Table 15).[119,120]

Table 15. QUAZAR AML-001: mean baseline FACIT-Fatigue and EQ-5D-3L health utility index scores by treatment group (HRQoL-evaluable population)

HRQoL Domain	Onureg (n = 225)	Placebo (n = 219)	Overall (N = 444)	General Population (N = 2,426[a]; 38,678[b])
FACIT-Fatigue scale,[c] mean (SD)	40.8 (8.6)	40.7 (8.3)	40.8 (8.4)	43.2[a]
EQ-5D-3L HUI,[c] mean (SD)	0.80 (0.10)	0.79 (0.14)	0.80 (0.12)	0.76[b]

EQ-5D-3L = 3-level EQ-5D; FACIT-Fatigue = Functional Assessment of Chronic Illness Therapy–Fatigue; HRQoL = health-related quality of life; HUI = health utility index; SD = standard deviation; US = United States.

[a] Applies to FACIT-Fatigue values provided for the sex- and age-matched normative data from the German general population.[120]

[b] Applies to EQ-5D-3L health utility index values provided for the US general population aged 65-74 years.[119]

[c] A higher score on the FACIT-Fatigue scale indicates a lower level of fatigue and a higher score on the EQ-5D-3L health utility index indicates a better health state. EQ-5D-3L HUI scores were derived using a Canadian population sample weight.

Source: Roboz et al. (2021)[118]

In both treatment groups, scores on the FACIT-Fatigue scale and the EQ-5D-3L health utility index remained slightly at or above baseline values over the entire treatment duration, indicating that HRQoL was maintained in all patients.[18,118] On the FACIT-Fatigue scale, differences in mean change from baseline between treatment groups were not statistically significant or clinically meaningful based on a prespecified minimally important difference (MID) of ± 3.0 (Figure 12). [18,121] A similar trend was observed for the EQ-5D-3L health utility index—no clinically meaningful differences were found based on a prespecified MID (defined as 0.08- and 0.10-point or greater change from baseline) (Figure 13). [18,122]

Although statistically significant differences in favour of the placebo group was noted in FACIT-Fatigue score at cycle 29 ($P = 0.034$), this difference was likely to have occurred by chance because the comparison was not statistically adjusted for multiplicity. The proportions of patients who experienced clinically meaningful HRQoL deterioration and the time to deterioration were comparable between groups (FACIT-Fatigue [median 41 vs. 44 weeks, respectively; $P = 0.698$] and EQ-5D-3L health utility index [200 vs. 164 weeks; $P = 0.633$]).[18,75,108] Additionally, mixed-effects models

analysis controlling for baseline HRQoL scores and other preselected covariates showed no clinically meaningful differences in least-squares mean changes from baseline between the treatment groups at any visit.[18] These findings show that treatment with Onureg improved survival while maintaining the HRQoL of patients with AML in first CR, providing further support for the use of Onureg as maintenance therapy in this indication.

[redacted]

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7.1.2.6 Exploratory efficacy endpoints

Measurable residual disease status

At baseline, 103 (43.3%) patients in the Onureg group and 116 (49.6%) patients in the placebo group were identified as MRD-positive, and 133 (55.9%) patients in the Onureg group and 111 (47.4%) patients in the placebo group were identified as MRD-negative.[18,108] In this study, MRD-negative during the treatment period was defined as patients who achieved MRD-negative status for at least 2 consecutive postbaseline assessments. The duration of MRD negativity was calculated from randomisation (for patients who were MRD-negative at baseline) or from the first of at least 2 consecutive MRD-negative assessments (for patients who were MRD-positive at baseline) until the last MRD-negative assessment or treatment discontinuation.[18,108]

Among patients who were MRD-positive at baseline, a higher proportion achieved MRD-negative status at any point during treatment in the Onureg group (38 of 103 [36.9%]) than in the placebo group (22 of 116 [19.0%]) (Table 16 and Figure 14).[18,108] Among those achieving MRD-negative status during treatment (i.e., MRD responders), a higher proportion in Onureg group achieved MRD negativity greater than 6 months (9 of 38 [23.7%] vs. 1 of 22 [4.5%]).[108] [redacted]

Furthermore, the median duration of MRD negativity was significantly extended with Onureg compared with placebo (11.0 months vs. 5.0 months; HR, 0.62; 95% CI, 0.48-0.78).[108]

Table 16. QUAZAR AML-001: summary of measurable residual disease status (ITT population)

MRD status at baseline[a]	Treatment group	n (%)	On-treatment negative MRD status,[b] % (95% CI)[c]
Positive	Onureg	103 (43)	[redacted]
	Placebo	116 (50)	[redacted]
Negative	Onureg	133 (56)	[redacted]
	Placebo	111 (47)	[redacted]
Missing	Onureg	2 (1)	[redacted]
	Placebo	7 (3)	[redacted]

CI = confidence interval; ITT = intent to treat; MRD = measurable residual disease.

[a] MRD status is measured at the 0.1% sensitivity level during the screening period (prior to randomisation).

[b] On-treatment negative is defined as patient who achieved at least 2 consecutive postbaseline MRD-negative status assessments.

[c] The 95% CI is based on exact binomial test.

Sources: Wei et al. (2020)[18]; Roboz et al. (2020)[108]; Celgene data on file (2020)[114]

It is worth noting that assessments of MRD are neither standardised nor widely used outside clinical trials. In this study, MRD assessment were only exploratory; therefore, the findings should be interpreted with caution. Nonetheless, the results suggest that maintenance therapy with Onureg may help patients who are in CR/CRi to achieve, maintain, or extend MRD-negative status compared with placebo. Treatment with Onureg may also induce MRD negativity after prolonged periods of MRD positivity. These findings further substantiate the results of subgroup analyses showing that Onureg provides OS and RFS benefits independent of baseline MRD status.[108]

Health-related quality of life

In addition to the HRQoL assessments included as secondary endpoints (Section 7.1.1.3), the EQ-5D-3L visual analogue scale (VAS) and the Physical Impairment Numeric Rating (PINR) scale were included as exploratory measures. Appendix D describes all tools used to assess HRQoL in the study.

At baseline, mean scores on both the EQ-5D-3L VAS and the PINR scale were similar across the Onureg and placebo groups (Table 17). Furthermore, the baseline EQ-5D-3L VAS scores were comparable to those of an age-matched general population; however, no population-based reference value was available for the PINR scale.

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Table 17. QUAZAR AML-001: mean baseline EQ-5D-3L VAS and PINR scores by treatment group (HRQoL-evaluable population)

HRQoL domain	Onureg (n = 225)	Placebo (n = 219)	Overall (N = 444)	General population (N = 38,678; N/A)
EQ-5D-3L VAS,[a] mean (SD)	74.6 (17.4)	75.4 (16.2)	75.0 (16.8)	75.1[b]
PINR scale,[a] mean (SD)				
Physical impairment	1.5 (2.1)	1.6 (2.3)	[redacted]	[redacted]
Difficulty completing outdoor physical tasks	2.5 (3.2)	2.3 (3.0)	[redacted]	[redacted]
Difficulty completing indoor tasks	1.5 (2.4)	1.6 (2.6)	[redacted]	[redacted]

EQ-5D-3L = 3-level EQ-5D; HRQoL = health-related quality of life; N/A = not applicable; PINR = Physical Impairment Numeric Rating; SD = standard deviation; US = United States; VAS = visual analogue scale.

[a] higher score indicates a better health state on the EQ-5D-3L VAS and a higher level of physical impairment for PINR items.

[b] Applies to EQ-5D-3L VAS values provided for the US general population aged 65-74 years.[119]

[c] No population-based reference values were available for the 3 PINR items.

Sources: Roboz et al. (2020)[75]; Celgene data on file (2019)[123]

Scores on the EQ-5D-3L VAS and the 3 PINR scale items gradually improved over time in both treatment groups.[75] On the EQ-5D-3L VAS, differences in mean change from baseline between treatment groups were not statistically significant or clinically meaningful based on a prespecified MID (−11/+11-point change from baseline for worsening/improvement).[124] A similar trend was observed for all 3 PINR items—no clinically meaningful differences were found based on prespecified MIDs.[124] Although statistically significant differences in favour of the placebo group were found at a few timepoints for the physical impairment and difficulty completing outdoor physical task items, these differences were likely to have occurred by chance because the comparisons were not adjusted for multiplicity.[75]

7.1.2.7 Safety

Safety data reported here are for all patients in the QUAZAR AML-001 trial who received ≥ 1 dose of study drug. Treatment-emergent AEs were monitored through 28 days of the last dose and are reported for the safety population (Onureg, n = 236; placebo, n = 233).[18]

Overall, Onureg was well tolerated, with a low rate of discontinuation due to TEAEs (Onureg, 13.1%; placebo, 4.3%) and no reported treatment-related deaths (Table 20).[18] Rates of SAEs and grade 3 or 4 TEAEs were relatively similar between groups (33.5% vs. 25.3% and 71.6% vs. 63.1%; Onureg vs. placebo, for grade 3 and 4 TEAEs, respectively); the most frequently reported grade 3 or 4 TEAEs in both groups (TEAEs reported in ≥ 10% patients in both arms) were neutropenia (41% vs. 24%), thrombocytopenia (22% vs. 21%), and anaemia (14% vs. 13%). Although gastrointestinal TEAEs were more common in the Onureg group (91.1%) than in the placebo group (61.8%), most of these events were low in severity (see Table 21).[18]

Extent of treatment exposure

The median treatment duration was 11.6 months (range, 0.5-74.3 months) in the Onureg group and 5.7 months (range, 0.7-68.5 months) in the placebo group (Table 18), whereas the median number of treatment cycles received was 12.0 (range, 1.0-80.0) in the Onureg group and 6.0 (range, 1.0-73.0) in the placebo group.[18,115] [redacted]

[redacted]

[redacted]

Table 18. QUAZAR AML-001: summary of treatment exposure (safety population)

Parameter	Onureg (n = 236)	Placebo (n = 233)
[redacted]		
Mean (SD)	[redacted]	[redacted]
Median (min, max)	[redacted]	[redacted]
Treatment duration,[b] person-years	[redacted]	[redacted]
[redacted]		
Mean (SD)	[redacted]	[redacted]
Median (min, max)	[redacted]	[redacted]
[redacted]		
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]		
[redacted]	[redacted]	[redacted]
[redacted]	12.0 (1.0, 80.0)	6.0 (1.0, 73.0)
[redacted]		
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]

max = maximum; min = minimum; SD = standard deviation.

[a] Treatment duration in months is defined as (treatment end date – first dose date +1)/30.4375. Treatment end date is last dose date + 14 days (the prescribed rest period of each cycle) or the death date, whichever is earlier.

[b] Total person-years of treatment duration is calculated as the sum of treatment duration(days)/365.25 across all patients.

[c] Average cycle length is defined as treatment duration in days/number of cycles.

[d] Average number of days dosed per cycle is defined as total number of days dosed during the entire treatment period/number of cycles.

Source: Celgene data on file (2020)[114]; Wei et al. (2020)[18]

Dose modifications

Any change from the planned dose/schedule of 300 mg × 14 days was reported as a dose adjustment, including dosing schedule extensions and dose/schedule reductions. [redacted] (Table 19).[18,105,114]

[redacted] Overall, 91 patients (19.3%) (Onureg, n = 51 [21%]; placebo, n = 40 [17%]) received an escalated 21-day dosing schedule with median time to dose escalation of 9.2 months (range, 1.0-52.7 months) in the Onureg arm and 6.0 months (0.5-19.3 months) in the placebo arm (Table 19). Patients received a median of 2 escalated dosing cycles in both the Onureg (range, 1-45) and placebo (range, 1-16) arms, but the proportion of patients who received more than 3 cycles of escalated dosing was higher in the Onureg arm (Onureg, 43%; placebo, 18%).[105,112] Based on an exploratory analysis, efficacy in patients who received the 21-day dose escalation was broadly consistent with the ITT data, confirming that the data for the ITT population may be used in the economic model (as described in Section 8.5.1).[105,112]

Table 19. QUAZAR AML-001: summary of dose modifications (safety population)

Parameter	Onureg (n = 236)	Placebo (n = 233)
Patients with at least 1 dose adjustment, n (%)[a]	[redacted]	[redacted]
Reason for dose adjustment, n (%)[a]		
AE	[redacted]	[redacted]
AML relapse/progression	[redacted]	[redacted]
Per protocol	[redacted]	[redacted]
Other	[redacted]	[redacted]
Patients with at least 1 dose adjustment due to an AE, n (%)	[redacted]	[redacted]
Time to first dose adjustment due to an AE, days	[redacted]	[redacted]
Mean (SD)	[redacted]	[redacted]
Median (min, max)	[redacted]	[redacted]
Patients with at least 1 dose adjustment due to AML relapse/progression	[redacted]	[redacted]
Time to first dose adjustment due to AML relapse/progression, days	[redacted]	[redacted]
Mean (SD)	[redacted]	[redacted]
Median (min, max)	[redacted]	[redacted]
Patients with 1 dose reduction, n (%)[b]	[redacted]	[redacted]
Patients with 2 dose reductions, n (%)[c]	[redacted]	[redacted]
Patients with an escalated 21-day dosing schedule, n (%)	51 (21)	40 (17)
Escalated dosing cycles received, median (range)	2 (1-45)	2 (1-16)
Patients with > 3 escalated dosing cycles, n (%)	22 (43.1)	7 (17.5)
Median time to dose escalation, months (range)	9.2 (1.0-52.7)	6.0 (0.5-19.3)

AE = adverse event; AML = acute myeloid leukaemia; max = maximum; min = minimum; SD = standard deviation.
[a] At least 1 dose adjustment reported in the case report form dosing page.
[b] Patients having a reduced dosage from 300 mg × 14 days to 200 mg × 14 days.
[c] Patients having a reduced dosage from 300 mg × 14 days to 200 mg × 14 days and then to 200 mg × 7 days.

Sources: Celgene data on file (2020)[114]; Dohner et al. (2020)[105]

Adverse events

The proportions of patients with TEAEs in each category were generally higher in the Onureg group than in the placebo group. However, when comparing the incidence of TEAEs, it is important to note that duration of exposure to study treatment was approximately twice as long in the Onureg group as in the placebo group (11.6 months vs. 5.7 months).[115] In both treatment groups, nearly all patients experienced at least 1 TEAE (Onureg, 97.9%; placebo, 96.6%) (Table 20).[18] [redacted] The rates of serious TEAEs (Onureg, 33.5%; placebo, 25.3%), grade 3 or 4 TEAEs (Onureg, 71.6%; placebo, 63.1%) and TEAEs leading to death (Onureg, 3.8%; placebo, 1.7%) were higher in the Onureg group than in the placebo group (below 10% difference). None of the TEAEs leading to death was considered to be related to study treatment. In the Onureg arm, 2 patients died from sepsis, 2 from cerebral haemorrhage, 1 from both sepsis and multiorgan failure, and 1 each from intracranial haemorrhage, cardiogenic shock, aspiration pneumonia, and suicide; in the placebo arm, 2 patients died from multiorgan failure, and 1 each from cerebral haemorrhage and general health deterioration.[18] Overall, 13.1% of patients in the Onureg arm and 4.3% of patients in the placebo arm experienced at least 1 TEAE that led to study discontinuation.[18]

Table 20. QUAZAR AML-001: summary of treatment-emergent adverse events (safety population)

TEAE category	Onureg (n = 236)	Placebo (n = 233)
≥ 1 TEAE, n (%)	231 (97.9)	225 (96.6)
[redacted]	[redacted]	[redacted]
≥ 1 Serious TEAE, n (%)	79 (33.5)	59 (25.3)
≥ 1 treatment-related serious TEAE, n (%)	22 (9.3)	5 (2.1)
≥ 1 Grade 3 or 4 TEAEa, n (%)	169 (71.6)	147 (63.1)
≥ 1 Treatment-related grade 3 or 4 TEAE,[a] n (%)	113 (47.9)	54 (23.2)
≥ 1 TEAE leading to death, n (%)	9 (3.8)	4 (1.7)
≥ 1 TEAE leading to dose reduction, n (%)	37 (15.7)	6 (2.6)
≥ 1 TEAE leading to dose interruption, n (%)	102 (43.2)	40 (17.2)
≥ 1 TEAE leading to dose reduction and interruption, n (%)	24 (10.2)	3 (1.3)
≥ 1 TEAE leading to study treatment discontinuation, n (%)	31 (13.1)	10 (4.3)

AML = acute myeloid leukaemia; MedDRA = Medical Dictionary for Regulatory Activities; TEAE = treatment-emergent adverse event.

[a] Graded using Common Terminology Criteria for Adverse Events version 4.0.

Notes: AML relapse, as defined by MedDRA high-level group term leukaemias, is excluded. TEAEs include adverse events that started between the first dose date and up to 28 days after the last dose date of study treatment.

Source: Wei et al. (2020)[18], Celgene data on file (2020)[114]

The most frequently reported TEAEs (reported for > 25% of patients in the Onureg group) were nausea (64.8% for Onureg vs. 23.6% for placebo), vomiting (59.7% vs. 9.9%), diarrhoea (50.4% vs. 21.5%), neutropenia (44.5% vs. 26.2%), constipation (38.6% vs. 24.0%), thrombocytopenia (33.5% vs. 27.0%), and fatigue (29.7% vs. 19.3%).[18,19] The most frequently reported TEAEs (reported for ≥ 10% of patients in the Onureg group) were nausea (59.3% for Onureg vs. 10.7% for placebo), vomiting (51.7% vs. 3.0%), diarrhoea (36.0% vs. 6.4%), and neutropenia (34.3% vs. 16.3%)

(Table 21).[18,19] It should be noted that at in the QUAZAR AML-001 trial, supportive care measures, including prophylaxis for gastrointestinal events, were permitted per treating physician's discretion and local practice.[106]

As noted above, grade 3 or 4 TEAEs were more frequent in the Onureg group (72%) than in the placebo group (63%); however, many of the most common AEs occurred at a similar frequency between groups.[15] The most frequently reported grade 3 or 4 TEAEs (reported for ≥ 5% of patients in the Onureg group) were neutropenia (41.1% for Onureg vs. 23.6% for placebo), thrombocytopenia (22.5% vs. 21.5%), anaemia (14.0% vs. 12.9%), febrile neutropenia (11.4% vs. 7.7%), leukopenia (7.6% vs. 6.0%), and diarrhoea (5.1% vs. 1.3%) (Figure 15). Grade 3 or 4 TEAEs for which the incidence differed by > 2% between treatment groups were neutropenia (41.1% for Onureg vs. 23.6% for placebo), febrile neutropenia (11.4% vs. 7.7%), diarrhoea (5.1% vs. 1.3%), vomiting (3.0% vs. 0%), nausea (2.5% vs. 0.4%), and fatigue (3.0% vs. 0.9%).[18,19]

Table 21. QUAZAR AML-001: treatment-emergent adverse events reported for ≥ 10% of patients (safety population)

	Onureg (n = 236), n (%)		Placebo (n = 233), n (%)	
TEAE	Any grade	Grade 3 or 4	Any grade	Grade 3 or 4
Patients with at least 1 TEAE	231 (98)	169 (72)	225 (97)	147 (63)
Nausea	153 (65)	6 (3)	55 (24)	1 (< 1)
Vomiting	141 (60)	7 (3)	23 (10)	0
Diarrhoea	119 (50)	12 (5)	50 (21)	3 (1)
Neutropenia	105 (44)	97 (41)	61 (26)	55 (24)
Constipation	91 (39)	3 (1)	56 (24)	0
Thrombocytopenia	79 (33)	53 (22)	63 (27)	50 (21)
Fatigue	70 (30)	7 (3)	45 (19)	2 (1)
Anaemia	48 (20)	33 (14)	42 (18)	30 (13)
Asthenia	44 (19)	2 (1)	13 (6)	1 (< 1)
Pyrexia	36 (15)	4 (2)	44 (19)	1 (< 1)
Arthralgia	32 (14)	2 (1)	24 (10)	1 (< 1)
Abdominal pain	31 (13)	2 (1)	16 (7)	0
Upper respiratory tract infection	31 (13)	1 (< 1)	32 (14)	0
Decreased appetite	30 (13)	2 (1)	15 (6)	2 (1)
Cough	29 (12)	0	39 (17)	0
Febrile neutropenia	28 (12)	27 (11)	18 (8)	18 (8)
Back pain	28 (12)	3 (1)	23 (10)	2 (1)
Leukopenia	25 (11)	18 (8)	19 (8)	14 (6)
Pain in extremity	25 (11)	1 (< 1)	12 (5)	0
Dizziness	25 (11)	0	21 (9)	0
Headache	23 (10)	0	26 (11)	1 (< 1)
Peripheral oedema	21 (9)	0	24 (10)	1 (< 1)

MedDRA = Medical Dictionary for Regulatory Activities; TEAE = treatment-emergent adverse event.
Note: Adverse events were evaluated from the date of first dose of treatment through 28 days after the last dose. TEAEs were coded using MedDRA version 22.0. A patient was counted only once for multiple events within preferred term/system organ class.
Sources: Wei et al. (2020)[18]; Wei et al. (2019)[19]

Details of the subgroup analysis for AEs in the QUAZAR AML-001 trial are presented in Appendix E.

7.2 Efficacy and safety of Onureg compared with close monitoring as maintenance therapy for patients with acute myeloid leukaemia

There is no standard of care maintenance therapy for patients with AML who achieve CR/CRi after intensive chemotherapy, and who are ineligible for allogeneic bone marrow or stem cell transplant in Denmark; therefore, close monitoring is the predominant strategy. In the QUAZAR AML-001 trial (described in Section 7), the comparator arm received placebo and close monitoring. Therefore, the results of this head-to-head trial provide the most robust comparison, and no indirect treatment comparisons have been performed.

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8 Health economic analysis

8.1 Model

8.1.1 Methods

8.1.1.1 Type of economic evaluation

A cost-utility analysis was conducted, with outcomes expressed as incremental costs per QALY as recommended by the DMC guidelines. Cost-effectiveness results were also reported as incremental costs per life-year gained.

8.1.1.2 Comparators

To assess the cost-effectiveness of Onureg plus BSC as a maintenance treatment for AML, no active anti-leukaemic therapy plus BSC (i.e., BSC alone) was chosen as the comparator for the analysis. This represents the standard of care in Danish current clinical practice because there are currently no approved or funded therapies indicated for the maintenance treatment of AML in Denmark.

Comparison with no active anti-leukaemic therapy plus BSC is also well aligned with the placebo plus BSC comparator arm of the QUAZAR AML-001 trial.

Throughout the QUAZAR AML-001 trial, patients in both the placebo and Onureg treatment groups were permitted to receive BSC, which may have included red blood cell (RBC) and platelet transfusions; use of an erythropoiesis-stimulating agent; antibiotic, antiviral, and/or antifungal therapy; nutritional support; and/or granulocyte colony-stimulating factor for patients experiencing neutropenic infections. The inclusion of BSC in the study design minimised the risk of providing patients with inadequate care and is consistent with current practice for patients with AML who are in remission after induction/consolidation therapy.

8.1.1.3 Perspective

The analysis was conducted from the Danish limited societal perspective as per DMC guidelines.[125]

8.1.1.4 Time horizon

According to DMC guidelines, the model time horizon should be of sufficient length to capture all costs and outcomes relevant to the treatments being compared and should match the natural course of the disease.[125] Because the interventions were expected to have differential impacts on mortality, a lifetime horizon (i.e., 30 years) was selected. After 30 years, no more than approximately 1% of patients are alive in the model ensuring all relevant costs and QALYs are being captured.

8.1.1.5 Discount rate

A 3.5% annual discount rate for costs and effects was used, as per the DMC guidelines.[125]

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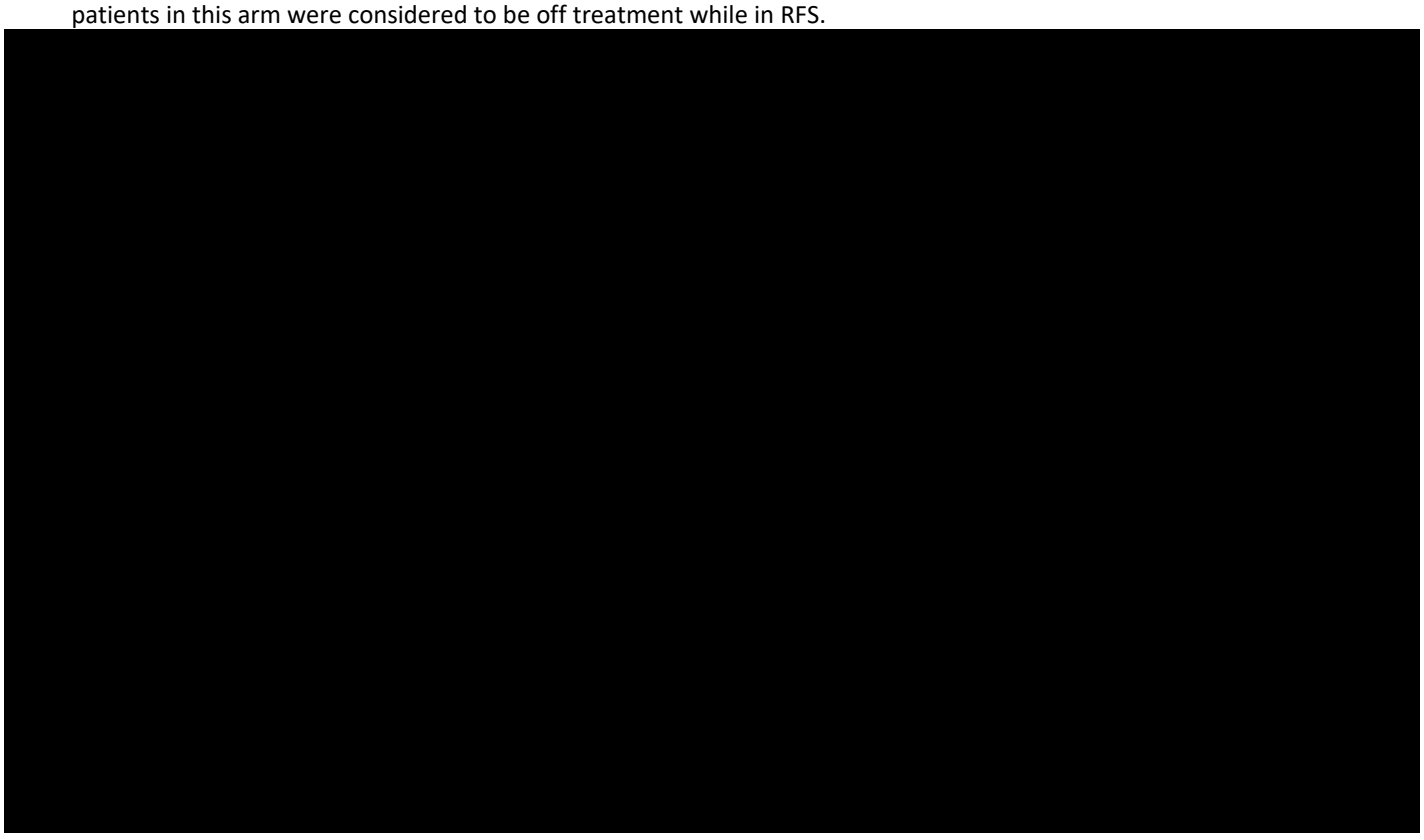
8.1.2 Modelling considerations

8.1.2.1 Model structure

A 3-state partitioned survival model was used to capture all costs and outcomes associated with Onureg and no active therapy. The 3-health-state partitioned survival model structure is common among oncology models in general because treatments are often measured by their ability to delay relapse or progression of disease in addition to prolonging survival. For AML in particular, this model structure aligns with several previously developed models in AML.[126-129]

As shown in Figure 16, the 3 key health states of the model were RFS (on and off treatment), relapse, and dead. The 3 health states represent the primary stages of disease in this patient population. These health states also correspond to the primary and secondary endpoints of the QUAZAR AML-001 trial. Patients enter the model in the RFS health state. The number of patients in each health state is estimated using the partitioned survival method. The partitioned survival approach allows for modelling of OS and RFS based on study-observed events, which is expected to reflect disease progression and the long-term expected survival profile of patients. At the end of each cycle, the proportion of patients in the RFS, relapse, and dead health states is calculated from parametric survival curves for RFS and OS estimated directly from the QUAZAR AML-001 trial. The number of patients occupying each state in the model is derived directly from the cumulative survival probabilities of RFS and OS (area under the curve approach), with proportion of patients in the RFS health state being calculated as the difference between OS and RFS. Adverse events were modelled as events rather than as health states, such that costs related to the occurrence of an AE were applied to the proportion of patients estimated to experience the AE.

Because there was no active therapeutic agent administered in addition to BSC for the no active therapy arm, all patients in this arm were considered to be off treatment while in RFS.



8.1.2.2 Cycle length and half-cycle correction

The cycle length selected for the model was 28 days to align with treatment cycles and to adequately capture events. This cycle length aligns with those observed in other existing AML models.[127,128] A half-cycle correction was applied to the calculation of life-years and QALYs to account for the transition of patients from one health state to another happening in a continuous process, representing an average transition halfway through a cycle (i.e., not at the beginning or end of a cycle).

8.1.2.3 Health states

In the model, all patients started in the RFS health state and could either move to another health state (i.e., relapse or death) or stay in the RFS state at the end of each cycle. The possible transitions are indicated by arrows in Figure 16. A description of each health state is shown in Table 22. Costs (see Section 8.5) and utilities (see Section 8.4) were applied to each health state.

Probability of remaining in relapse-free survival

Patients remained in the RFS health state until relapse or death due to any cause, whichever occurred first. The probability of remaining in the RFS health state was informed by the RFS curves for Onureg and no active therapy, which were extrapolated from KM data of the QUAZAR AML-001 trial (September 2020 data cut) (see Section 8.3.1.5).

Probability of transitioning from relapse-free survival to relapse

The proportion of patients transitioning from RFS to relapse in each cycle was calculated as the proportion of patients who were still alive in each treatment arm informed by the extrapolated OS curve, minus the proportion of patients remaining in the RFS state (informed by the extrapolated RFS curve).

Probability of overall survival

The probability of OS was informed by the OS curves for Onureg and no active therapy, which were extrapolated from KM data of the QUAZAR AML-001 trial (September 2020 data cut) (see Section 8.3.1.4).

Table 22. Model health states

Health state	Description
RFS (on or off treatment)	All patients enter the model in the RFS state at the point at which they begin maintenance treatment; state defined as interval from date of first dose to documented relapse or death due to any cause Cost categories: ▪ Drug acquisition ▪ Treatment administration ▪ Adverse event ▪ Disease management
Relapse	Informed as the difference between the RFS and OS curves at each timepoint Cost categories: ▪ Disease management ▪ Subsequent therapy ▪ HSCT ▪ End-of-life care (applied in the cycle that patients transition from relapse to death)

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Health state	Description
Death	▪ Death due to any cause; informed by OS curves ▪ Patients can transition to the death state from any other state ▪ Death is an absorbing state in the model; once patients enter this health state, they do not leave

HSCT = haematopoietic stem cell transplantation; OS = overall survival; RFS = relapse-free survival.

8.1.2.4 Model validation

The model underwent internal validation, with a thorough review of all calculations and data inputs. The model inputs were also validated by a clinical expert. This included a review of the model face validity in terms of RFS/OS curve extrapolation (see Section 8.3.1), appropriateness of data sources, and key clinical assumptions.

8.2 Relationship between the data for relative efficacy, parameters used in the model, and relevance for Danish clinical practice

8.2.1.1 Target population

The target population of the economic evaluation aligned with the indication for oral Onureg as assessed in QUAZAR AML-001.15 Onureg is indicated for adult patients with AML who achieved CR/CRi following intensive first-line chemotherapy with or without consolidation chemotherapy and who were ineligible for HSCT.4

The baseline characteristics of patients in QUAZAR AML-001 are expected to reflect those of patients seen in Danish clinical practice in the subgroup of eligible patients with AML, as confirmed by clinical experts.

8.2.2 Relationship between the clinical documentation, data used in the model and Danish clinical practice

8.2.2.1 Patient population

The patient population of the economic evaluation is aligned with the indication for oral Onureg as assessed in QUAZAR AML-001.[15] The baseline characteristics of patients in QUAZAR AML-001 are expected to reflect those of patients seen in Danish clinical practice in the subgroup of eligible patients with AML, as confirmed by clinical experts. Table 23 summarises patient baseline characteristics from the trial and used in the analysis. In the ITT population, the mean age of the subjects was 67.9 years with 51.9% male subjects. Patients had poor/intermediate cytogenetic risk at the time of induction therapy and an ECOG PS of 0, 1, 2, or 3.[15] There were no restrictions on the patient population in terms of genetic mutations.[15]

Table 23. Patient characteristics in QUAZAR AML-001 used in the model (ITT population)

Patient characteristic	QUAZAR AML-001 (N = 472)
Mean age, years (SD)	67.9 (5.66)
Proportion males	51.9%
Mean weight, kg (SD)	74.41 (17.406)
Mean height, cm (SD)	166.27 (10.001)
Cytogenetic risk category	
Intermediate	86.0%
Poor	14.0%

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Patient characteristic	QUAZAR AML-001 (N = 472)
ECOG performance status	
0	48.1%
1	43.9%
2	7.6%
3	0.4%

AML = acute myeloid leukaemia; ECOG = Eastern Cooperative Oncology Group; ITT = intent to treat; SD = standard deviation.
Source: Wei et al. (2020)[18]; QUAZAR AML-001 clinical study report (CSR) (data on file)[114]

8.2.2.2 Intervention

Oral Onureg was implemented in the economic model in line with the SmPC (see Table 4 for details) and in accordance with its usage in the QUAZAR AML-001 trial. As summarised in Table 24, intervention is as expected in Danish clinical practice (as defined in Section 5.2).

Table 24. Intervention

Intervention	Clinical documentation (including source)	Used in the model (number/value including source)	Expected Danish clinical practice (including source if known)
Posology	The recommended dosage is Onureg 300 mg orally once daily as defined in the Onureg SmPC (2020)[4]	Oral administration of 300 mg once daily	Anticipated to be oral administration of 300 mg once daily
Length of treatment (time on treatment) (mean/median)	Mean time on Onureg treatment from QUAZAR AML-001 of [redacted] cycles.[114]	Mean time on Onureg treatment is modelled directly based on the KM data in the economic model	Time on Onureg treatment is anticipated to be similar to that observed in the QUAZAR AML-001 trial
Criteria for discontinuation	Subjects received study treatment as long as they benefited from the treatment or until treatment was discontinued for other reasons (adverse events, withdrawal, eligibility for HSCT, death, etc.) [114]	Treatment discontinuation is modelled based on treatment duration in the trial	The SmPC states treatment should continue until relapse or unacceptable toxicity, which is in line with the trial and model and we anticipate will be practice in Denmark[4]
The pharmaceutical's position in Danish clinical practice	The QUAZAR-AML-001 trial included patients aged ≥ 55 years with AML in first CR following induction therapy who had not had HSCT[114]	Population/positioning from the trial	The SmPC population is in line with the trial population and we anticipate this will be the position in Danish practice[4]

AML = acute myeloid leukaemia; CR = complete response; HSCT = haematopoietic stem cell transplantation; KM = Kaplan-Meier; SmPC = summary of product characteristics.

8.2.2.3 Comparators

The standard of care comparator in Denmark is close monitoring, which is represented by the placebo arm in the QUAZAR AML-001 trial. In the economic model, this is defined as no active therapy.

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8.2.2.4 Relative efficacy outcomes

Efficacy outcomes from the QUAZAR-AML 001 clinical trial that are used in the model are provided in Table 25 and Table 26.

Table 25. Summary of text regarding *value*

Clinical efficacy outcome	Clinical documentation	Used in the model (value)
Primary endpoint in the study Overall survival (OS)	Overall Survival is the primary endpoint in the QUAZAR AML-001 trial.[18,19]	Extrapolation of OS data is discussed in Section 8.3.1.1
Secondary endpoint: Relapse-free survival (RFS)	Relapse-free survival is the primary endpoint in the QUAZAR AML-001 trial.[18,19]	Extrapolation of RFS data is discussed in Section 8.3.1.1

OS = overall survival; RFS = relapse-free survival.

Table 26. Summary of text regarding *relevance*

Clinical efficacy outcome	Clinical documentation (measurement method)	Relevance of outcome for Danish clinical practice	Relevance of measurement method for Danish clinical practice
Primary endpoint in the study: OS	Overall survival is the primary endpoint in the QUAZAR AML-001 trial.[18,19]	Anticipated to be relevant to Danish clinical practice	Anticipated to be relevant to Danish clinical practice
Secondary endpoint: RFS	Relapse-free survival is the primary endpoint in the QUAZAR AML-001 trial.[18,19]	Anticipated to be relevant to Danish clinical practice	Anticipated to be relevant to Danish clinical practice

OS = overall survival; RFS = relapse-free survival.

8.3 Extrapolation of relative efficacy

8.3.1 Time-to-event data

To estimate the RFS and OS over the 30-year model time horizon, survival beyond the QUAZAR AML-001 trial time horizon had to be informed by extrapolation. It is common for oncology economic evaluations developed to support HTA submissions to only use parametric survival analysis fitted to data derived from pivotal trials for the interventions of interest and extrapolated over the full model time horizon. Full methods used for extrapolation of time-to-event data and results are presented in Appendix G; however, the sections below summarise the overall methods and selection of distributions for the base-case extrapolation.

8.3.1.1 Efficacy data sources

Overall survival, RFS, and time on treatment outcomes for both Onureg and no active therapy in the economic evaluation were informed with data from the QUAZAR AML-001 trial. As presented in Section 7.1.1, the QUAZAR study originally consisted of 3 phases: the prerandomisation phase (Screening Phase), the treatment phase, and the follow-up phase. The study was unblinded according to the protocol after the follow-up phase (in July 2019). However, the study protocol was amended during the trial to include an extension phase. The study was unblinded after the follow-up phase (in July 2019). The extension phase allowed subjects receiving Onureg who were demonstrating clinical benefit to continue to receive Onureg after unblinding until they met the criteria for study discontinuation or until Onureg became commercially available and reimbursed. In addition, all subjects in the placebo group and subjects

who were previously discontinued from the treatment phase (irrespective of randomisation group) and continuing in the follow-up phase were followed for survival in the extension phase. No crossover between treatment groups was allowed at any point during the study.

Due to the addition of the trial extension phase, 2 data cuts are available for the survival analysis: the data cut for the primary analysis from July 2019 and a subsequent data cut from September 2020, which was taken during the extension phase after study unblinding. For modelling of survival, more mature data are seen to provide more robust long-term extrapolations. Thus, we considered how to best use the 2 data cuts while maintaining the integrity of the trial results. While OS data were collected robustly during the extension phase, RFS was collected less rigorously, in that although blast counts were still analysed for RFS, these were not validated at a central laboratory, as they had been prior to the unblinding of the trial. As an effect of this, the RFS data in the July 2019 database lock were considered more robust than those from the September 2020 database lock. Therefore, the July 2019 RFS data were used in the cost-effectiveness model for RFS and time on treatment.

On the other hand, OS data were still routinely collected through the extension phase, so the September 2020 data were considered both robust and the most mature data to use in the cost-effectiveness model. This was considered appropriate given several findings. Firstly, the September 2020 data are consistent with the July 2019 data, with unchanged median OS and HR. Secondly, the September 2020 data provide additional reliability for the tail end of the OS Kaplan-Meier (KM) curves. At the July 2019 cutoff date, the number of subjects at risk at 48 months were 26 and 19 for the Onureg and placebo arms, respectively; by month 66, there were just 5 patients at risk in the Onureg arm, and 6 for the placebo arm. There was also a high degree of censoring from 24 months (see Section 7.1.1). With fewer subjects remaining at risk after 48 months, survival estimates beyond this point become less reliable and additional follow-up may influence the tail end of the curves. The September 2020 data provide an additional approximately 14 months of follow-up and greater reliability to the shape of the tails.

Based on the above, it was therefore decided that the most robust approach was to use the July 2019 data cut data for modelling of RFS and time on treatment, and the September 2020 data cut data for modelling of OS.

8.3.1.2 Methodology used for curve fitting

Standard guidance for fitting and selecting survival functions was followed.[130,131] Figure 17 presents the process for identifying the most appropriate parametric survival models for RFS and OS.

The steps required to determine the most appropriate parametric survival curves to use in the economic model included the following:

- Testing the proportional effects assumption: the log-cumulative hazards and Schoenfeld residual plot were assessed to determine if the data from QUAZAR AML-001 indicate proportional effects. This assessment was done by testing the significance of the Grambsch and Therneau's correlation test between Schoenfeld residuals and log of time and by visual inspection to determine if the survival curves of Onureg and no active therapy arms were parallel.
- In the event that proportional effects held, a range of joint parametric survival distributions were explored, with models fitted to both arms of QUAZAR AML-001 simultaneously.
- When the proportional effects assumption did not hold, only individual survival models were assessed, in which survival models were fitted to each arm of the QUAZAR AML-001 study independently.
- Within the various parametric survival distributions, the Akaike information criterion (AIC) and Bayesian information criterion (BIC) goodness-of-fit statistics were assessed to identify the best fitting survival models to the trial data.
- The final choice of parametric survival distributions used for the base-case model was based on the following:

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  - The best fitting survival models by AIC and BIC statistics, which provide goodness of fit (compared with the KM data from QUAZAR AML-001).
  - Visual fit of the extrapolations to the QUAZAR AML-001 KM data. In general, when visually inspecting the fit of the extrapolated curves against the KM data, less weight was accorded to the tails of the KM data to avoid overfitting because of level of censoring and the small number of patients at risk (and therefore greater uncertainty).
  - Clinical plausibility and external validation of the extrapolated survival estimates.
  - We did not impose the constraint that a common distribution should be selected across both arms. Latimer (2013)[131] states that when strong clinical rationale is presented, there may be instances in which it is appropriate to select different distributions for the intervention and comparator. Given that this comparison assesses an active therapy with a distinct method of action versus no active therapy, it is clinically plausible that the underlying hazard function in each arm may develop differently over time.
- If standard parametric curves were not providing adequate survival estimates according to the above selection criteria, spline models with up to 2 knots were investigated in addition to the standard parametric survival models.

It is important to consider goodness of fit because it measures the fit of the extrapolation against the trial data that are available. However, it is equally, if not more, important to consider the clinical plausibility of the extrapolated portion of the curve because it is the area with the highest uncertainty owing to lack of trial data. Thus, clinical experts were consulted with regards to guiding the long-term extrapolation. There is, however, a paucity of long-term survival data within this patient population. Therefore, clinical guidance was primarily sought on expected long-term survival for Onureg in relation to no active therapy. The clinical input received highlighted that treatment with Onureg likely will result in delayed recurrence but not necessarily cure. Thus, predicted RFS and OS would likely converge over time. However, if anything, Onureg would result in long-term survival benefit and not be expected to result in long-term worse survival compared with no active therapy at any point in time.

8.3.1.3 Survival analysis

All survival modelling was conducted using the FlexSurv package in R and modelled using the FlexSurvReg function. Parametric survival models were fitted to individual patient-level data from the QUAZAR AML-001 trial. For each endpoint, 7 parametric models were considered for the extrapolation of patient-level data (exponential, Weibull, Gompertz, log-normal, log-logistic, gamma, and generalised gamma). When adequate fit or plausible long-term extrapolations could not be achieved with these standard models, spline models (1 internal knot hazard linear predictor, 2 internal knot hazard linear predictor, 1 internal odds linear predictor, 2 internal odds linear predictor, 1 internal normal linear predictor, and 2 internal normal linear predictor) were fitted and assessed. The following parameters were modelled:

- Overall survival (see Section 8.3.1.4)
  - Used to estimate proportion of patients alive at each cycle of the model and in the Relapse health state
- Relapse-free survival (see Section 8.3.1.5)
  - Used to calculate proportion of patients in the Relapse free and Relapse health state

The following sections provide details of the survival models for each of these parameters.

8.3.1.4 Overall survival

Testing of proportional hazards assumption

Visual inspection of the log-cumulative hazards and Schoenfeld residuals plots was undertaken to assess proportionality of treatment effects over time. Inspection of the OS log-cumulative hazard plot suggested that the 2 lines were not parallel (Figure 19).

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Similarly, the Schoenfeld residual plot displayed a nonhorizontal line and the Grambsch-Therneau global Schoenfeld residual test value was statistically significant (*P* value = 0.0008).

Based on this, it was decided that non-proportionality was the most plausible assumption for the current analyses. For completeness, both joint and individual survival models were fitted to the data with both options being available in the economic model. However, given that the proportional hazard assumption was not considered plausible, joint survival models were not considered for base case curve selection.

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Assessing goodness of fit of parametric survival models and selection of base case distribution

Assessment of visual fit of the standard parametric models showed that none of the individual models provided a combination of both good fit to the KM data and plausible long-term projections. For example, the best fitting distribution with regards to AIC and BIC (Generalized gamma) provided a reasonable fit to the KM data for both arms, but resulted in clinically implausible long-term predictions with significantly lower overall survival predicted for Onureg compared with no active therapy (Figure 21). The statistically second best fitting, on the other hand, (log-logistic) had a poor visual fit to the data for both arms, overpredicting the middle section of the data and underpredicting the tail (Figure 22). A similar pattern was seen for all standard distributions fitted per arm individually (see Appendix G). Further, if considering statistical fit assessed based on AIC and BIC, Generalized gamma would be the only distribution to consider because no other distribution was within rule of thumb presented by Burnham Burnham and Anderson (2004)[132] of difference of AIC larger than 4, constituting a meaningful difference in fit. The difficulty for the independent models to adequately fit the data and provide clinically plausible long-term extrapolations could be due to the significant censoring towards the tail of the data leading to what appears to be a unnatural convergence of the 2 survival curves towards the end of follow up.

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AZA = azacytidine; ITT = intent to treat.

In fact, from assessing visual fit, several of the joint models fitted provided better visual fit to the KM data and clinically plausible long-term predictions than the individually fitted curves. This is exemplified with the best statistically fitting joint distribution, Generalized gamma, in 0.

The improved fit of these joint models could be due to the pooling of both arms, resulting in better statistical estimation compared with the smaller sample when fitting distributions to each arm independently. However, due to

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the violation of proportional hazards presented above, joint models were not considered appropriate for the base-case analysis. Therefore, to improve the fit of individual survival extrapolations, spline models were investigated as outlined in Section 8.3.1.2 to better capture the complex hazard function observed in the QUAZAR AML-001 trial and produce plausible long-term extrapolations.

As shown in Appendix G, overall spline models demonstrated a good visual fit to the observed clinical trial data. All spline models also provided improved statistical fit as assessed by AIC compared with the standard distributions. Thus, from a within-trial perspective the spline models could be seen as preferable to the standard parametric distributions. However, all spline models did result in clinically implausible crossing of OS between arms in the long-term extrapolations (see best fitting distribution in Figure 24 as an example). However, this crossing of curves was less pronounced and occurring at a later stage than the crossing observed with standard parametric functions. Thus, the impact of the crossing would have less of an impact on the modelled outcome.

As noted in Section 8.3.1.2, the clinical input received stated that it could be plausible that survival between the treatment arms would approach each other over time, but not plausible that Onureg treatment would result in poorer outcome in the long term given the treatment effect seen within trial. Thus, to overcome the issue with clinically implausible long-term survival predictions but ensure good within trial fit, spline models were deemed the most appropriate to use given the good within trial fit. However, to ensure clinical plausibility of long-term survival, a cap function was implemented in the model where the mortality for Onureg was capped so that it cannot exceed the mortality predicted for NAT.

Given the above, modelling of OS in the base-case analysis was based on spline 1 internal knot odds linear predictor distribution. The selection of spline 1 internal knot odds linear predictor was based on the following:

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- AIC and BIC relative to all other standard parametric and spline based survival functions, indicating best statistical fit
- Good visual fit to the KM data
- The median predicted survival from 1 internal knot odds linear predictor aligned closely to the QUAZAR AML-001 data (1.99 years vs. 2.06 years in the Onureg arm, and 1.23 years vs. 1.23 years in the no active therapy arm, respectively)
- Crossing of Onureg survival and no active therapy survival occurred at a later more clinically plausible timepoint than many of the other distributions
- The tails of 1 internal knot odds linear predictor curve extrapolations did not extend indefinitely

Figure 25 shows the KM OS curves from QUAZAR AML-001 (September 2020 data cut) along with the extrapolated OS time-varying spline curves using 1 internal knot odds linear predictor distribution, as well as the mortality cap incorporated into the model. As can be seen from Figure 25, the resulting survival extrapolation is well aligned with the clinical input received because the survival in both arms converges towards the end of the model without Onureg survival crossing the no active therapy arm.

8.3.1.5 Relapse-Free Survival

Figure 26 shows the RFS KM curves from the QUAZAR AML-001.

Testing of proportional hazards assumption

As for OS, the log-cumulative hazards plot and Schoenfeld residuals plot indicated that the proportional hazards assumption was violated for RFS. A visual inspection of the RFS log-cumulative hazard plot suggested that the 2 lines were not parallel (Figure 27).

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Similarly, the Schoenfeld residual plot displayed a nonhorizontal line and the Grambsch-Therneau global Schoenfeld residual test value was statistically significant (*P* value = 0.001; Figure 28).

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Based on these results, as for OS, it was decided that non-proportionality was the most plausible assumption for the current analyses. For completeness, both joint and individual survival models were fitted to the data with both options being available in the economic model. However, given that the proportional hazard assumption was not considered plausible, joint survival models were not considered for base-case curve selection.

Assessing goodness of fit of parametric survival models and selection of base case distribution

The results of the survival analysis for RFS were following the same pattern as with OS. That is, standard parametric models provided a poor fit to the data and/or resulting in crossing survival extrapolations early on (see Appendix G for full results). Therefore, spline models were fitted to the RFS data to investigate if this would result in improved within-trial fit as well as plausible long-term survival as for OS.

All spline models provided good visual and statistical fit to the data compared with the standard parametric functions. Further, none of the spline models resulted in non-clinically plausible crossing of Onureg and no active therapy RFS. Spline models were therefore considered to provide more appropriate extrapolations than the standard parametric models.

Of the spline models, the 2 knot spline models provided the best statistical fit to the data. However, the long-term RFS these models predicted seemed optimistic for Onureg in particular. Therefore, the simpler 1 knot models were considered to be the best fitting options. Of the 1 knot models, the 1 internal knot odds linear predictor distribution provided the best statistical fit and a good visual fit to the data. This selection was further aligned with the distribution selected as the base-case distribution for OS. Thus, this was selected as the base-case distribution for RFS. As extrapolations of RFS with spline models did not result in crossing curves, no cap on hazards were needed, same as for

the OS extrapolation. However, as OS and RFS were fitted independently, a cap function was implemented in the model to ensure that RFS could not exceed OS, which would be clinically implausible.

The resulting RFS in the model for the base case can be seen in Figure 29

8.3.1.6 Time on treatment

As can be seen from Figure 30, the time on treatment in the QUAZAR AML-001 trial was mature, based on the September 2020 datacut. As such, no extrapolation was required for estimating the time on treatment in the model. Therefore, the time to treatment discontinuation KM data for Onureg were selected for modelling duration of therapy in the base-case analysis. In a scenario, the use of the mean time on Onureg treatment from QUAZAR AML-001 of [redacted] cycles was explored.[114] These 2 scenarios would be expected to provide very similar results with the slight difference that, when the mean duration from the trial is used, the exact timing of events will be used, compared with the using the KM data, where the model cycles will "smooth" out the duration of therapy to some extent.

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[redacted]

8.3.2 Subsequent therapy

After relapse, a proportion of surviving patients were assumed to receive a single line of subsequent therapy. Subsequent therapies were included as a cost input only, with no impact on outcomes (e.g., survival, quality of life) because it was assumed that effects would be captured in the OS curve from the trial. Costs for subsequent therapy were applied once as patients in the model transitioned from the RFS to the relapse health state. Costs for subsequent therapies are described in Section 8.5.5.

The proportion of patients receiving a subsequent therapy and the mix of subsequent therapies were informed by QUAZAR AML-001 and were validated by clinical advisers (Table 27).

Table 27. Subsequent therapies received in QUAZAR AML-001

Parameter	Low-dose cytarabine	Azacitidine injection	Decitabine	3+7: daunorubicin + cytarabine	Total
Onureg	14.3%	8.4%	4.6%	26.1%	53.4%
No active therapy	10.7%	15.4%	6.8%	33.8%	66.7%

Source: QUAZAR AML-001 CSR, Table 14.1.10.3[114]

8.3.3 Haematopoietic stem cell transplantation

Haematopoietic stem cell transplantation was modelled as part of subsequent therapy rather than as a separate health state because, like other subsequent therapies, the data to inform second CR resulting from HSCT were not available. This assumption was supported by clinical opinion. Moreover, this approach aligns with other models in AML.[129,133,134]

In QUAZAR AML-001, a small proportion of patients treated with Onureg received HSCT after relapse (6.3%).[114] In models in which HSCT is included as a health state, the proportion of patients receiving HSCT tends to be substantially

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higher, and HSCT is often administered during first CR rather than after relapse. For example, in the RATIFY trial, 57% of patients treated with midostaurin underwent HSCT.[55] The HSCT procedure was performed during the first CR in 25.4% of patients treated with midostaurin.[55] Similarly, in the ALFA-0701 trial, 23.7% of patients treated with gemtuzumab ozogamicin underwent HSCT.[135] Among these patients, 53.1% received HSCT during the first CR[135]. In contrast, patients in QUAZAR AML-001 who received another therapy (e.g., HSCT) for AML without documented relapse were censored on the date of the last bone marrow assessment, before receiving the other therapy.[114] Thus, the efficacy of these subsequent therapies did not contribute to RFS.[114] Furthermore, the OS HR in favour of Onureg was maintained when censoring for HSCT (HR, 0.67; 95% CI, 0.53-0.84; QUAZAR AML-001).[114]

In the Onureg model, the proportion of patients in each treatment arm undergoing HSCT was informed by QUAZAR AML-001. In total, 6.3% of patients treated with Onureg and 13.7% of patients on no active therapy were assumed to undergo HSCT (QUAZAR AML-001 CSR).[114] The utility decrement associated with HSCT (see Section 8.4.3) and the costs of HSCT (see Section 8.5.6) were also considered in the model.

8.3.4 Adverse reaction outcomes

The QUAZAR AML-001 trial demonstrated that Onureg is generally well tolerated.[114] The safety population included all randomised patients who received at least 1 dose of study treatment (n = 236 for Onureg; n = 233 for placebo).[114] Treatment-emergent AEs included AEs that occurred between the first dose and up to 28 days after the last dose of study treatment. Within the safety set, 71.6% of patients in the Onureg group and 63.1% in the placebo group experienced a grade 3 or 4 TEAE.[114] A total of 3.8% and 1.7% of TEAEs led to death in the Onureg and placebo groups, respectively. None of the TEAEs that led to death were considered treatment related.[114]

The model included grade 3 or 4 AEs occurring in ≥ 5% of patients in the treatment arm of the QUAZAR AML-001 trial population as well as those AEs identified by clinical advisers to have a substantial impact on quality of life. Of note, clinical advisers indicated that leukopenia would be captured within the existing list of AEs; thus, leukopenia was not included as a separate AE in the model to avoid double counting. Table 28 summarises the AEs included in the model and the percentage of patients experiencing each AE in each model arm.

Table 28. Adverse reaction outcomes

Adverse reaction outcome	Onureg	No active therapy	Source
Neutropenia	41.1%	23.6%	QUAZAR AML-001 CSR
Thrombocytopenia	22.5%	21.5%	QUAZAR AML-001 CSR
Anaemia	14.0%	12.9%	QUAZAR AML-001 CSR
Febrile neutropenia	11.4%	7.7%	QUAZAR AML-001 CSR
Diarrhoea	5.1%	1.3%	QUAZAR AML-001 CSR
Vomiting	3.0%	0.0%	QUAZAR AML-001 CSR
Nausea	2.5%	0.4%	QUAZAR AML-001 CSR
Fatigue	3.0%	0.9%	QUAZAR AML-001 CSR

CSR = clinical study report.

Source: QUAZAR AML-001 clinical study report (CSR) (data on file)[114]

8.4 Documentation of health-related quality of life

8.4.1 Overview of health state utility values

In the QUAZAR AML-001 trial, EQ-5D data were collected for patients who were relapse free (on and off treatment). However, the QUAZAR AML-001 did not capture data on HRQoL for patients beyond the treatment period and into relapse. Therefore, utility values to inform the relapse health state, as well as potential alternative values for scenario analyses of the relapse health state, were sought from the literature.

An SLR was conducted in June 2021 to identify and summarise health utility values for adults (aged ≥ 18 years) with AML receiving high-intensity first-line therapy (induction with or without consolidation) with or without maintenance therapy. In total, 8 studies reported utility values by health state, which included 4 utility elicitation studies and 4 economic evaluations. Appendix H provides further information about the individual studies.

Based on the findings from the SLR, 3 utility sources from the literature were chosen for use in the model based on previous HTA feedback and clinical plausibility: Joshi et al. (2019)[136], Tremblay et al. (2018)[127], and Stein et al. (2019)[129] Table 29 presents the health state utility values (HSUVs) from these 3 literature sources and the QUAZAR AML-001 trial.

Table 29. Overview of health state utility value options for use in the economic model

Source	Health state	Utility value	SE	Data source/notes
Joshi et al. (2019)[136]	RFS: on treatment	0.890	0.15	Joshi et al. (2019)[136]
	RFS: off treatment	0.890	0.15	Joshi et al. (2019)[136]
	Relapse	0.510	0.46	Joshi et al. (2019)[136]
QUAZAR AML-001 (Danish EQ-5D-5L value-set)	RFS: Onureg	0.889	0.147	Celgene data on file (2020)[114]
	RFS: Placebo	0.899	0.139	Celgene data on file (2020)[114]
	RFS: Pooled data	0.893	0.144	Celgene data on file (2020)[114]
Tremblay et al. (2018)[127,a]	RFS: on treatment	0.810	0.20	Batty et al. (2014)[137] assumption for SE
	RFS: off treatment	0.830	0.20	Leunis et al. (2014)[37] assumption for SE
	Relapse	0.530	0.20	Pan et al. (2010)[138] assumption for SE
Stein et al. (2019)[129]	RFS: on treatment	0.870	0.20	Stein et al. (2018)[139] and clinical expert opinion, assumption for SE
	RFS: off treatment	0.870	0.20	Stein et al. (2018)[139] and clinical expert opinion, assumption for SE
	Relapse	0.620	0.20	Stein et al. (2018)[139] and clinical expert opinion, assumption for SE

EQ-5D-5L = 5-level EQ-5D; RFS = relapse-free survival; SE = standard error.

[a] In the Tremblay 2018 data set, the health state utility values were assumed to incorporate disutility related to toxicity and adverse events resulting from treatment.

8.4.2 Health state utility values used in the health economic model

As stated above, EQ-5D-3L for RFS was collected as part of the QUAZAR AML-001 trial. Treatment-specific utility values are used in the base case analysis. In alignment with the DMC guidelines, all utility values were mapped from EQ-5D-

3L to 5-level EQ 5D (EQ-5D-5L). Details of the utility mapping from EQ-5D-3L to 5-level EQ-5D (EQ-5D-5L) Danish utility values are included in Appendix I.

As stated previously, QUAZAR AML-001 did not collect utility data during relapse. Therefore, the utility value for relapse was informed by the SLR described in Section 8.4.1. Of the 3 studies identified in the SLR, Joshi et al. (2019) used a composite time trade-off methodology to elicit health state utilities for AML from 210 individuals in the UK general population,[136] whereas Tremblay et al. (2018) used HSUVs reported from various literature sources.[127] Stein et al. (2019) used HSUVs reported from a single study (Stein 2018).[129,139] In Stein et al. (2018), treatment-related AML health states were defined based on the literature and interviews with clinicians.[139] An online discrete-choice experiment survey was then conducted to capture preferences for the health states from a nationally representative sample of 300 adults in the US.[139] Based on this, the utility from Joshi et al. (2019)[136] of 0.51 was used to inform the relapse value in the base case. A further scenario analysis is conducted in which Joshi et al. (2019)[136] was selected to inform all health states (RFS on treatment, RFS off treatment, and relapse) for consistency across all utility inputs in the model.

In alignment with the DMC guidelines, the HSUVs in the model were adjusted for age to account for the increasing comorbidity and declining quality of life with increasing age. [140] The index used to adjust the utility values per age category are presented in Table 30.

Table 30. Age related utility deterioration

Age bracket	General population utility	Estimated adjustment index from baseline	Data source for general population utility values
50-69	0.818	1.000	Medicinradet (2021)[140]
70-79	0.813	0.994	
80+	0.721	0.881	

8.4.3 Utility decrements for adverse events

Utility decrements were included in the model to capture the impact of TEAEs on HRQoL. A clinical adviser was consulted regarding which AEs have a significant impact on HRQoL. Table 31 shows utility decrement values from the literature for each identified AE. The duration of each AE was informed by clinical adviser opinion. The total disutility due to AEs that a patient experiences on Onureg or no active therapy was determined based on the percentage of patients experiencing each AE and the disutility of that AE and is shown in Table 32. These are not included in the model base case, as treatment specific utilities are used.

Table 31. Average disutility decrement per adverse event

Adverse event	Reported utility decrement	Duration of adverse event (weeks)[a]	Default disutility decrement used in model	Data source for utility decrement
Neutropenia	0.090	4.0	0.090	Nafees et al. (2008)[141]
Thrombocytopenia	0.108	4.0	0.108	Tolley et al. (2013)[142]
Anaemia	0.100	10.0	0.250	Stein et al. (2018)[139]
Febrile neutropenia	0.090	1.0	0.023	Nafees et al. (2008)[141]
Diarrhoea	0.176	0.6	0.026	Stein et al. (2018)[139]

Adverse event	Reported utility decrement	Duration of adverse event (weeks)[a]	Default disutility decrement used in model	Data source for utility decrement
Vomiting	0.048	1.3	0.016	Nafees et al. (2008)[141]
Nausea	0.048	1.3	0.016	Nafees et al. (2008)[141]
Fatigue	0.073	10.0	0.184	Nafees et al. (2008)[141]

[a] Durations informed by clinical adviser opinion. Neutropenia and thrombocytopenia assumed to last 1 full 28-day cycle. Vomiting considered to last for the same duration as nausea.

Table 32. Average total adverse event disutility per patient

Maintenance treatment	Average total disutility per patient
Onureg	0.1064
No active therapy	0.0804

A utility decrement for HSCT was included in the model to capture the impact of HSCT on HRQoL. A study by Matza et al. (2019)[143] was found to report a health state utility for HSCT. Because HSCT is an event in the model rather than a health state, the difference between health states (−0.21 difference between transplant and durable remission) was used to derive a disutility that was then applied for one 28-day cycle.[143] The HSCT disutility was applied in the first model cycle to 6.3% of patients treated with Onureg and 13.7% of patients on no active therapy.

8.5 Resource use and costs

Danish-specific estimates of costs were used in the model. Unit costs were obtained from Danish public sources and the published literature. Where resource utilisation data were not available from the literature, resource utilisation data were based on clinical input. Costs were included in the model in 2020 DKK; when costs were only available from previous years, they were inflated to the current price year.

The types of costs in the model included were as follows:

- Drug acquisition costs (Section 8.5.1)
- Treatment administration costs (e.g., chemotherapy management fees, premedications) (Section 8.5.2)
- Adverse events costs (Section 8.5.3)
- Disease management costs (Section 8.5.4)
- Subsequent therapy costs (Section 8.5.5)
- End-of-life costs (Section 8.5.7)

8.5.1 Drug acquisition costs

All patients were assumed to initiate treatment in the first model cycle. Drug acquisition costs were applied to each cycle in the RFS state for patients on treatment. Drug acquisition costs for Onureg were calculated based on treatment dose, number of administrations per cycle, number of cycles as defined by the treatment protocol, and the Danish unit price. No drug costs were assigned to the no active therapy comparator.

The recommended starting dose of Onureg was 300 mg orally once daily on days 1 through 14 of repeated 28-day treatment cycles.[4] The base-case analysis focused exclusively on the 14-day dosing schedule. The recommended

starting dose of Onureg was 300 mg orally once daily on days 1 through 14 of repeated 28-day treatment cycles.[73] The base-case analysis focused exclusively on the 14-day dosing schedule.

There were 4 dosing regimens available for Onureg in QUAZAR AML-001[114]:

- The recommended dose of 300 mg once daily for the first 14 days of every 28-day treatment cycle
- The extended dose to 300 mg for 21 days in the case of relapse (5%-15% blasts in the peripheral blood or bone marrow)
- A maximum of 1 dose reduction to a daily dose of 200 mg for 14 days in the event of toxicity
- A maximum of 1 treatment schedule (frequency) modification from 14 days to 7 days of 200 mg in the event of continuing toxicity that did not respond to the initial dose reduction

In the base case cost-effectiveness model, the 21-day dosing schedule was excluded for 2 reasons. First, it is not expected to occur in clinical practice given it is not possible to determine when patients experienced relapses (i.e., blast counts are not regularly performed outside the clinical trial setting). Second, the 21-day dosing schedule has minimal impact on the ICER. Based on an exploratory analysis, efficacy in patients who received the 21-day dose escalation was broadly consistent with the ITT data.[112] Table 33 summarises the dosing schedules for Onureg.

Table 33. Drug dosing schedules for Onureg

Dose	Dosing	Schedule	Route	Doses per cycle	Cycle length	Number of Packs per cycle (7 tablets per pack)	Total dose per administration	Total dose per cycle
200 mg[a]	Fixed	Days 1-7	Oral	7	28	1	179 mg	1,254 mg
200 mg[a]	Fixed	Days 1-14	Oral	14	28	2	179 mg	2,509 mg
300 mg[a]	Fixed	Days 1-14	Oral	14	28	2	269 mg	3,763 mg

[a] Summary of Product Characteristics

Table 34 provides the formulations and unit costs for Onureg, along with the calculated costs per cycle. Drug costs were obtained from Danish national sources. Only the recommended dose was used in the base case analysis. Drug dispensing fees or markups were not included in the drug acquisition costs. The base case analysis also included relative dose intensity of [redacted] based on QUAZAR AML-001 trial.[114] The relative dose intensity is deemed appropriate to include in the model costing than for example dose compliance, as it accounts for non-compliance as well as missed doses and management of toxicity. Separate scenario analyses were also conducted to test the inclusion of dose extension and dose reduction. Table 35 presents the proportion of patients receiving dose modifications and duration of time spent on dose extension in each of these scenarios. It was assumed that patients receiving dose extension or dose reduction were mutually exclusive.

Table 34. Drug acquisition costs

Treatment	Unit strength	Unit description	Unit list price	Discount on list price	Cost per cycle
Onureg days 1-7	200 mg	Tablet (7 per pack)	48,245.73	0%	[redacted]

Onureg days 1-14	200 mg	Tablet (7 per pack)	48,245.73	0%	[redacted]
Onureg days 1-14	300 mg	Tablet (7 per pack)	48,245.73	0%	[redacted]

Table 35. Proportion of patients receiving modified dose regimens

	Data input
Proportion of patients receiving extended dose of Onureg	21.6%
Percentage of treatment duration spent on extended dose of Onureg	17.2%
Proportion of patients receiving only 1 dose reduction	18.2%
Proportion of patients receiving 2 dose reductions	5.9%

Note: These values were only used to inform scenario analyses. The base case analysis assumed all patients received the recommended dosage of 300 mg once daily on days 1-14 of repeated 28-day treatment cycles.
Source: QUAZAR AML-001 CSR[114]

8.5.2 Treatment administration costs

Given that Onureg is an oral maintenance therapy, there were no chair time costs or hospitalisation costs associated with administration. All administration and monitoring costs for Onureg are anticipated to be captured by the healthcare professional monitoring visit DRG cost shown in Table 40, which is applied once per cycle.

Table 36. Treatment administration unit costs and frequency for Onureg

Premedication	Cost per day	Number of days	Regimen	Sources
Ondansetron	24.00	5	8 mg taken orally every 12 hours, days 1-5	Laegemiddelstyrelsen (Danish Medicines Agency), Ondansetron

8.5.3 Adverse event costs

Costs related to the occurrence of an AE were applied to the proportion of patients estimated to experience the AE. Costs were included for treatment-emergent grade 3 or 4 AEs occurring in ≥ 5% of patients in the treatment arm of the QUAZAR AML-001 trial population as well as those AEs identified by clinical advisers to have a substantial impact on quality of life. To determine the costs of AEs, the proportion of patients estimated to be treated in each setting was multiplied by the inpatient and outpatient costs of each AE. The proportion of patients treated in the inpatient setting versus the outpatient setting was estimated based on clinical opinion. Adverse event costs were sourced from Danish national sources and are shown in Table 37.

Table 37. Adverse event unit costs

Adverse event	Diagnosis-related group (DRG) code	Percentage treated as inpatient	Inpatient unit cost	Percentage treated as outpatient	Outpatient unit cost (DRG70AK01)
Neutropenia	DRG16MA98	0%	DKK 3,114.00	100%	DKK 285.00
Thrombocytopenia	DRG16MA03	5%	DKK 35,483.00	95%	DKK 285.00
Anaemia	DRG16PR02	0%	DKK 4,628.00	100%	DKK 285.00
Febrile neutropenia	DRG16MA98	95%	DKK 3,114.00	5%	DKK 285.00

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Adverse event	Diagnosis-related group (DRG) code	Percentage treated as inpatient	Inpatient unit cost	Percentage treated as outpatient	Outpatient unit cost (DRG70AK01)
Diarrhoea	DRG06MA11	5%	DKK 5,130.00	95%	DKK 285.00
Vomiting	DRG06MA98	5%	DKK 2,277.00	95%	DKK 285.00
Nausea	DRG06MA98	0%	DKK 2,277.00	100%	DKK 285.00
Fatigue	DRG06MA98	5%	DKK 2,277.00	95%	DKK 285.00

DKK = Danish krone.

Source: Sundhedsdatastyrelsen (2021)[144]

The proportion of patients experiencing each event was multiplied by the average cost per event and then summed to derive a total AE cost per comparator, which was applied in the first model cycle (Table 38).

Table 38. Total adverse event costs

Maintenance treatment	Average total adverse event cost per patient
Onureg	1,013.10
No active therapy	784.02

8.5.4 Disease management costs

8.5.4.1 Resource use costs

The economic evaluation accounted for healthcare resource use associated with routine patient monitoring, including physician visits, nurse visits, laboratory tests, chemistry and liver panels, blood transfusions, and bone marrow aspirates/biopsies. A clinical adviser informed the frequency of resource use by health state and treatment arm. The proportions of patients receiving RBCs and platelet transfusions in relapse were informed by the QUAZAR AML-001 trial.[114]

Table 39 summarises resource use per cycle and by treatment arm. It was expected that resource use requirements would be similar between patients treated with Onureg and no active therapy, with the exception that the Onureg arm may require weekly complete blood count (CBC)/differential laboratory tests and more frequent bone marrow aspirates/biopsies while in RFS on treatment.

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Table 39. Frequency of resource use per cycle

Component of resource use	Onureg			No active therapy	
	RFS: on treatment	RFS: off treatment	Relapse	RFS: off treatment	Relapse
Healthcare professional monitoring visit	1	1	1	1	1
Proportion of patients receiving RBC transfusion	0%	0%	22.7%	0%	21.8%
Proportion of patients receiving platelet transfusion	0%	0%	19.3%	0%	21.8%
Bone marrow aspirate/biopsy	0.3	0.2	0	0.2	0

CBC = complete blood count; RBC = red blood cell; RFS = relapse-free survival.

Sources: Resource used informed by clinical adviser opinion. Transfusion data from QUAZAR AML-001 CSR, Table 14.1.9.3.1.[114]

Table 43 presents resource use unit costs. Specific Danish unit costs were identified from the literature reported by various Danish sources. For simplicity, the cost of healthcare professional monitoring visit is assumed to capture the cost of hematalogist visits and nurse visits in the model, and are applied once per cycle. To account for patient travel cost for each hospital visit the travel cost is added to healthcare professional monitoring per visit in the base case setting. The value of travel costs is estimated based on the state tax-free driving allowance (travel allowance) of DKK 3.52/km (2020). According to the DMC guidelines, the distance to a hospital was 14 km in driving distance in 2017, which corresponds to the travel cost to and from hospital of approximately DKK 100 per visit. In addition, we included patient time assumed to be equivalent to DKK 185 per hour, which was updated from DKK 179 presented in DMC guidelines.[69] In the base case setting it is assumed that the patient and transport costs incurred per visit, and that additional resource use elements would be included in these visits. However, the current model is fully flexible to apply the patient and transport costs separately for each element of resource use if desired by the user. A scenario analysis was therefore conducted by applying the patient and transport costs separately for each element of resource use including the RBC transfsuion, platelet transfusion and bone marrow aspirate/biopsy to test the impact of this approch on results. The inclsuion of patient travel and patient costs to these resource use elements had minimal impact on the ICER as shown in Table 55.

Table 40. Resource use unit costs

Resource	Unit cost	Source(s)/notes
Healthcare professional monitoring visit[a]	DKK 3,488.41	Sundhedsdatastyrelsen, DRG Tariffs 2021 (DRG17MA98)
RBC transfusion	DKK 4,628.00	Sundhedsdatastyrelsen, DRG Tariffs 2021 (DRG16PR02)
Platelet transfusion	DKK 6,042.00	Sundhedsdatastyrelsen, DRG Tariffs 2021 (DRG16PR01)
Bone marrow aspirate/biopsy	DKK 14,526.00	Sundhedsdatastyrelsen, DRG Tariffs 2021 (DRG17PR01)

CBC = complete blood count; DKK = Danish krone; PPP = purchasing power parity; RBC = red blood cell.

[a] Monitoring fee includes patient travel and patient cost per visit in the base case setting.

Source: Sundhedsdatastyrelsen (2021)[144]

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8.5.4.2 Best supportive care costs

Best supportive care costs were included in the model to capture ongoing disease management costs. All patients in the model received BSC regardless of treatment arm because this was assumed to represent standard ongoing disease management for patients with AML. The economic evaluation considered components of BSC listed in Table 41, including antibiotics, antifungals, and hydroxyurea. A clinical adviser informed the percentage of patients in each health state expected to receive each component of BSC. It was assumed that there were no differences in BSC between patients treated with Onureg and those on no active therapy.

Table 41. Proportion of patients receiving each component of best supportive care

	Onureg			No active therapy	
Drug	RFS: on treatment	RFS: off treatment	Relapse	RFS: off treatment	Relapse
Hydroxyurea	0%	0%	40%	0%	40%
Amoxicillin	0%	0%	0%	0%	0%
Ciprofloxacin	0%	0%	30%	0%	30%
Posaconazole	0%	0%	5%	0%	5%
Fluconazole	0%	0%	10%	0%	10%
Voriconazole	0%	0%	0%	0%	0%
Tranexamic acid	0%	0%	30%	0%	30%

RFS = relapse-free survival.

The dosing regimens for BSC treatments were obtained from the National Comprehensive Cancer Network® (NCCN®) Clinical Practice Guidelines in Oncology (NCCN Guidelines®).[27] Additional dosing information on posaconazole, fluconazole, and voriconazole was obtained from the literature.[145,146] All unit costs were obtained from Danish national sources (Table 42).

Table 42. Best supportive care costs

	Hydroxyurea	Amoxicillin	Ciprofloxacin	Posaconazole	Fluconazole	Voriconazole	Tranexamic acid
Dose	40 mg	500 mg	500 mg	200 mg	400 mg	200 mg	1,000 mg
Dosing	Weight	Fixed	Fixed	Fixed	Fixed	Fixed	Fixed
Doses per cycle	7	14	14	21	1	14	21
Unit size	500 mg	500 mg	500 mg	100 mg	350 mg	50 mg	5000 mg
Unit cost	DKK 2.95	DKK 0.69	DKK 0.90	DKK 188.33	DKK 80.91	DKK 3.33	DKK 180.00
Cost per milligram	0.0059	0.0014	0.0018	1.8833	0.2312	0.0667	0.0360
Cost per cycle	1.65	9.59	12.60	7,910.00	92.47	186.67	756.00

DKK = Danish krone.

Sources: Best supportive care regimens informed by NCCN Guidelines®.[27] Mean weight of 74.41 kg from QUAZAR AML-001 used to inform hydroxyurea dosing.[114] Unit costs informed by pharmacy purchasing costs from Laegemiddelstyrelsen (Danish Medicine Agency)[147]

The frequency of use for each resource and the unit costs, the percentage of patients requiring each component of BSC, and the unit costs for BSC were used to calculate the total disease management cost per cycle for each model comparator (Table 43).

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Table 43. Disease management costs per cycle

Maintenance treatment	RFS: on treatment	RFS: off treatment	Relapse
Onureg	7,119.91	5,957.83	6,341.05
No active therapy	0.00	5,957.83	6,450.45

RFS = relapse-free survival.

8.5.5 Subsequent therapy costs

Upon relapse, a proportion of surviving patients were assumed to receive a single course of subsequent therapy. The dosing regimens of each subsequent therapy are shown in Table 44, and the corresponding drug acquisition costs per cycle are shown in Table 45. The treatment administration unit costs associated with each subsequent therapy are shown in Table 46 and for pre-treatments in Table 47 and do not include vial sharing. Clinical adviser opinion informed treatment administration details and frequency of use (Table 48). The per-cycle drug acquisition and treatment administration costs of each subsequent therapy were multiplied by the estimated duration (Table 49) and proportion of patients receiving each subsequent therapy to calculate the average total subsequent therapy cost per patient as DKK 58,041 for patients treated with Onureg and DKK 86,334 for patients receiving no active therapy (Table 50). This total average cost was applied as a one-time cost in the model at the cycle when surviving patients transitioned from the RFS health state to relapse. A scenario analysis was conducted to evaluate the exclusion of subsequent therapy costs.

Table 44. Subsequent therapy drug dosing schedules

Components	Low-dose cytarabine	Azacitidine injection	Decitabine	3+7: daunorubicin	3+7: cytarabine
Dose	20 mg	75 mg/m^2	20 mg/m^2	60 mg/m^2	200 mg/m^2
Dosing	Fixed	BSA[a]	BSA[a]	BSA[a]	BSA[a]
Schedule	Days 1-10, every 12 hours	Days 1-7	Days 1-5	Days 1-3	Days 1-7
Route	Subcutaneous	Subcutaneous	Intravenous	Intravenous	Intravenous
Number of doses per cycle	20	7	5	3	7
Cycle length	28 days	28 days	28 days	28 days	28 days
Total dose per administration	20 mg	139 mg	37 mg	111 mg	371 mg
Total dose per cycle	400 mg	973 mg	185 mg	334 mg	2,595 mg

BSA = body surface area.

[a] Mean height (166.26 cm) and weight (74.41 kg) from QUAZAR AML-001 CSR (Table 14.1.5.1.1).[114] BSA calculated using Mosteller formula: ([height (cm) × weight (kg)] ÷ 3,600)$^{1/2}$.

Sources: Low-dose cytarabine,[27] azacitidine injection,[148] decitabine,[149] 3+7 daunorubicin and cytarabine.[150]

Table 45. Subsequent therapy drug acquisition costs per cycle

Components	Low-dose cytarabine	Azacitidine injection	Decitabine	3+7: daunorubicin	3+7: cytarabine
Unit strength	1000 mg	100 mg	50 mg	20 mg	1000 mg
Unit description	Vial	Vial	Vial	Vial	Vial
Unit list price	150.00	2,326.00	8,527.86	698.55	150.00
Discount on list price	0%	0%	0%	0%	0%
Number of doses per unit: no vial sharing	1.00	2.00	1.00	6.00	1.00
Cost per cycle	3,000.00	32,568.90	42,639.30	12,573.90	1,050.00

Sources: Unit costs informed by pharmacy purchasing costs from Laegemiddelstyrelsen (Danish Medicine Agency)[147]

Table 46. Subsequent therapy treatment administration unit costs

Component	Unit cost	Description	Sources
Chemotherapy administration fees: High Dose Chemotherapy (Applied per cycle)[a]	3488.41	DRG Administration of high / low dose chemotherapy	Sundhedsdatastyrelsen, DRG Tariffs 2021 (DRG17MA98)

[a] Chemotherapy administration fee includes patient travel and patient cost per visit in the base case setting.

Table 47. Premedication administration unit costs

Premedications	Cost per day	Regimen	Daily dose (mg)	Unit costs	Unit size (mg)	Sources
Allopurinol	0.30	300 mg taken orally daily	300.00	0.10	100.00	Laegemiddelstyrelsen (Danish Medicines Agency), Apotekets indkøbspris, Allopurinol
Ondansetron	24.00	8 mg taken orally every 12 hours on days 1-5	16.00	30.00	20.00	Laegemiddelstyrelsen (Danish Medicines Agency), Apotekets indkøbspris, Ondansetron
Dexamethasone	1.51	0.5 mg taken orally every 12 hours	1.00	6.05	4.00	Laegemiddelstyrelsen (Danish Medicines Agency), Apotekets indkøbspris, Dexamethasone

Table 48. Subsequent therapy treatment administration frequency

Components	Low-dose cytarabine	Azacitidine injection	Decitabine	3+7: daunorubicin
Chemotherapy administration fees: High Dose Chemotherapy (Applied per cycle)	4	6	4	2
Days of premedication per cycle	**Low-dose cytarabine**	**Azacitidine injection**	**Decitabine**	**3+7: daunorubicin**
Allopurinol	28	28	28	14
Ondansetron	0	7	5	7
Dexamethasone	0	0	0	7

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IV = intravenous; SC = subcutaneous.

Table 49. Subsequent therapy costs per cycle and duration of treatment

Components	Low-dose cytarabine	Azacitidine injection	Decitabine	3+7: daunorubicin + cytarabine
Drug cost per cycle	3000.00	32,568.90	42,639.30	13,623.90
Administration cost per cycle	13,962.02	21,106.83	14,082.02	7,159.60
Number of cycles	4	6	4	2

Sources for duration of subsequent therapy: low-dose cytarabine, Alberta Health Services 2019[152] due to no number of cycles shown in EMA SMPC; All other cycles are based on maximum / minimum number of cycles as shown in EMA SMPC. Some

Table 50. Total subsequent therapy costs

Maintenance treatment	Average subsequent therapy cost per patient
Onureg	58,040.55
No active therapy	86,333.96

8.5.6 Haematopoietic stem cell transplantation costs

Costs related to HSCT were applied to the proportion of patients estimated to undergo an HSCT procedure. Although HSCT was considered as a subsequent line of therapy (i.e., under the relapse health state), the cost of DKK 659,974 was applied in the first model cycle to ensure full capture. This value reflected the cost per procedure based on DRG26MP22 (Allogen stamcelletransplantation) code sourced from Danish national sources.[144]

8.5.7 End-of-life (terminal care) costs

The model considered the cost of terminal care to account for the increased cost of care during the final months of life for patients with cancer. The cost was applied as a one-time cost of DKK 43,901 in the cycle when death occurred. The cost is estimated based on the number of days a patient is expected to remain in hospital. A patient, on average, is assumed to stay in hospital for 14 days.[144]

8.6 Results

8.6.1 Model assumptions

Several assumptions, as described in the previous sections, were required in the model; these are summarised in Table 51. These assumptions are in line with previous economic models in AML.

Table 51. Model assumptions for the base case and rationale

Assumption	Rationale/support
Patient data were aggregated and may contain a heterogenous patient population (e.g., patients are not stratified based on CR vs. CRi at enrolment or consolidation vs. no consolidation).	Patient population is considered as 1 cohort because the survival curves consider data from all patients. Onureg showed a similar OS and RFS benefit regardless of the use of consolidation therapy after induction.
No active therapy was the most appropriate comparator to Onureg.	There are no therapies approved for maintenance treatment of AML in Denmark.
Second CR was not captured as a health state.	Utilities, costs, and transition data are not available to inform second CR.

Assumption	Rationale/support
All patients in the same health state have the same utility value regardless of treatment arm.	Patients within the same health state are expected to have the same utility independent of treatment assignment.
A proportion of patients may receive 1 line of subsequent therapy. Subsequent therapies were assumed to have no impact on outcomes (e.g., survival, quality of life).	Efficacy of subsequent therapy was not considered, only costs. It was assumed that efficacy for subsequent therapies was captured in the existing OS curves for both treatment arms.
HSCT was considered as an event rather than a health state.	QUAZAR AML-001 trial required patients to be ineligible for HSCT at enrolment. Data to inform second CR resulting from HSCT were not available.
In the scenario analysis that included dose extension, only the costs were considered; the timing of dose extension was not considered.	Dose extension was included within the mean time on treatment reported from QUAZAR AML-001.
BSC was the same regardless of treatment status.	BSC was assumed to represent standard ongoing disease management for patients with AML.

AML = acute myeloid leukaemia; BSC = best supportive care; CR = complete remission; CRi = complete remission with incomplete blood count recovery; HSCT = haematopoietic stem cell transplantation; OS = overall survival; RFS = relapse-free survival.

8.6.2 Base-case overview

Table 52 provides an overview of the key base-case model settings.

Table 52. Base-case overview

Model parameters	Base case deterministic value	Sources/notes
Perspective	Limited societal perspective	Based on Danish guidelines
Time horizon	Lifetime (30 years)	Based on Danish guidelines
Utilities	Treatment-specific utility values	To account for adverse event disutilities
Cycle length	28 days	To reflect treatment cycles based on SmPC
Include relative dose intensity	Yes	To account for delayed and missed doses in the treatment period
Include patient travel and patient cost per visit	Yes	Based on Danish guidelines
Include Disutilities Associated with AEs	No	These are not included in the model base case, as treatment specific utilities are used
Weight	74.41 kg	QUAZAR AML-001 CSR (Table 14.1.5.1.1)[114]
Body surface area	1.85 m^2	QUAZAR AML-001 CSR (Table 14.1.5.1.1)[114]
OS curves	Time-varying splines, 1 internal knot odds linear predictor	Phase 3 QUAZAR AML-001 trial, September 2020 data cut
RFS curves	Time-varying splines, 1 internal knot odds linear predictor	Phase 3 QUAZAR AML-001 trial, September 2020 data cut
Apply no active therapy cap	Yes	Based on assessment of clinical plausibility of survival extrapolations
Apply Gen Population cap	Yes	Based on assessment of clinical plausibility of survival extrapolations
Time on treatment	Modelled directly based on KM curves	Phase 3 QUAZAR AML-001 trial

CSR = clinical study report; KM = Kaplan-Meier; OS = overall survival; RFS = relapse-free survival; SmPC = summary of product characteristics.

8.6.3 Base-case results

Table 53 presents the base-case results.

Table 53. Base-case results

Per patient	Onureg	BSC	Difference
Life-years gained			
Total life-years gained	4.09	3.15	0.94
Life-years gained (total RFS)	2.50	1.66	0.84
Life-years gained (RFS: on treatment)	1.57	0.00	1.57
Life-years gained (RFS: off treatment)	0.93	1.66	−0.73
Life-years gained (relapse)	1.59	1.50	0.10
QALYs			
Total QALYs	2.97	2.20	0.76
QALYs (total RFS)	2.17	1.46	0.71
QALYs (RFS: on treatment)	1.39	0.00	1.39
QALYs (RFS: off treatment)	0.78	1.46	-0.68
QALYs (relapse)	0.80	0.75	0.05
QALYs (adverse reactions)	0.0000	0.0000	0.00
QALYs (HSCT disutility)	−0.0010	−0.0022	0.0012
Costs			
Total costs	2,258,923	415,042	1,843,881
Drug costs	1,809,844	0	1,809,844
RFS: on treatment			
Treatment administration costs	2,512	0	2,512
Disease management costs	145,618	0	145,618
Adverse event costs	1,013	784	229
RFS: off treatment			
Disease management costs	72,280	128,892	-56,612
Relapse			
Disease management costs	131,841	125,798	6,043
Subsequent therapy costs	15,679	29,214	-13,535
SCT costs	41,578	90,416	-48,838
End-of-life costs	38,557	39,938	-1,380
Incremental results	Intervention vs. comparator		
ICER (per QALY)	2,419,302		

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BSC = best supportive care; HSCT = haematopoietic stem cell transplantation; ICER = incremental cost-effectiveness ratio; QALY = quality-adjusted life-year; RFS = relapse-free survival; SCT = stem cell transplantation.

8.7 Sensitivity analyses

8.7.1 Deterministic sensitivity analyses

Table 54 presents the results of the deterministic sensitivity analyses. All parameters in the one-way sensitivity analysis were varied by 20%.

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Table 54. One-way sensitivity analyses results

	Low Value ICER (DKK)	High Value ICER (QALYs)	ICER (DKK/QALY)
Base case	-		2,419,302
Health state utility - RFS on treatment NAT	1,749,486	3,082,181	1,332,695
Health state utility - Relapse Onureg	3,058,068	2,001,277	1,056,791
Health state utility - RFS on treatment Onureg	2,959,419	1,970,722	988,696
Health state utility - Relapse NAT	2,022,637	3,009,505	986,868
Health state utility - RFS off treatment Onureg	3,043,837	2,144,594	899,243
Discount rate - Effects	2,335,136	2,502,790	167,654
Disease management costs - RFS on treatment - Onureg	2,381,090	2,457,514	76,424
Disease management costs - Relapse - Onureg	2,384,705	2,453,899	69,194
Disease management costs - RFS off treatment - No Active Therapy	2,453,125	2,385,479	67,646
Disease management costs - Relapse - No Active Therapy	2,452,313	2,386,291	66,022
% of Patients Receiving SCT - No Active Therapy	2,444,443	2,394,190	50,253
Discount rate - Costs	2,442,492	2,396,916	45,576
Disease management costs - RFS off treatment - Onureg	2,400,335	2,438,269	37,934
Cost of stem cell transplant (SCT) procedure	2,432,118	2,406,486	25,632
% of Patients Receiving SCT - Onureg	2,407,750	2,430,860	23,109
Subsequent therapy costs - No Active Therapy	2,426,968	2,411,636	15,332
AE disutility - No Active Therapy	2,404,628	2,419,302	14,674
Subsequent therapy costs - Onureg	2,415,187	2,423,416	8,229
Time horizon	2,426,687	2,419,115	7,572
Total disutility per transplant procedure	2,420,058	2,418,546	1,513
Per cycle treatment administration cost - Onureg	2,418,643	2,419,961	1,318
Cost of end of life care (one-time cost)	2,419,664	2,418,940	725
Cost to treat AEs - Onureg	2,419,036	2,419,568	532
Cost to treat AEs - No Active Therapy	2,419,508	2,419,096	411

AE = adverse event; DKK = Danish krone; ICER = incremental cost-effectiveness ratio; QALY = quality-adjusted life-year; RFS = relapse-free survival; SCT = stem cell transplant.

The tornado diagram is presented in Figure 31. As shown, the parameters which have the most impact on the ICER are mean time on treatment and discount rate on outcomes.

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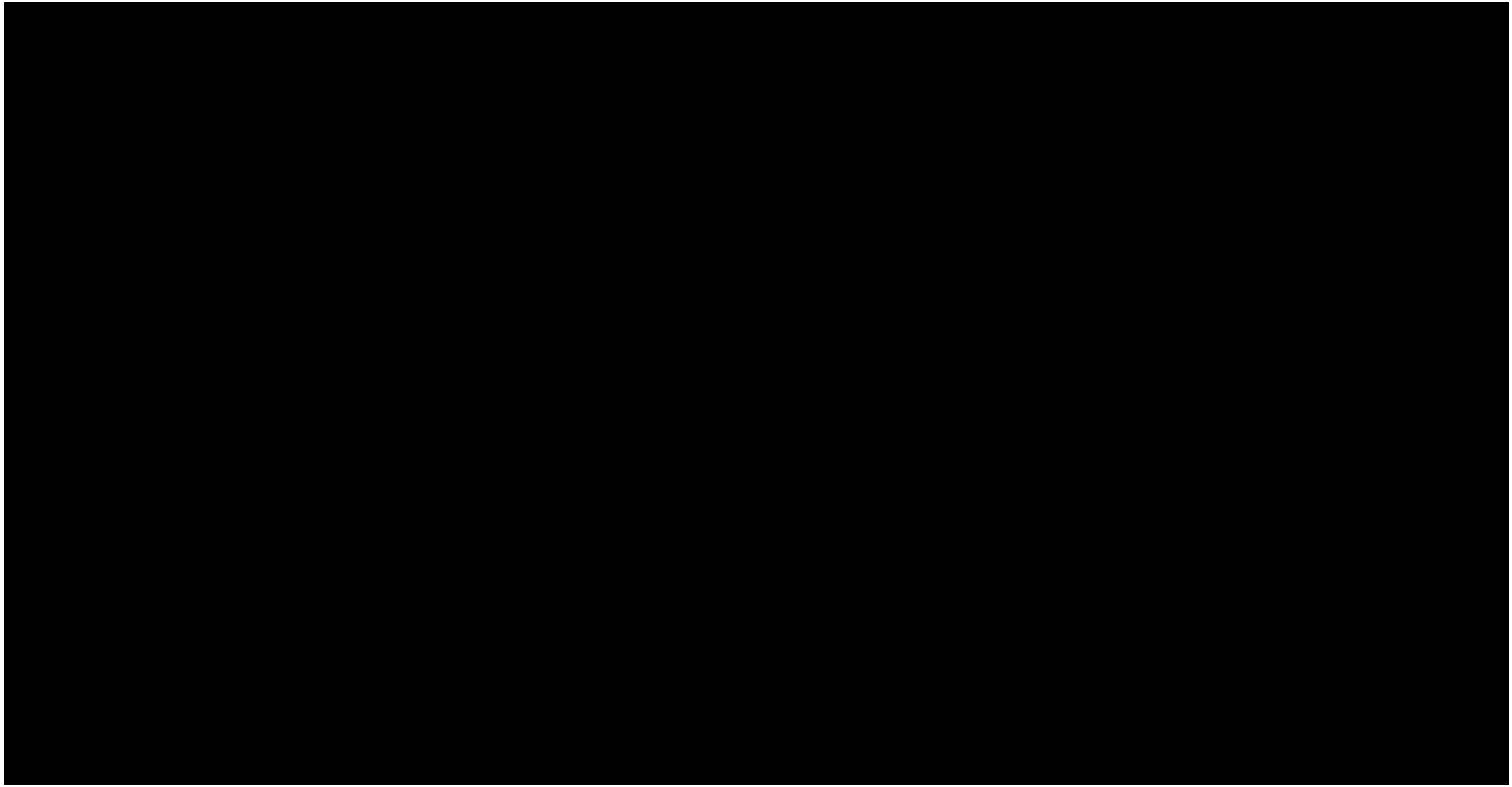

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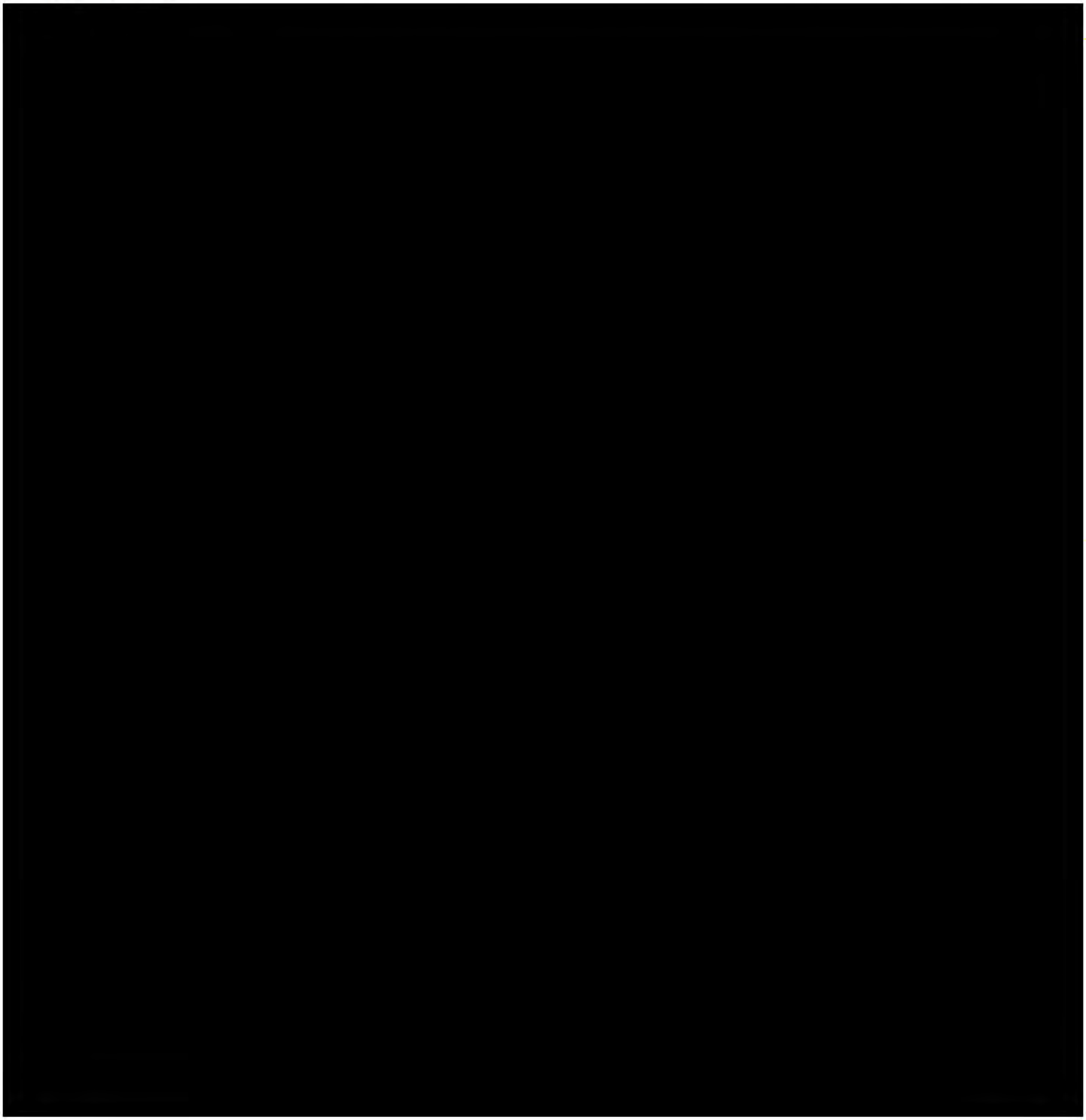
8.7.2 Probabilistic sensitivity analyses

Figure 32 presents the scatter plot of incremental costs versus incremental QALYs for Onureg versus no active therapy from 1,000 iterations. All iterations were in the northeast quadrant, indicating that Onureg was more costly and more effective than no active therapy in 100% of the probabilistic iterations. Figure 33 presents the cost-effectiveness acceptability curve (CEAC), showing the probability of being the most cost-effective therapy at different willingness-to-pay thresholds.



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CEAC = cost-effectiveness acceptability curve.

8.7.3 Scenario analyses

Results of the various scenario analyses described above are presented in Table 55. As can be seen from the table the majority of scenario analyses had minimal impact on the ICER.

Table 55. Scenario analyses results

	Incremental LY	Incremental QALY	Incremental Costs	ICER
Base case	0.94	0.76	1,843,881	2,419,302
20-year time horizon	0.92	0.75	1,842,265	2,460,821
35-year time horizon	0.94	0.76	1,843,890	2,419,122
No discounting	1.15	0.93	1,939,248	2,096,456
3% discount	0.96	0.78	1,856,441	2,375,319
Utility: Stein 2019	0.94	0.77	1,843,881	2,384,415
Utility: Tremblay 2018	0.94	0.70	1,843,881	2,631,552
Utility: pooled values	0.94	0.78	1,843,881	2,358,925
Include patient travel and patient cost per visit to all resource use elements	0.94	0.76	1,844,945	2,420,698
Exclude SCT costs and disutility	0.94	0.76	1,892,719	2,487,269
Exclude subsequent therapy costs	0.94	0.76	1,857,416	2,437,060
Exclude patient travel and patient costs	0.94	0.76	1,840,777	2,415,230
Vial sharing: Yes	0.94	0.76	1,846,210	2,422,358
Time on treatment: Until relapse or death: Onureg	0.94	0.76	2,906,902	3,814,060
Time on treatment - Onureg: July 2019 Datacut	0.94	0.76	1,686,417	2,212,698
Joint curves assuming proportional hazards to model OS	1.06	0.82	1,853,978	2,256,318
Dose extension: Yes	0.94	0.76	1,877,582	2,463,519
Relative Dose intensity: No	0.94	0.76	2,053,952	2,694,930

AE = adverse event; ICER = incremental cost-effectiveness ratio; LY = life-year; QALY = quality-adjusted life-year; SCT = stem cell transplant.

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9 Budget impact analysis

The impact of introducing Onureg in the treatment landscape of AML was estimated using a 5-year budget-impact model.

9.1 Market share

This section provides an overview of Onureg uptake. Table 56 shows uptake figures used in the budget-impact analysis.

Table 56. Market shares

Situation without Onureg					
	Year 1	**Year 2**	**Year 3**	**Year 4**	**Year 5**
Onureg	0%	0%	0%	0%	0%
No Active Therapy	100%	100%	100%	100%	100%
Situation with Onureg					
Onureg	50%	70%	80%	80%	80%
No Active Therapy	50%	30%	20%	20%	20%

Table 57 shows the resulting number of patients based on the uptake shown above. Please note that the number of patients in the 'Situation with Onureg' is higher, due to life-extension associated with Onureg therapy.

Table 57. Number of patients based on market share

Situation without Onureg					
	Year 1	**Year 2**	**Year 3**	**Year 4**	**Year 5**
Onureg	0	0	0	0	0
No Active Therapy	44	69	85	98	108
Situation with Onureg					
Onureg	22	53	79	92	103
No Active Therapy	22	21	17	20	22

9.2 Budget impact

9.2.1.1 Base-case analysis

The introduction of Onureg therapy leads to an increase in budgets over all 5 years compared with a situation without Onureg therapy (see Table 58). In accordance with the Danish Medicines Council's methodological guidance, the budget impact results reflect the healthcare payer perspective and therefore do not include the patient and transport costs.

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Table 58. Base-case results – budget impact

Budget years	Year 1	Year 2	Year 3	Year 4	Year 5
Situation without Onureg	DKK 8,940,396	DKK 9,986,452	DKK 10,441,191	DKK 10,711,139	DKK 10,891,601
Situation with Onureg	DKK 26,391,012	DKK 41,343,263	DKK 51,340,453	DKK 56,060,137	DKK 58,345,495
Budget impact	DKK 17,450,615	DKK 31,356,811	DKK 40,899,262	DKK 45,348,998	DKK 47,453,894

DKK = Danish krone.

10 Discussion on the submitted documentation

10.1 Interpretations and conclusions of the clinical evidence

The approval of Onureg is based on 1 pivotal trial (QUAZAR AML-001) that enrolled 472 patients with AML in first remission after induction chemotherapy who were not candidates for HSCT.[18,19] This was a head-to-head trial comparing Onureg with close monitoring, which is the standard of care in this maintenance setting in Denmark, and the treatment pathway in the trial reflects that in Denmark. Furthermore, the baseline characteristics of patients in QUAZAR AML-001 are expected to reflect those of patients seen in Danish clinical practice for AML who are eligible for Onureg.

In QUAZAR AML-001, Onureg demonstrated a clinically and statistically significant improvement in overall OS compared with placebo. Median OS was 24.7 months (95% CI, 18.7-30.5 months) for patients treated with Onureg versus 14.8 months (95% CI, 11.7-17.6 months) for those treated with placebo (HR, 0.69; 95% CI, 0.55-0.86; $P < 0.001$).[18,19] [redacted] These results were further supported by the secondary outcomes of RFS, time to relapse, and HRQoL as assessed by the FACIT-Fatigue and the EQ-5D-3L.[15]

10.1.1 Strengths and limitations of the clinical evidence

QUAZAR AML-001 was a phase 3, international, multicentre, randomised, double-blind, placebo-controlled study. Risk of bias assessment suggests that it was well-conducted with a low risk of bias. Although the trial was placebo-controlled, this reflects the current standard of care in Denmark, where after induction (with or without consolidation) therapy, patients who are not suitable for HSCT are carefully monitored until relapse. Therefore, the trial results provide direct comparative data versus standard of care, and no indirect treatment comparison was required. The primary outcome in the trial was OS, and the results were sufficiently mature at the time of database lock to detect a clinically and statistically meaningful difference in survival; therefore, surrogate outcomes only provide supportive data. It is important to note differences in outcome definition between the QUAZAR AML-001 trials and other trials in AML. QUAZAR AML-001 was designed to assess the efficacy of Onureg in the maintenance setting, and both OS and RFS were measured from the time of randomisation (after achieving CR with induction therapy).[15] In contrast, some trials have measured survival from the time of induction or at the time CR was reported. Trials such as RATIFY were

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not designed to independently assess the effect of maintenance therapy.[55] These differences in study design and time of outcome measurements mean that the trial results cannot naively be compared.

10.2 Interpretation and conclusions of economic evidence

This economic evaluation considered the cost-effectiveness of Onureg plus BSC compared with no active therapy plus BSC in the maintenance treatment of adult patients with AML who have achieved CR/CRi and are ineligible for HSCT in Denmark. Compared with no active therapy, treatment with Onureg was more costly (DKK 1,843,881) and more effective (0.78 QALYs), with an ICER of DKK 2,419,302 per QALY gained. The probabilistic results were aligned with the deterministic results. Overall, Onureg is estimated to result in more life-years and QALYs and to increase the time patients spend in the RFS state.

10.2.1 Strengths and limitations of the economic evaluation

A key strength of this economic evaluation was the use of robust and mature clinical evidence from the September 2020 database cutoff of the QUAZAR AML-001 trial to inform survival. A second strength was the use of existing evidence to support model development and parameterisation. An SLR of previous cost-effectiveness models was conducted to inform the design of the model. This ensured that previously noted limitations were addressed in the current model, wherever possible. An SLR was also conducted to inform utility values for the model. Finally, resource use and costing were informed by Danish data and reflect Danish clinical practice. The model concept, structure, assumptions, and inputs were reviewed by a leading Danish haematologist who actively treats AML to ensure accuracy.

A common limitation in lifetime models is the assumption that the defined parametric functions accurately estimate the long-term survival of patients when only short-term clinical data are available. The KM curves from QUAZAR AML-001 (September 2020 data cut) that informed the OS and RFS extrapolations in the model were mature, which helps to mitigate some of this uncertainty. Furthermore, care was taken to select a modelling approach and curves that balanced good statistical fit with clinical plausibility, and extensive analyses of parametric extrapolations were conducted to assess any uncertainty in extrapolation (see Appendix G).

11 List of experts

Because of impartiality concerns, no clinicians have been consulted formally “for the record” for this application submission. Input has been during informal discussions with clinical experts in Denmark. The Medicines Council is encouraged to validate the clinical input provided in this application with the expert committee.

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Application for the assessment of oral azacitidine (Onureg®) as maintenance therapy for patients with acute myeloid leukaemia

Appendices

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Appendix A. Literature search for efficacy and safety of intervention and comparator(s)

A systematic literature review (SLR) of randomised controlled trials (RCTs) was conducted to identify the comparative efficacy and safety data of maintenance treatments for adults (aged ≥ 18 years) with acute myeloid leukaemia (AML) who have achieved complete remission (CR) or complete remission with incomplete platelet recovery (CRi) and are ineligible for stem cell transplant (SCT). The SLR addressed the following research question: What is the clinical trial evidence for the efficacy and safety of AML maintenance treatments?

A protocol was developed which included the PICOS (Population, Intervention, Comparators, Outcomes, Study design) criteria and methodology. The clinical evidence SLR protocol was designed and reported in accordance with guidelines from the PROSPERO international prospective register of systematic reviews.[1] The literature search was developed using an iterative process by an experienced medical information specialist in consultation with the review team. The search was peer-reviewed independently prior to execution by a second information specialist using the PRESS Checklist.[2,3]

An electronic database search was originally performed on 18 January 2020 and updated on 19 February 2021. Details for the databases searched in the original and updated SLRs are presented in Table A-1 and Table A-2. The database search strategies (Table A-7 and Table A-8) were composed of 3 sets of date limits, with each date limit applying to a specific study design:

- For randomised controlled trials, search results were limited to 2005 to present.
- For review articles such as systematic literature reviews, meta-analyses, and/or network meta-analyses, search results were limited to 2015 to present.
- For conference abstracts, search results were limited to 2018 to present.

The above date of publication limits were applied primarily for 2 reasons: 1) maintenance therapies for the population of interest were deemed to be a more recent introduction to the AML space, with any relevant studies predating 2005 to be very unlikely and 2) to focus the search (i.e., control the volume of search results).

Table A-1. Bibliographic databases included in the literature search (original review)

Database	Platform	Relevant period for the search	Date of search completion
Embase	Ovid	2015 to current	18 January 2020
MEDLINE[a]	Ovid	2015 to current	18 January 2020
Cochrane Database of Systematic Reviews	Ovid EBMR	2015 to current	18 January 2020
Database of Abstracts of Reviews of Effects	Ovid EBMR	2015 to current	18 January 2020
Health Technology Assessment Database	Ovid EBMR	2015 to current	18 January 2020
Cochrane Central Register of Controlled Trials	Ovid EBMR	2015 to current	18 January 2020

EBMR = Evidence-Based Medicine Reviews.

[a] Including Epub ahead of print and in-process & other non-indexed citations.

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Table A-2. Bibliographic databases included in the literature search (review update)

Database	Platform	Relevant period for the search	Date of search completion
Embase	Ovid	18 January 2020 to current	19 February 2021
MEDLINE[a]	Ovid	18 January 2020 to current	19 February 2021
Cochrane Database of Systematic Reviews	Ovid EBMR	18 January 2020 to current	19 February 2021
Cochrane Central Register of Controlled Trials	Ovid EBMR	18 January 2020 to current	19 February 2021

EBMR = Evidence-Based Medicine Reviews.

Note: Database of Abstracts of Reviews of Effects and the Health Technology Assessment Database had been discontinued from Ovid EBMR.

[a] Including Epub ahead of print and in-process & other non-indexed citations.

A supplementary search of clinicaltrials.gov and the Food and Drug Administration (FDA) database was performed on 2-4 March 2020 and 15 March 2021 for the original and updated reviews, respectively (Table A-3 and Table A-4).

Table A-3. Registers included in the search (original review)

Database	Platform	Search strategy	Date of search
US NIH registry & results database	https://clinicaltrials.gov	AML Acute myeloid leukemia	2-4 March 2020
FDA	https://www.fda.gov/	Manual search	2-4 March 2020

AML = acute myeloid leukaemia; FDA = Food and Drug Administration; NIH = National Institutes of Health; US = United States.

Table A-4. Registers included in the search (review update)

Database	Platform	Search strategy	Date of search
US NIH registry & results database	https://clinicaltrials.gov	AML Acute myeloid leukemia	15 March 2021
FDA	https://www.fda.gov/	Manual search	15 March 2021
EU Clinical Trials Register	https://www.clinicaltrialsregister.eu/ctr-search/search	AML and drug terms	14 June 2021

AML = acute myeloid leukaemia; EU = European Union; FDA = Food and Drug Administration; NIH = National Institutes of Health; US = United States.

Conference abstracts published in 2018 or 2019 were searched in the original review, as presented in Table A-5. In addition, late breaking abstracts from these conferences were searched on 23-28 April 2020. Abstracts published in 2020 or 2021 for the same conferences were searched in the updated review on 10 March 2021. In addition to the registry and conference abstract searches, the bibliographies of relevant systematic review articles identified during the database screening were also reviewed to obtain any additional relevant references. American Society of Clinical Oncology (ASCO) conference abstracts for the years 2018 and 2019, plus the ASCO meeting date of 29-31 May 2020 were captured by the Embase search.

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Table A-5. Conference material included in the literature search (original and updated reviews)

Conference	Source of abstracts	Search strategy	Words/terms searched
ASH (Meeting dates 2019 and 2020)	https://www.hematology.org/	Search by individual words in the congress material	▪ Acute myeloid leukemia ▪ Acute myelogenous leukemia ▪ AML ▪ Acute myeloid leukaemia ▪ Acute myelogenous leukaemia
EBMT (Meeting dates 2018, 2019, 2020, and 2021)	https://www.ebmt.org/	Search by individual words in the congress material	▪ Acute myeloid leukemia ▪ Acute myelogenous leukemia ▪ AML ▪ Acute myeloid leukaemia ▪ Acute myelogenous leukaemia
EHA (Meeting date 2019)	https://ehaweb.org/	Search by individual words in the congress material	▪ Acute myeloid leukemia ▪ Acute myelogenous leukemia ▪ AML ▪ Acute myeloid leukaemia ▪ Acute myelogenous leukaemia
SOHO (Meeting date 2018, 2019, and 2020)	https://www.sohoonline.org/	Search by individual words in the congress material	▪ Acute myeloid leukemia ▪ Acute myelogenous leukemia ▪ AML ▪ Acute myeloid leukaemia ▪ Acute myelogenous leukaemia

ASH = American Society of Hematology; EBMT = European Society for Blood and Marrow Transplantation; EHA = European Hematology Association; SOHO = Society of Hematologic Oncology.

Appendix A.1 Study selection

Eligibility criteria were established using the PICOS framework (Table A-6). The SLR included RCTs of adults (≥ 18 years) with de novo AML or AML secondary to prior myelodysplastic disease who are in CR or CRi receiving maintenance therapy. Maintenance therapy was defined as treatment with lower intensity than, and administered after induction therapy, with or without consolidation.[4] The initial SLR, conducted for all markets and therefore included comparators not relevant to Denmark. Therefore an additional screening step was used to narrow the included articles down to relevant intervention and comparators in the maintenance setting in Denmark – Onureg and placebo.

Table A-6. Inclusion and exclusion criteria

Item	Inclusion criteria	Exclusion criteria
Population	▪ Male and female adults (≥ 18 years) ▪ Histologically confirmed de novo AML or AML secondary to prior myelodysplastic disease – Receiving maintenance therapy after first CR/CRi (following induction with intensive chemo (with or without consolidation) in 1L) – SCT ineligible at CR/CRi ▪ Intermediate/poor cytogenetic risk or favourable-risk cytogenetics	▪ Patients < 18 years ▪ Relapsed or refractory AML ▪ Prior bone marrow or stem cell transplant ▪ Ineligible for intensive induction chemotherapy at 1L ▪ Achieved CR/CRi following therapy with hypomethylating agents or prior therapy with hypomethylating agents for MDS within 4 months of developing AML
Intervention	▪ Onureg	
Comparators	▪ Best supportive care (BSC, e.g., hydroxyurea) ▪ Azacitidine (IV, SC, Oral) ▪ Decitabine ▪ LDAC (Cytarabine) ▪ Idarubicin	▪ SCT ▪ High-intensity therapies: – "7+3" – 7 + 3 + midostaurin

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Item	Inclusion criteria	Exclusion criteria
	▪ Daunorubicin ▪ Gemtuzumab ozogamicin ▪ Venetoclax + decitabine/azacitidine/cytarabine ▪ Glasdegib ▪ Enasidenib (IDH2) ▪ Ivosidenib (IDH1) ▪ Sorafenib (FLT3) ▪ Midostaurin (FLT3) ▪ Immunotherapies (BCG vaccination, IFN-a, IL-2) ▪ 6-Mercaptopurine ▪ Ceplene + IL-2 ▪ Tipifarnib ▪ Dasatinib ▪ Lenalidomide ▪ Quizartinib ▪ rhIL-11 ▪ Lomustine ▪ Methotrexate ▪ Norethandrolone ▪ OCV-501 (WT1 peptide vaccine) ▪ Lirilumab ▪ All-trans retinoic acid (ATRA) ▪ Histamine dihydrochloride and IL-2 ▪ Thioguanine, cyclophosphamide ▪ FLT3L ▪ Nivolumab	– 7 + 3 + gemtuzumab ozogamicin – 7 + 3 + cladribine – 7 + 3 + mitoxantrone – HiDAC (Cytarabine) – HiDAC + midostaurin – Vyxeos (daunorubicin + cytarabine) ▪ Therapies for R/R AML: – FLAG-IDA, MEC, gilteritinib
Outcomes	▪ Effectiveness: – Overall Survival – Relapse-free survival/Event-free survival/Disease-free survival/Progression-free survival – Time to relapse from CR/CRi – Time to discontinuation from treatment ▪ Safety/tolerability: – Any adverse events (e.g., Neutropenia, Infections) – Treatment-related adverse events – Serious adverse events – Withdrawals due to adverse events – Patient-reported outcomes (FACIT-Fatigue, EQ-5D)	▪ Studies that do not report any relevant outcomes
Study design	▪ RCTs in any country (phases II, III & II/III) ▪ Systematic reviews and meta-analyses of RCTs (included at the title and abstract stage only)	▪ Non-randomised, single-arm, or observational studies ▪ Open-label extension phases of RCTs ▪ Pre-clinical studies, case reports, expert opinion articles, letters, narrative (non-systematic) reviews ▪ Phase 1 ▪ Pilot studies
Language	▪ Articles in English	▪ All non-English articles
Additional screen for relevant intervention and comparator	▪ Onureg in the maintenance setting ▪ Placebo in the maintenance setting	▪ Any other treatment for AML

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1L = first line; AML = acute myeloid leukaemia; BCG = Bacille Calmette-Guérin; BSC = best supportive care; CR = complete remission; CRi = complete remission with incomplete platelet recovery; EQ-5D = EuroQol-5 Dimension; FACIT = Functional Assessment of Chronic Illness Therapy; FLAG-IDA = fludarabine-cytarabine-filgrastim-idarubicin; FLT3(L) = fms-like tyrosine kinase 3 (ligand); HiDAC = High Dose Ara-C; IDH 1(2) = isocitrate dehydrogenase 1(2); IFN-a = interferon alpha; IL-2(11) = interleukin-2(11); IV = intravenous; LDAC = Low Dose Ara-C; MDS = myelodysplastic syndrome; MEC = mitoxantrone, etoposide, and cytarabine; PICOS = Population, Intervention, Comparators, Outcomes, Study design; RCT = randomised controlled trial; R/R = relapse/refractory; SC = subcutaneous; SCT = stem cell transplant; WT1 = Wilms tumour gene 1.

Note: Bibliographies of relevant systematic reviews were reviewed to obtain any additional relevant references; however, the review articles themselves were not included as per the PICOS criteria.

Two reviewers independently reviewed the study records, article titles, and abstracts identified in the literature search to assess study eligibility. Citations considered to describe potentially eligible articles were independently reviewed in full-text form for formal inclusion in the final review. Disagreements between reviewers were resolved during a consensus meeting. Any discrepancies between the 2 reviewers that could not be resolved by consensus were referred to and resolved by a third reviewer. Screening was performed in DistillerSR (Evidence Partners, Ontario, Canada) at both the title and abstract screening phase and full-text screening phase.

Appendix A.2 Search strategy

Broad and inclusive database searches were developed that did not include restrictive search terms for the intervention and comparators (Table A-7 and Table A-8). The searches were carried out in Ovid platform with all database searches combined in the 1 search strategy.

Table A-7. Ovid search strategy (original review)

No.	Query	Results
1	exp Leukemia, Myeloid, Acute/	93,638
2	(acute adj2 myelo* adj2 leu#?emi*).tw,kf.	118,115
3	(acute adj2 (nonlympho* or non-lympho*) adj2 leu#?emi*).tw,kf.	6,852
4	(acute adj2 granulocytic adj2 leu#?emi*).tw,kf.	338
5	((AML or ANLL) and (leu#?emi* or myelo* or nonlympho* or non-lympho*)).tw,kf.	88,638
6	(AML or ANLL).tw,kf. and exp Leukemia, Myeloid/	43,459
7	(acute adj2 basophilic adj2 leu#?emi*).tw,kf.	135
8	(acute adj2 eosinophilic adj2 leu#?emi*).tw,kf.	70
9	(acute adj2 erythroblastic adj2 leu#?emi*).tw,kf.	50
10	(erythroleu#?emi* or erythro-leu#?emi* or erythr?emic myelosis or diguglielmo* or di guglielmo*).tw,kf.	13,447
11	((mast-cell* or mastcell*) adj2 leu#?emia*).tw,kf.	965
12	((megakaryocytic or mega-karyocytic) adj2 leu#?emi*).tw,kf.	858
13	((megakaryoblastic or mega-karyoblastic) adj2 leu#?emi*).tw,kf.	2,279
14	(acute adj2 monoblastic adj2 leu#?emi*).tw,kf.	801
15	(acute adj2 monocytic adj2 leu#?emi*).tw,kf.	2,524
16	(acute adj2 promyelocytic adj2 leu#?emi*).tw,kf.	16,842
17	(acute adj2 progranulocytic adj2 leu#?emi*).tw,kf.	32
18	(Schilling-Type adj1 myelo* adj2 leu#?emi*).tw,kf.	0
19	or/1-18	199,501
20	exp Animals/ not (exp Animals/ and Humans/)	16,978,023
21	19 not 20 [ANIMAL-ONLY REMOVED]	146,307

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No.	Query	Results
22	(comment or editorial or news or newspaper article).pt.	2,024,048
23	(letter not (letter and randomized controlled trial)).pt.	2,159,043
24	21 not (22 or 23) [OPINION PIECES REMOVED]	138,024
25	systematic review.pt.	128,535
26	exp systematic reviews as topic/	27,417
27	meta analysis.pt.	110,543
28	exp meta-analysis as topic/	60,216
29	(meta-analy* or metanaly* or metaanaly* or met analy* or integrative research or integrative review* or integrative overview* or research integration or research overview* or collaborative review*).tw,kf.	432,280
30	(systematic review* or systematic overview* or evidence-based review* or evidence-based overview* or (evidence adj3 (review* or overview*)) or meta-review* or meta-overview* or meta-synthes* or rapid review* or "review of reviews" or umbrella review? or technology assessment* or HTA or HTAs).tw,kf.	534,417
31	exp Technology assessment, biomedical/	25,447
32	(cochrane or health technology assessment or evidence report or systematic reviews).jw.	58,467
33	(network adj (MA or MAs)).tw,kf.	29
34	(NMA or NMAs or MTC or MTCs or MAIC or MAICs).tw,kf.	17,858
35	indirect* compar*.tw,kf.	6,681
36	(indirect treatment* adj1 compar*).tw,kf.	979
37	(mixed treatment* adj1 compar*).tw,kf.	1,550
38	(multiple treatment* adj1 compar*).tw,kf.	438
39	(multi-treatment* adj1 compar*).tw,kf.	11
40	simultaneous* compar*.tw,kf.	2,400
41	mixed comparison?.tw,kf.	132
42	or/25-41	896,206
43	24 and 42 [REVIEWS]	1,238
44	limit 43 to yr="2015-current" [REVIEWS - 5 YEARS]	747
45	(controlled clinical trial or randomized controlled trial or pragmatic clinical trial or equivalence trial).pt.	1,160,850
46	clinical trials as topic/	300,899
47	exp Randomized Controlled Trials as Topic/	313,900
48	(randomi#ed or randomi#ation? or randomly or RCT or placebo*).tw,kf.	3,288,971
49	((singl* or doubl* or trebl* or tripl*) adj (mask* or blind* or dumm*)).tw,kf.	671,217
50	trial.ti.	799,970
51	or/45-50	4,170,516
52	24 and 51 [RCTS]	10,909
53	limit 52 to yr="2005-current" [Limit not valid in DARE; records were retained]	6,560
54	44 or 53 [REVIEWS, TRIALS]	7,044
55	**54 use ppez [MEDLINE RECORDS]**	**2,241**
56	exp acute myeloid leukemia/	93,638
57	acute leukemia/ and myeloid leukemia/	496
58	(acute adj2 myelo* adj2 leu#?emi*).tw,kw.	119,019
59	(acute adj2 (nonlympho* or non-lympho*) adj2 leu#?emi*).tw,kw.	6,881

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No.	Query	Results
60	(acute adj2 granulocytic adj2 leu#?emi*).tw,kw.	605
61	((AML or ANLL) and (leu#?emi* or myelo* or nonlympho* or non-lympho*)).tw,kw.	89,459
62	(AML or ANLL).tw,kw. and exp myeloid leukemia/	43,692
63	(acute adj2 basophilic adj2 leu#?emi*).tw,kw.	135
64	(acute adj2 eosinophilic adj2 leu#?emi*).tw,kw.	70
65	(acute adj2 erythroblastic adj2 leu#?emi*).tw,kw.	49
66	(erythroleu#?emi* or erythro-leu#?emi* or erythr?emic myelosis or diguglielmo* or di guglielmo*).tw,kw.	13,505
67	((mast-cell* or mastcell*) adj2 leu#?emi*).tw,kw.	1,127
68	((megakaryocytic or mega-karyocytic) adj2 leu#?emi*).tw,kw.	872
69	((megakaryoblastic or mega-karyoblastic) adj2 leu#?emi*).tw,kw.	2,296
70	(acute adj2 monoblastic adj2 leu#?emi*).tw,kw.	807
71	(acute adj2 monocytic adj2 leu#?emi*).tw,kw.	2,532
72	(acute adj2 promyelocytic adj2 leu#?emi*).tw,kw.	16,912
73	(acute adj2 progranulocytic adj2 leu#?emi*).tw,kw.	35
74	(Schilling-Type adj2 myelo* adj2 leu#?emi*).tw,kw.	0
75	or/56-74 [AML]	200,805
76	exp animal experimentation/ or exp animal model/ or exp animal experiment/ or nonhuman/ or exp vertebrate/	49,269,157
77	exp human/ or exp human experimentation/ or exp human experiment/	39,281,090
78	76 not 77	9,992,874
79	75 not 78 [ANIMAL-ONLY REMOVED]	187,753
80	editorial.pt.	1,155,948
81	letter.pt. not (letter.pt. and randomized controlled trial/)	2,158,990
82	79 not (80 or 81) [OPINION PIECES REMOVED]	178,465
83	meta-analysis/	289,403
84	"systematic review"/	351,534
85	"meta analysis (topic)"/	41,180
86	"systematic review (topic)"/	24,415
87	(meta-analy* or metanaly* or metaanaly* or met analy* or integrative research or integrative review* or integrative overview* or research integration or research overview* or collaborative review*).tw,kw.	440,872
88	(systematic review* or systematic overview* or evidence-based review* or evidence-based overview* or (evidence adj3 (review* or overview*)) or meta-review* or meta-overview* or meta-synthes* or "review of reviews" or umbrella review? or technology assessment* or HTA or HTAs).tw,kw.	541,237
89	biomedical technology assessment/	24,330
90	(cochrane or health technology assessment or evidence report).jw.	52,052
91	or/83-90	953,024
92	82 and 91 [REVIEWS]	1,967
93	limit 92 to yr="2015-current" [REVIEWS - 5 YR LIMIT]	1,173
94	randomized controlled trial/ or controlled clinical trial/	1,360,398
95	"clinical trial (topic)"/	107,270

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No.	Query	Results
96	exp "controlled clinical trial (topic)"/	180,248
97	(randomi#ed or randomi#ation or randomly or RCT or placebo*).tw,kw.	3,343,585
98	((singl* or doubl* or trebl* or tripl*) adj (mask* or blind* or dumm*)).tw,kw.	695,716
99	trial.ti.	799,970
100	or/94-99	4,155,555
101	82 and 100 [RCTS, PHASE II/III TRIALS]	14,365
102	limit 101 to yr="2005-current" [RCTs - 2005-current]	10,356
103	93 or 102 [REVIEWS, TRIALS]	11,108
104	conference abstract.pt.	3,696,512
105	103 not 104	7,242
106	103 and 104	3,866
107	limit 106 to yr="2018-current" [Limit not valid in DARE; records were retained]	544
108	105 or 107 [MOST RECENT 2 YRS CONFERENCE ABSTRACTS RETAINED]	7,786
109	**108 use oemezd [Embase records]**	**3,609**
110	exp Leukemia, Myeloid, Acute/	93,638
111	(acute adj2 myelo* adj2 leu#?emi*).ti,ab,kw.	118,957
112	(acute adj2 (nonlympho* or non-lympho*) adj2 leu#?emi*).ti,ab,kw.	6,877
113	(acute adj2 granulocytic adj2 leu#?emi*).ti,ab,kw.	605
114	((AML or ANLL) and (leu#?emi* or myelo* or nonlympho* or non-lympho*)).ti,ab,kw.	89,410
115	(AML or ANLL).ti,ab,kw. and exp Leukemia, Myeloid/	43,690
116	(acute adj2basophilic adj2 leu#?emi*).ti,ab,kw.	0
117	(acute adj2 eosinophilic adj2 leu#?emi*).ti,ab,kw.	70
118	(acute adj2 erythroblastic adj2 leu#?emi*).ti,ab,kw.	49
119	(erythroleu#?emi* or erythro-leu#?emi* or erythr?emic myelosis or diguglielmo* or di guglielmo*).ti,ab,kw.	13,505
120	((mast-cell* or mastcell*) adj2 leu#?emi*).ti,ab,kw.	1,127
121	((megakaryocytic or mega-karyocytic) adj2 leu#?emi*).ti,ab,kw.	872
122	((megakaryoblastic or mega-karyoblastic) adj2 leu#?emi*).ti,ab,kw.	2,296
123	(acute adj1 monoblastic adj2 leu#?emi*).ti,ab,kw.	789
124	(acute adj2 monocytic adj2 leu#?emi*).ti,ab,kw.	2,532
125	(acute adj2 promyelocytic adj2 leu#?emi*).ti,ab,kw.	16,902
126	(acute adj2 progranulocytic adj2 leu#?emi*).ti,ab,kw.	35
127	(Schilling-Type adj2 myelo* adj2 leu#?emi*).ti,ab,kw.	0
128	or/110-127	200,478
129	conference abstract.pt.	3,696,512
130	128 not 129	168,153
131	128 and 129	32,325
132	limit 131 to yr="2018-current" [Limit not valid in DARE; records were retained]	5,373
133	130 or 132	173,526
134	limit 133 to yr="2005-current" [Limit not valid in DARE; records were retained]	91,938
135	**134 use cctr [TRIALS, 2005-CURRENT]**	3,379

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No.	Query	Results
136	limit 128 to yr="2015-current" [Limit not valid in DARE; records were retained]	54,087
137	**136 use coch [REVIEWS, 2015-CURRENT]**	8
138	135 or 137 [REVIEWS, TRIALS]	3,387
139	**138 use coch,cctr [COCHRANE DSR, CENTRAL RECORDS]**	3,387
140	exp Leukemia, Myeloid, Acute/	93,638
141	(acute adj2 myelo* adj2 leu#?emi*).tw.	117,669
142	(acute adj2 (nonlympho* or non-lympho*) adj2 leu#?emi*).tw.	6,850
143	(acute adj2 granulocytic adj2 leu#?emi*).tw.	338
144	((AML or ANLL) and (leu#?emi* or myelo* or nonlympho* or non-lympho*)).tw.	88,238
145	(AML or ANLL).tw. and exp Leukemia, Myeloid/	43,328
146	(acute adj2 basophilic adj2 leu#?emi*).tw.	135
147	(acute adj2 eosinophilic adj2 leu#?emi*).tw.	70
148	(acute adj2 erythroblastic adj2 leu#?emi*).tw.	49
149	(erythroleu#?emi* or erythro-leu#?emi* or erythr?emic myelosis or diguglielmo* or di guglielmo*).tw.	13,408
150	((mast-cell* or mastcell*) adj2 leu#?emi*).tw.	1,090
151	((megakaryocytic or mega-karyocytic) adj2 leu#?emi*).tw.	852
152	((megakaryoblastic or mega-karyoblastic) adj2 leu#?emi*).tw.	2,265
153	(acute adj2 monoblastic adj2 leu#?emi*).tw.	801
154	(acute adj2 monocytic adj2 leu#?emi*).tw.	2,511
155	(acute adj2 promyelocytic adj2 leu#?emi*).tw.	16,800
156	(Schilling-Type adj2 myelo* adj2 leu#?emi*).tw.	0
157	(acute adj2 progranulocytic adj2 leu#?emi*).tw.	32
158	or/140-157	199,215
159	limit 158 to yr="2015-current" [Limit not valid in DARE; records were retained]	53,736
160	**159 use dare,clhta [DARE, HTA RECORDS]**	85
161	55 or 109 or 139 or 160 [ALL DATABASES]	9,322
162	limit 161 to yr="2015-current" [Limit not valid in DARE; records were retained]	5,133
163	remove duplicates from 162	3,835
164	161 not 162	4,189
165	remove duplicates from 164	2,866
166	163 or 165 [TOTAL UNIQUE RECORDS]	6,701
167	166 use ppez [MEDLINE UNIQUE RECORDS]	2,231
168	166 use oemezd [EMBASE UNIQUE RECORDS]	2,029
169	166 use coch [DSR UNIQUE RECORDS]	8
170	166 use dare [DARE UNIQUE RECORDS]	50
171	166 use clhta [HTA UNIQUE RECORDS]	35
172	166 use cctr [CENTRAL RECORDS]	2,348

Note: EBM Reviews - Cochrane Central Register of Controlled Trials (December 2019); EBM Reviews - Cochrane Database of Systematic Reviews (2005 to January 10, 2020); EBM Reviews - Database of Abstracts of Reviews of Effects (1st Quarter 2016); EBM Reviews - Health Technology Assessment (4th Quarter 2016); Embase (1974 to 2020 January 17); Ovid MEDLINE(R) and Epub Ahead of Print, In-Process & Other Non-Indexed Citations and Daily (1946 to January 17, 2020).

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Table A-8. Ovid search strategy (review update)

No.	Query	Results
1	exp Leukemia, Myeloid, Acute/	102,975
2	(acute adj2 myelo* adj2 leu#?emi*).tw,kf.	127,500
3	(acute adj2 (nonlympho* or non-lympho*) adj2 leu#?emi*).tw,kf.	6,892
4	(acute adj2 granulocytic adj2 leu#?emi*).tw,kf.	343
5	((AML or ANLL) and (leu#?emi* or myelo* or nonlympho* or non-lympho*)).tw,kf.	96,109
6	(AML or ANLL).tw,kf. and exp Leukemia, Myeloid/	48,726
7	(acute adj2 basophilic adj2 leu#?emi*).tw,kf.	138
8	(acute adj2 eosinophilic adj2 leu#?emi*).tw,kf.	71
9	(acute adj2 erythroblastic adj2 leu#?emi*).tw,kf.	50
10	(erythroleu#?emi* or erythro-leu#?emi* or erythr?emic myelosis or diguglielmo* or di guglielmo*).tw,kf.	13,634
11	((mast-cell* or mastcell*) adj2 leu#?emia*).tw,kf.	994
12	((megakaryocytic or mega-karyocytic) adj2 leu#?emi*).tw,kf.	878
13	((megakaryoblastic or mega-karyoblastic) adj2 leu#?emi*).tw,kf.	2,367
14	(acute adj2 monoblastic adj2 leu#?emi*).tw,kf.	819
15	(acute adj2 monocytic adj2 leu#?emi*).tw,kf.	2,666
16	(acute adj2 promyelocytic adj2 leu#?emi*).tw,kf.	17,764
17	(acute adj2 progranulocytic adj2 leu#?emi*).tw,kf.	32
18	(Schilling-Type adj1 myelo* adj2 leu#?emi*).tw,kf.	0
19	or/1-18	212,945
20	exp Animals/ not (exp Animals/ and Humans/)	18,178,116
21	19 not 20 [ANIMAL-ONLY REMOVED]	156,984
22	(comment or editorial or news or newspaper article).pt.	2,177,594
23	(letter not (letter and randomized controlled trial)).pt.	2,303,912
24	21 not (22 or 23) [OPINION PIECES REMOVED]	147,846
25	systematic review.pt.	154,476
26	exp systematic reviews as topic/	30,791
27	meta analysis.pt.	127,435
28	exp meta-analysis as topic/	66,065
29	(meta-analy* or metanaly* or metaanaly* or met analy* or integrative research or integrative review* or integrative overview* or research integration or research overview* or collaborative review*).tw,kf.	485,741
30	(systematic review* or systematic overview* or evidence-based review* or evidence-based overview* or (evidence adj3 (review* or overview*)) or meta-review* or meta-overview* or meta-synthes* or rapid review* or "review of reviews" or umbrella review? or technology assessment* or HTA or HTAs).tw,kf.	577,594
31	exp Technology assessment, biomedical/	26,445
32	(cochrane or health technology assessment or evidence report or systematic reviews).jw.	63,425
33	(network adj (MA or MAs)).tw,kf.	37
34	(NMA or NMAs or MTC or MTCs or MAIC or MAICs).tw,kf.	19,969
35	indirect* compar*.tw,kf.	7,061
36	(indirect treatment* adj1 compar*).tw,kf.	1,169

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No.	Query	Results
37	(mixed treatment* adj1 compar*).tw,kf.	1,517
38	(multiple treatment* adj1 compar*).tw,kf.	474
39	(multi-treatment* adj1 compar*).tw,kf.	12
40	simultaneous* compar*.tw,kf.	2,619
41	mixed comparison?.tw,kf.	144
42	or/25-41	975,714
43	24 and 42 [REVIEWS]	1,377
44	limit 43 to yr="2015-current" [REVIEWS - 5 YEARS]	891
45	(controlled clinical trial or randomized controlled trial or pragmatic clinical trial or equivalence trial).pt.	1,211,925
46	clinical trials as topic/	309,568
47	exp Randomized Controlled Trials as Topic/	349,328
48	(randomi#ed or randomi#ation? or randomly or RCT or placebo*).tw,kf.	3,605,010
49	((singl* or doubl* or trebl* or tripl*) adj (mask* or blind* or dumm*)).tw,kf.	719,773
50	trial.ti.	902,940
51	or/45-50	4,526,731
52	24 and 51 [RCTS]	11,940
53	limit 52 to yr="2005-current"	7,617
54	44 or 53 [REVIEWS, TRIALS]	8,206
55	**54 use ppez [MEDLINE RECORDS]**	**2,530**
56	exp acute myeloid leukemia/	102,975
57	acute leukemia/ and myeloid leukemia/	515
58	(acute adj2 myelo* adj2 leu#?emi*).tw,kw.	128,438
59	(acute adj2 (nonlympho* or non-lympho*) adj2 leu#?emi*).tw,kw.	6,921
60	(acute adj2 granulocytic adj2 leu#?emi*).tw,kw.	611
61	((AML or ANLL) and (leu#?emi* or myelo* or nonlympho* or non-lympho*)).tw,kw.	96,992
62	(AML or ANLL).tw,kw. and exp myeloid leukemia/	49,010
63	(acute adj2 basophilic adj2 leu#?emi*).tw,kw.	138
64	(acute adj2 eosinophilic adj2 leu#?emi*).tw,kw.	71
65	(acute adj2 erythroblastic adj2 leu#?emi*).tw,kw.	49
66	(erythroleu#?emi* or erythro-leu#?emi* or erythr?emic myelosis or diguglielmo* or di guglielmo*).tw,kw.	13,696
67	((mast-cell* or mastcell*) adj2 leu#?emi*).tw,kw.	1,156
68	((megakaryocytic or mega-karyocytic) adj2 leu#?emi*).tw,kw.	892
69	((megakaryoblastic or mega-karyoblastic) adj2 leu#?emi*).tw,kw.	2,381
70	(acute adj2 monoblastic adj2 leu#?emi*).tw,kw.	825
71	(acute adj2 monocytic adj2 leu#?emi*).tw,kw.	2,673
72	(acute adj2 promyelocytic adj2 leu#?emi*).tw,kw.	17,833
73	(acute adj2 progranulocytic adj2 leu#?emi*).tw,kw.	35
74	(Schilling-Type adj2 myelo* adj2 leu#?emi*).tw,kw.	0
75	or/56-74 [AML]	214,254

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No.	Query	Results
76	exp animal experimentation/ or exp animal model/ or exp animal experiment/ or nonhuman/ or exp vertebrate/	52,097,339
77	exp human/ or exp human experimentation/ or exp human experiment/	41,727,917
78	76 not 77	10,371,135
79	75 not 78 [ANIMAL-ONLY REMOVED]	200,962
80	editorial.pt.	1,248,574
81	letter.pt. not (letter.pt. and randomized controlled trial/)	2,303,596
82	79 not (80 or 81) [OPINION PIECES REMOVED]	190,908
83	meta-analysis/	336,166
84	"systematic review"/	430,443
85	"meta analysis (topic)"/	44,732
86	"systematic review (topic)"/	26,071
87	(meta-analy* or metanaly* or metaanaly* or met analy* or integrative research or integrative review* or integrative overview* or research integration or research overview* or collaborative review*).tw,kw.	495,088
88	(systematic review* or systematic overview* or evidence-based review* or evidence-based overview* or (evidence adj3 (review* or overview*)) or meta-review* or meta-overview* or meta-synthes* or "review of reviews" or umbrella review? or technology assessment* or HTA or HTAs).tw,kw.	584,633
89	biomedical technology assessment/	25,330
90	(cochrane or health technology assessment or evidence report).jw.	54,143
91	or/83-90	1,044,160
92	82 and 91 [REVIEWS]	2,177
93	limit 92 to yr="2015-current" [REVIEWS - 5 YR LIMIT]	1,378
94	randomized controlled trial/ or controlled clinical trial/	1,451,431
95	"clinical trial (topic)"/	111,114
96	exp "controlled clinical trial (topic)"/	205,199
97	(randomi#ed or randomi#ation or randomly or RCT or placebo*).tw,kw.	3,667,059
98	((singl* or doubl* or trebl* or tripl*) adj (mask* or blind* or dumm*)).tw,kw.	748,188
99	trial.ti.	902,940
100	or/94-99	4,516,287
101	82 and 100 [RCTS, PHASE II/III TRIALS]	15,476
102	limit 101 to yr="2005-current" [RCTs - 2005-current]	11,424
103	93 or 102 [REVIEWS, TRIALS]	12,316
104	conference abstract.pt.	4,042,951
105	103 not 104	8,274
106	103 and 104	4,042
107	limit 106 to yr="2018-current"	719
108	105 or 107 [MOST RECENT 2 YRS CONFERENCE ABSTRACTS RETAINED]	8,993
109	**108 use oemezd [EMBASE RECORDS]**	**4,232**
110	exp Leukemia, Myeloid, Acute/	102,975
111	(acute adj2 myelo* adj2 leu#?emi*).ti,ab,kw.	128,393
112	(acute adj2 (nonlympho* or non-lympho*) adj2 leu#?emi*).ti,ab,kw.	6,918

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No.	Query	Results
113	(acute adj2 granulocytic adj2 leu#?emi*).ti,ab,kw.	611
114	((AML or ANLL) and (leu#?emi* or myelo* or nonlympho* or non-lympho*)).ti,ab,kw.	96,952
115	(AML or ANLL).ti,ab,kw. and exp Leukemia, Myeloid/	49,009
116	(acute adj2basophilic adj2 leu#?emi*).ti,ab,kw.	0
117	(acute adj2 eosinophilic adj2 leu#?emi*).ti,ab,kw.	71
118	(acute adj2 erythroblastic adj2 leu#?emi*).ti,ab,kw.	49
119	(erythroleu#?emi* or erythro-leu#?emi* or erythr?emic myelosis or diguglielmo* or di guglielmo*).ti,ab,kw.	13,696
120	((mast-cell* or mastcell*) adj2 leu#?emi*).ti,ab,kw.	1,156
121	((megakaryocytic or mega-karyocytic) adj2 leu#?emi*).ti,ab,kw.	892
122	((megakaryoblastic or mega-karyoblastic) adj2 leu#?emi*).ti,ab,kw.	2,381
123	(acute adj1 monoblastic adj2 leu#?emi*).ti,ab,kw.	807
124	(acute adj2 monocytic adj2 leu#?emi*).ti,ab,kw.	2,673
125	(acute adj2 promyelocytic adj2 leu#?emi*).ti,ab,kw.	17,827
126	(acute adj2 progranulocytic adj2 leu#?emi*).ti,ab,kw.	35
127	(Schilling-Type adj2 myelo* adj2 leu#?emi*).ti,ab,kw.	0
128	or/110-127	213,936
129	conference abstract.pt.	4,042,951
130	128 not 129	179,441
131	128 and 129	34,495
132	limit 131 to yr="2018-current"	7,519
133	130 or 132	186,960
134	limit 133 to yr="2005-current"	104,962
135	**134 use cctr [TRIALS, 2005-CURRENT]**	**3,922**
136	limit 128 to yr="2015-current"	66,954
137	**136 use coch [REVIEWS, 2015-CURRENT]**	**10**
138	135 or 137 [REVIEWS, TRIALS]	3,932
139	138 use coch,cctr [COCHRANE DSR, CENTRAL RECORDS]	3,932
140	55 or 109 or 139 [ALL DATABASES]	10,694
141	limit 140 to yr="2020 -Current"	1,145
142	remove duplicates from 141	787
143	("20200101" or "20200102" or "20200103" or "20200104" or "20200105" or "20200106" or "20200107" or "20200108" or "20200109" or "20200110" or "20200111" or "20200112" or "20200113" or "20200114" or "20200115" or "20200116" or "20200117").up.	73,530
144	("20200101" or "20200102" or "20200103" or "20200104" or "20200105" or "20200106" or "20200107" or "20200108" or "20200109" or "20200110" or "20200111" or "20200112" or "20200113" or "20200114" or "20200115" or "20200116" or "20200117").dc.	110,897
145	("20200101" or "20200102" or "20200103" or "20200104" or "20200105" or "20200106" or "20200107" or "20200108" or "20200109" or "20200110" or "20200111" or "20200112" or "20200113" or "20200114" or "20200115" or "20200116" or "20200117").dt.	59,170
146	143 or 144 or 145	239,924
147	142 not 146 [All databases - update results 18 Jan 2020 - Current]	773

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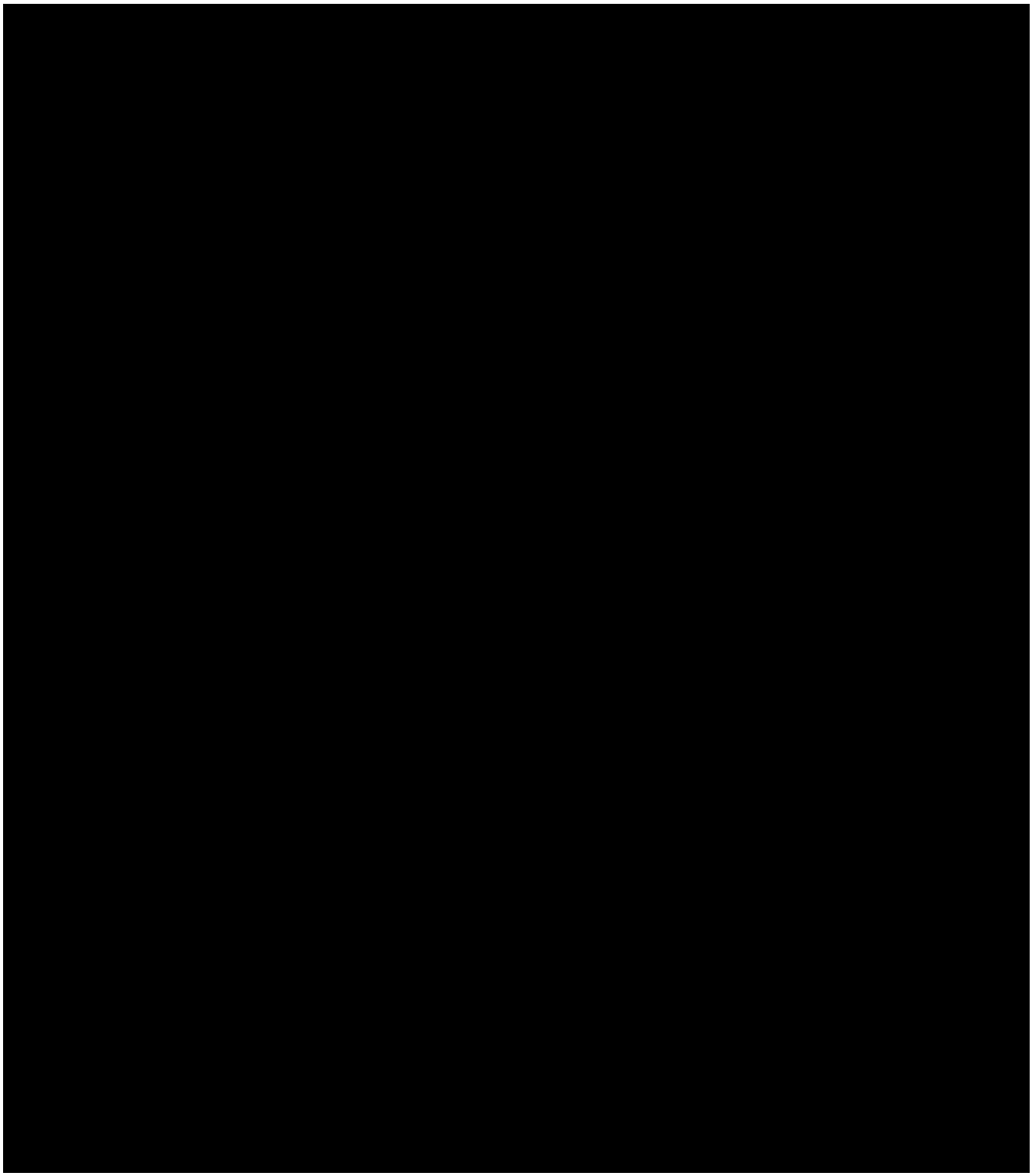
Appendix A.3 Systematic selection of studies

The original literature search for clinical evidence identified 6,701 articles through database searches. One additional article from the supplementary searches was identified. After removing duplicates, there were 6,411 articles for title and abstract review. Of these, 6,207 were excluded at the title and abstract screening phase because they did not meet the prespecified inclusion criteria. Among the 204 references remaining, 179 were excluded at the full-text screening phase. The remaining 25 references, representing 22 unique trials, were included in this review. Figure A-1 presents the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flow diagram for the selection of these studies in the original review.



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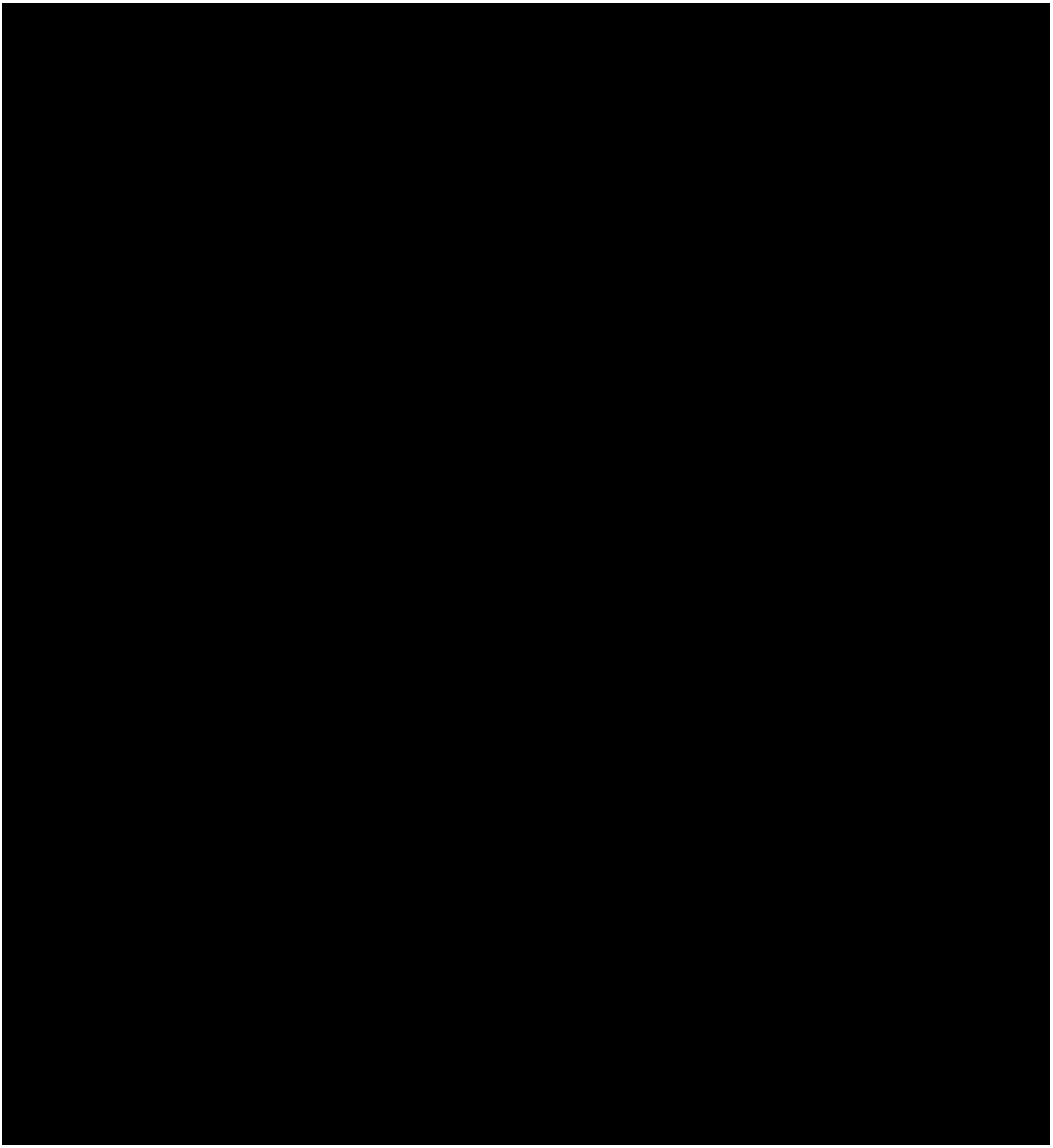
n = number; (N)MA = (network) meta-analysis; PRISMA = Preferred Reporting for Systematic Reviews and Meta-Analyses; RCT = randomised controlled trial; SLR = systematic literature review.

The updated literature search for clinical evidence identified 773 articles through database searches. Twenty-five additional articles were identified through the previous SLR and 3 additional articles were identified from the supplementary grey literature search. After removing duplicates, there were 801 articles for title and abstract review. Of these, 752 were excluded at the title and abstract screening phase because they did not meet the prespecified inclusion criteria. Among the 49 articles remaining, 16 were excluded at the full-text screening phase. The remaining 33 articles, representing 24 unique trials, were included in this review. Figure A-2 presents the PRISMA flow diagram for the selection of these studies.



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n = number; PRISMA = Preferred Reporting for Systematic Reviews and Meta-Analyses; (N)MA = (network) meta-analysis; SLR = systematic literature review.

A detailed list of the excluded studies at the full-text screening phase for the original and updated review is provided in Table A-9 and Table A-10, respectively.

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Table A-9. Studies excluded at the full-text screening phase (original review)

Ref ID	Citation	Reason for exclusion
5078	EUCTR2009-017340-14-GB. "WT1 Immunity via DNA fusion Gene Vaccination in Haematological Malignancies by intramuscular injection followed by intramuscular electroporation. - WIN: anti-WT1 DNA fusion gene vaccine in haematological malignancies." #journal# who.int/trialsearch/Trial2.aspx?TrialID=EUCTR2009-017340-14-GB. 2010. (2010///): 017340. EBM Reviews - Cochrane Central Register of Controlled Trials	Non-human
254	Liu KQ, Wang Y , Zhao Z ,Lin D, Zhou CL, Liu BC, Gong XY, Zhao XL, Wei SN, Zhang GJ, Gong BF, Li Y, Liu YT, Mi YC, Wang JX, Wei H. "A single-center, randomized controlled trial of PEG-rhG-CSF and common rhG-CSF to promote neutrophil recovery after induction chemotherapy in newly diagnosed acute myeloid leukemia." Chung Hua Hsueh Yeh Hsueh Tsa Chi 40 (2019/06/14/): 497. DB - Ovid MEDLINE(R) and Epub Ahead of Print, In-Process & Other Non-Indexed Citations and Daily Chung-Hua Hsueh Yeh Hsueh Tsa Chih: Chinese Journal of Hematology. 40(6):497-501, 2019 Jun 14	Non-English
1179	EN Parovichnikova, VV Troitskaia, GA Kliasova, LA Kuz'mina, AN Sokolov, EV Paramonova, GM Galstian, SA Kessel'man, MI Drokov, VA Vasil'eva, TN Obukhova, SM Kulikov, VG Savchenko. "Treating patients with acute myeloid leukemias (AML) according to the protocol of the AML-01.10 Russian multicenter randomized trial: the coordinating center's results." Terapevticheskii Arkhiv 86 (2014///): 14. DB - Ovid MEDLINE(R) and Epub Ahead of Print, In-Process & Other Non-Indexed Citations and Daily Terapevticheskii Arkhiv. 86(7):14-23, 2014	Non-English
1810	JY Su, CK Chang, X. Zhang, LY Zhou, LQ Song, L. Xu, LY Wu, Q. He, X. Li. "Efficacy of induction chemotherapy for patients with high-risk myelodysplastic syndrome (MDS) or MDS-transformed acute myeloid leukemia with CHG regimen and its comparison with regimen GAG and HA." Zhongguo Shi Yan Xue Ye Xue Za Zhi 17 (2009/04//): 459. DB - Ovid MEDLINE(R) and Epub Ahead of Print, In-Process & Other Non-Indexed Citations and Daily Zhongguo Shi Yan Xue Ye Xue Za Zhi. 17(2):459-63, 2009 Apr	Non-English
1956	EN Parovichnikova, VG Savchenko, VG Isaev, AN Sokolov, SM Kulikov, GA Kliasova, VV Ryzhko, SK Kravchenko, ND Khoroshko, TS Konstantinova, TP Zagoskina, IS Ziuzgin, GB Rekhtman, VI Moskov, IV Sokolova, LV Anchukova, VA Lapin, AB Loginov, VA Tumakov, AV Korobkin, GI Miliutina, OS Samoilova, VI Mal'tsev, AS Pristupa, SN Men'shakova, NP Domnikova, LV Gavrilova, NA Obidina, OV Porokhina, KD Kaplanov, LI Medvedeva, NK Khuazheva, GI Pilipenko, ME Golubeva, AG Maksimov, MA Ploskikh, NV Khlevnaia. "The results of a multicenter randomized trial on the treatment of acute myeloid leukemia of adults." Terapevticheskii Arkhiv 79 (2007///): 14. DB - Ovid MEDLINE(R) and Epub Ahead of Print, In-Process & Other Non-Indexed Citations and Daily Terapevticheskii Arkhiv. 79(7):14-9, 2007	Non-English
3742	L.-F. He, J.-H. Zhu, J.-R. Han. "Interleukin-2 as maintenance therapy in the treatment of acute myeloid leukemia: a Meta-analysis." Chinese Journal of Cancer Prevention and Treatment 21 (2014///): 1739. DB - Embase	Non-English
5843	K. Metzeler, C. Buske, J. Braess, K. Spiekermann, SK Bohlander, M. Feuring-Buske, B. Wormann, C. Sauerland, A. Heinecke, T. Buchner, W. Hiddemann. "Therapy results by acute myeloid leukaemia with an unfavourable karyotype: an analysis of patients from the AMLCG-2000 study." Medizinische Klinik 102 (2007///): 37, 2007. EBM Reviews - Cochrane Central Register of Controlled Trials	Non-English
73	M. Kenealy, M. Hertzberg, W. Benson, K. Taylor, I. Cunningham, W. Stevenson, D. Hiwase, R. Eek, D. Zantomio, S. Jong, M. Wall, P. Blombery, T. Gerber, M. Debrincat, D. Zannino, JF Seymour. "Azacitidine with or without lenalidomide in higher risk myelodysplastic syndrome & low blast acute myeloid leukemia." Haematologica 104 (2019/04//): 700. DB - Ovid MEDLINE(R) and Epub Ahead of Print, In-Process & Other Non-Indexed Citations and Daily Haematologica. 104(4):700-709, 2019 04	Population
125	S. Cooley, F. He, V. Bachanova, GM Vercellotti, TE DeFor, JM Curtsinger, P. Robertson, B. Grzywacz, KC Conlon, TA Waldmann, DH McKenna, BR Blazar, DJ Weisdorf, JS Miller. "First-in-human trial of rhIL-15 and haploidentical natural killer cell therapy for advanced acute myeloid	Population

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Ref ID	Citation	Reason for exclusion
	leukemia." Blood Adv 3 (2019/07/09/): 1970. DB - Ovid MEDLINE(R) and Epub Ahead of Print, In-Process & Other Non-Indexed Citations and Daily Blood Advances. 3(13):1970-1980, 2019 Jul 09	
153	WP Zhang, ZW Wang, XX Hu, J. Chen, D. Yang, XM Song, L. Gao, X. Ni, L. Chen, XX Xia, H. Zhou, GS Tang, H. Cheng, YR Luo, HM Li, JM Yang, JM Wang. "Preconditioning with fludarabine, busulfan and cytarabine versus standard BuCy2 for patients with acute myeloid leukemia: a prospective, randomized phase II study." Bone Marrow Transplantation 54 (2019/06//): 894. DB - Ovid MEDLINE(R) and Epub Ahead of Print, In-Process & Other Non-Indexed Citations and Daily Bone Marrow Transplantation. 54(6):894-902, 2019 Jun	Population
257	BC Medeiros, K. McCaul, S. Kambhampati, DA Pollyea, R. Kumar, LR Silverman, A. Kew, L. Saini, CL Beach, R. Vij, X. Wang, J. Zhong, RP Gale. "Randomized study of continuous high-dose lenalidomide, sequential azacitidine and lenalidomide, or azacitidine in persons 65 years and over with newly-diagnosed acute myeloid leukemia." Haematologica 103 (2018/01//): 101. DB - Ovid MEDLINE(R) and Epub Ahead of Print, In-Process & Other Non-Indexed Citations and Daily Haematologica. 103(1):101-106, 2018 01	Population
274	U. Platzbecker, JM Middeke, K. Sockel, R. Herbst, D. Wolf, CD Baldus, U. Oelschlagel, A. Mutherig, L. Fransecky, R. Noppeney, G. Bug, KS Gotze, A. Kramer, T. Bochtler, M. Stelljes, C. Groth, A. Schubert, M. Mende, F. Stolzel, C. Borkmann, AS Kubasch, Bonin M. von, H. Serve, M. Hanel, U. Duhrsen, J. Schetelig, C. Rollig, M. Kramer, G. Ehninger, M. Bornhauser, C. Thiede. "Measurable residual disease-guided treatment with azacitidine to prevent haematological relapse in patients with myelodysplastic syndrome and acute myeloid leukaemia (RELAZA2): an open-label, multicentre, phase 2 trial." Lancet Oncology 19 (2018/12//): 1668. DB - Ovid MEDLINE(R) and Epub Ahead of Print, In-Process & Other Non-Indexed Citations and Daily	Population
447	LJ Nastoupil, P. McLaughlin, L. Feng, SS Neelapu, F. Samaniego, FB Hagemeister, A. Ayala, JE Romaguera, AH Goy, E. Neal, M. Wang, L. Fayad, MA Fanale, Y. Oki, JR Westin, MA Rodriguez, F. Cabanillas, NH Fowler. "High ten-year remission rates following rituximab, fludarabine, mitoxantrone and dexamethasone (R-FND) with interferon maintenance in indolent lymphoma: Results of a randomized Study." British Journal of Haematology 177 (2017/04//): 263. DB - Ovid MEDLINE(R) and Epub Ahead of Print, In-Process & Other Non-Indexed Citations and Daily British Journal of Haematology. 177(2):263-270, 2017 04	Population
487	T. Prebet, Z. Sun, ME Figueroa, R. Ketterling, A. Melnick, PL Greenberg, J. Herman, M. Juckett, MR Smith, L. Malick, E. Paietta, M. Czader, M. Litzow, J. Gabrilove, HP Erba, SD Gore, MS Tallman. "Prolonged administration of azacitidine with or without entinostat for myelodysplastic syndrome and acute myeloid leukemia with myelodysplasia-related changes: results of the US Leukemia Intergroup trial E1905." Journal of Clinical Oncology 32 (2014/04/20/): 1242. DB - Ovid MEDLINE(R) and Epub Ahead of Print, In-Process & Other Non-Indexed Citations and Daily Journal of Clinical Oncology. 32(12):1242-8, 2014 Apr 20	Population
610	PF He, JD Zhou, DM Yao, JC Ma, XM Wen, ZH Zhang, XY Lian, ZJ Xu, J. Qian, J. Lin. "Efficacy and safety of decitabine in treatment of elderly patients with acute myeloid leukemia: A systematic review and meta-analysis." Oncotarget 8 (2017/06/20/): 41498. DB - Ovid MEDLINE(R) and Epub Ahead of Print, In-Process & Other Non-Indexed Citations and Daily Oncotarget. 8(25):41498-41507, 2017 Jun 20	Population
615	S. Yun, ND Vincelette, I. Abraham, KD Robertson, ME Fernandez-Zapico, MM Patnaik. "Targeting epigenetic pathways in acute myeloid leukemia and myelodysplastic syndrome: a systematic review of hypomethylating agents trials." Clin Epigenetics 8 (2016///): 68. DB - Ovid MEDLINE(R) and Epub Ahead of Print, In-Process & Other Non-Indexed Citations and Daily Clinical Epigenetics. 8:68, 2016	Population
632	C. Gao, J. Wang, Y. Li, H. Zhao, R. Li, L. Hou, Y. Zhang, S. Tian, H. Liang, C. Wang, X. Chen, J. Wang. "Incidence and risk of hematologic toxicities with hypomethylating agents in the treatment of myelodysplastic syndromes and acute myeloid leukopenia: A systematic review and meta-analysis." Medicine 97 (2018/08//): e11860, 2018. DB - Ovid MEDLINE(R) and Epub Ahead of Print, In-Process & Other Non-Indexed Citations and Daily Medicine. 97(34):e11860, 2018 Aug	Population

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Ref ID	Citation	Reason for exclusion
787	G. Montalban-Bravo, X. Huang, K. Naqvi, E. Jabbour, G. Borthakur, CD DiNardo, N. Pemmaraju, J. Cortes, S. Verstovsek, T. Kadia, N. Daver, W. Wierda, Y. Alvarado, M. Konopleva, F. Ravandi, Z. Estrov, N. Jain, A. Alfonso, M. Brandt, T. Sneed, HC Chen, H. Yang, C. Bueso-Ramos, S. Pierce, E. Estey, Z. Bohannan, HM Kantarjian, G. Garcia-Manero. "A clinical trial for patients with acute myeloid leukemia or myelodysplastic syndromes not eligible for standard clinical trials." Leukemia 31 (2017/02//): 318. DB - Ovid MEDLINE(R) and Epub Ahead of Print, In-Process & Other Non-Indexed Citations and Daily TC - [Erratum in: Leukemia. 2017 Jul;31(7):1659; PMID: 28338082 [https://www.ncbi.nlm.nih.gov/pubmed/28338082]] Leukemia. 31(2):318-324, 2017 02	Population
848	A. Di Stasi, AM Jimenez, K. Minagawa, M. Al-Obaidi, K. Rezvani. "Review of the Results of WT1 Peptide Vaccination Strategies for Myelodysplastic Syndromes and Acute Myeloid Leukemia from Nine Different Studies." #journal# 6 (2015///): 36. DB - Ovid MEDLINE(R) and Epub Ahead of Print, In-Process & Other Non-Indexed Citations and Daily Frontiers in Immunology. 6:36, 2015	Population
849	C. Arthur, J. Cermak, J. Delaunay, J. Mayer, G. Mazur, X. Thomas, A. Wierzbowska, MM Jones, E. Berrak, H. Kantarjian. "Post hoc analysis of the relationship between baseline white blood cell count and survival outcome in a randomized Phase III trial of decitabine in older patients with newly diagnosed acute myeloid leukemia." #journal# 6 (2015///): 25. DB - Ovid MEDLINE(R) and Epub Ahead of Print, In-Process & Other Non-Indexed Citations and Daily Journal of Blood Medicine. 6:25-9, 2015	Population
965	U. Krug, WE Berdel, RP Gale, C. Haferlach, S. Schnittger, C. Muller-Tidow, J. Braess, K. Spiekermann, P. Staib, D. Beelen, H. Serve, C. Schliemann, M. Stelljes, L. Balleisen, G. Maschmeyer, A. Gruneisen, H. Eimermacher, A. Giagounidis, H. Rasche, R. Hehlmann, E. Lengfelder, E. Thiel, A. Reichle, C. Aul, WD Ludwig, W. Kern, T. Haferlach, W. Kopcke, D. Gorlich, MC Sauerland, A. Heinecke, BJ Wormann, W. Hiddemann, T. Buchner. "Increasing intensity of therapies assigned at diagnosis does not improve survival of adults with acute myeloid leukemia." Leukemia 30 (2016/06//): 1230. DB - Ovid MEDLINE(R) and Epub Ahead of Print, In-Process & Other Non-Indexed Citations and Daily Leukemia. 30(6):1230-6, 2016 06	Population
1251	SE Coutre, M. Othus, B. Powell, CL Willman, W. Stock, E. Paietta, D. Levitan, M. Wetzler, EC Attar, JK Altman, SD Gore, T. Maher, KJ Kopecky, MS Tallman, RA Larson, FR Appelbaum. "Arsenic trioxide during consolidation for patients with previously untreated low/intermediate risk acute promyelocytic leukaemia may eliminate the need for maintenance therapy." British Journal of Haematology 165 (2014/05//): 497. DB - Ovid MEDLINE(R) and Epub Ahead of Print, In-Process & Other Non-Indexed Citations and Daily British Journal of Haematology. 165(4):497-503, 2014 May	Population
1265	JE Kolitz, SL George, DM Benson, K. Maharry, G. Marcucci, R. Vij, BL Powell, SL Allen, DJ DeAngelo, TC Shea, W. Stock, CE Bakan, V. Hars, E. Hoke, CD Bloomfield, MA Caligiuri, RA Larson, Alliance for Clinical Trials in Oncology. "Recombinant interleukin-2 in patients aged younger than 60 years with acute myeloid leukemia in first complete remission: results from Cancer and Leukemia Group B 19808." Cancer 120 (2014/04/01/): 1010. DB - Ovid MEDLINE(R) and Epub Ahead of Print, In-Process & Other Non-Indexed Citations and Daily TC - [Comment in: Cancer. 2014 Apr 1;120(7):940-1; PMID: 24382703 [https://www.ncbi.nlm.nih.gov/pubmed/24382703]] Cancer. 120(7):1010-7, 2014 Apr 01	Population
1298	S. Nand, M. Othus, JE Godwin, CL Willman, TH Norwood, DS Howard, SE Coutre, HP Erba, FR Appelbaum. "A phase 2 trial of azacitidine and gemtuzumab ozogamicin therapy in older patients with acute myeloid leukemia." Blood 122 (2013/11/14/): 3432. DB - Ovid MEDLINE(R) and Epub Ahead of Print, In-Process & Other Non-Indexed Citations and Daily Blood. 122(20):3432-9, 2013 Nov 14	Population
1354	L. Ades, S. Chevret, E. Raffoux, A. Guerci-Bresler, A. Pigneux, N. Vey, T. Lamy, F. Huguet, A. Vekhoff, JF Lambert, B. Lioure, Botton S. de, E. Deconinck, A. Ferrant, X. Thomas, B. Quesnel, B. Cassinat, C. Chomienne, H. Dombret, L. Degos, P. Fenaux, European APL group. "Long-term follow-up of European APL 2000 trial, evaluating the role of cytarabine combined with ATRA and Daunorubicin in the treatment of nonelderly APL patients." #journal# 88 (2013/07//): 556. DB -	Population

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Ref ID	Citation	Reason for exclusion
	Ovid MEDLINE(R) and Epub Ahead of Print, In-Process & Other Non-Indexed Citations and Daily American Journal of Hematology. 88(7):556-9, 2013 Jul	
1515	RB Walter, BC Medeiros, BL Powell, CA Schiffer, FR Appelbaum, EH Estey. "Phase II trial of vorinostat and gemtuzumab ozogamicin as induction and post-remission therapy in older adults with previously untreated acute myeloid leukemia." Haematologica 97 (2012/05//): 739. DB - Ovid MEDLINE(R) and Epub Ahead of Print, In-Process & Other Non-Indexed Citations and Daily Haematologica. 97(5):739-42, 2012 May	Population
1667	T. Fischer, RM Stone, DJ DeAngelo, I. Galinsky, E. Estey, C. Lanza, E. Fox, G. Ehninger, EJ Feldman, GJ Schiller, VM Klimek, SD Nimer, DG Gilliland, C. Dutreix, A. Huntsman-Labed, J. Virkus, FJ Giles. "Phase IIB trial of oral Midostaurin (PKC412), the FMS-like tyrosine kinase 3 receptor (FLT3) and multi-targeted kinase inhibitor, in patients with acute myeloid leukemia and high-risk myelodysplastic syndrome with either wild-type or mutated FLT3." Journal of Clinical Oncology 28 (2010/10/01/): 4339. DB - Ovid MEDLINE(R) and Epub Ahead of Print, In-Process & Other Non-Indexed Citations and Daily Journal of Clinical Oncology. 28(28):4339-45, 2010 Oct 01	Population
1806	K. Wheatley, AH Goldstone, T. Littlewood, A. Hunter, AK Burnett. "Randomized placebo-controlled trial of granulocyte colony stimulating factor (G-CSF) as supportive care after induction chemotherapy in adult patients with acute myeloid leukaemia: a study of the United Kingdom Medical Research Council Adult Leukaemia Working Party." British Journal of Haematology 146 (2009/06//): 54. DB - Ovid MEDLINE(R) and Epub Ahead of Print, In-Process & Other Non-Indexed Citations and Daily British Journal of Haematology. 146(1):54-63, 2009 Jun	Population
1809	U. Keilholz, A. Letsch, A. Busse, AM Asemissen, S. Bauer, IW Blau, WK Hofmann, L. Uharek, E. Thiel, C. Scheibenbogen. "A clinical and immunologic phase 2 trial of Wilms tumor gene product 1 (WT1) peptide vaccination in patients with AML and MDS." Blood 113 (2009/06/25/): 6541. DB - Ovid MEDLINE(R) and Epub Ahead of Print, In-Process & Other Non-Indexed Citations and Daily Blood. 113(26):6541-8, 2009 Jun 25	Population
2073	T. Buchner, WE Berdel, C. Schoch, T. Haferlach, HL Serve, J. Kienast, S. Schnittger, W. Kern, J. Tchinda, A. Reichle, E. Lengfelder, P. Staib, WD Ludwig, C. Aul, H. Eimermacher, L. Balleisen, MC Sauerland, A. Heinecke, B. Wormann, W. Hiddemann. "Double induction containing either two courses or one course of high-dose cytarabine plus mitoxantrone and postremission therapy by either autologous stem-cell transplantation or by prolonged maintenance for acute myeloid leukemia." Journal of Clinical Oncology 24 (2006/06/01/): 2480. DB - Ovid MEDLINE(R) and Epub Ahead of Print, In-Process & Other Non-Indexed Citations and Daily TC - [Comment in: J Clin Oncol. 2006 Dec 1;24(34):5471-2; author reply 5472-3; PMID: 17135654 [https://www.ncbi.nlm.nih.gov/pubmed/17135654]][Erratum in: J Clin Oncol. 2011 Jul 1;29(19):2739]	Population
2086	M. Brune, S. Castaigne, J. Catalano, K. Gehlsen, AD Ho, WK Hofmann, DE Hogge, B. Nilsson, R. Or, AI Romero, JM Rowe, B. Simonsson, R. Spearing, EA Stadtmauer, J. Szer, E. Wallhult, K. Hellstrand. "Improved leukemia-free survival after postconsolidation immunotherapy with histamine dihydrochloride and interleukin-2 in acute myeloid leukemia: results of a randomized phase 3 trial." Blood 108 (2006/07/01/): 88. DB - Ovid MEDLINE(R) and Epub Ahead of Print, In-Process & Other Non-Indexed Citations and Daily Blood. 108(1):88-96, 2006 Jul 01	Population
2135	S. Miyawaki, H. Sakamaki, S. Ohtake, N. Emi, F. Yagasaki, K. Mitani, S. Matsuda, Y. Kishimoto, Y. Miyazaki, N. Asou, T. Matsushima, M. Takahashi, Y. Ogawa, S. Honda, R. Ohno, Japan Adult Leukemia Study Group. "A randomized, postremission comparison of four courses of standard-dose consolidation therapy without maintenance therapy versus three courses of standard-dose consolidation with maintenance therapy in adults with acute myeloid leukemia: the Japan Adult Leukemia Study Group AML 97 Study." Cancer 104 (2005/12/15/): 2726. DB - Ovid MEDLINE(R) and Epub Ahead of Print, In-Process & Other Non-Indexed Citations and Daily Cancer. 104(12):2726-34, 2005 Dec 15	Population
2301	U. Platzbecker, JM Middeke, K. Sockel, R. Herbst, LR Fransecky, D. Wolf, S. Martin, A. Kramer, R. Noppeney, J. Novotny, G. Bug, K. Gotze, K. Spiekermann, M. Stelljes, C. Groth, M. Subklewe, A. Schubert, A. Mutherig, T. Bochtler, M. Mende, AS Kubasch, M. Hanel, U. Duhrsen, J. Schetelig, C.	Population

Ref ID	Citation	Reason for exclusion
	Rollig, CD Baldus, G. Ehninger, C. Muller-Tidow, H. Serve, M. Kramer, M. Bornhauser, C. Thiede. "Azacitidine for pre-emptive treatment of measurable-residual disease in MDS/AML patients at high risk of hematological relapse: Results of the second cohort of the RELAZA2 trial." Blood Conference: (2019///): #pages#. DB - Embase	
2343	VV Troitskaya, EN Parovichnikova, AN Sokolov, AV Kokhno, ZT Fidarova, OA Gavrilina, TI Lobanova, EO Gribanova, SK Kravchenko, GM Galstyan, SM Kulikov, JA Chabaeva, VG Savchenko. "The choice of treatment for elderly AML-patients: 7+3 or low doses ARA-C." Blood Conference: (2019///): #pages#. DB - Embase	Population
2375	DA Sallman, AE DeZern, G. Garcia-Manero, DP Steensma, GJ Roboz, MA Sekeres, T. Cluzeau, KL Sweet, AF McLemore, K. McGraw, J. Puskas, L. Zhang, J. Yao, Q. Mo, L. Nardelli, Ali N. Al, E. Padron, G. Korbel, EC Attar, HM Kantarjian, JE Lancet, P. Fenaux, AF List, RS Komrokji. "Phase 2 results of APR-246 and azacitidine (AZA) in patients with TP53 mutant myelodysplasic syndromes (MDS) and oligoblastic acute myeloid leukemia (AML)". Blood Conference: (2019///): #pages#. DB - Embase	Population
2419	N. Jaekel, S. Schulze, U. Siebolts, A. Haak, N. Pazaitis, M. Cross, D. Niederwieser, M. Hanel, G. Maschmeyer, M. Wass, L. Heukamp, R. Menon, M. Bertrand, C. Wickenhauser, O. Brosteanu, HK Al-Ali. "Impact of somatic mutations on outcome in patients > 60 years old with newly diagnosed AML treated with response-adapted sequential azacitidine and induction chemotherapy within the DRKS00004519 trial (RAS-AZIC) of the East German study group of hematology and oncology (OSHO)". Blood Conference: (2019///): #pages#. DB - Embase	Population
4133	AK Burnett, K. Wheatley, AH Goldstone, R. Stevens, I. Hann, RK Hills. "Long-term result of the MRC AML10 trial." Clinical Advances in Hematology and Oncology 4 (2006///): 445. DB - Embase	Population
4410	NCT00414310. "Decitabine (DAC) w/ or w/o Valproic Acid (VPA) in Myelodysplastic Syndrome (MDS) and Acute Myelogenous Leukemia (AML)". #journal# gov/show/NCT00414310. 2006. (2006///): #pages#. EBM Reviews - Cochrane Central Register of Controlled Trials	Population
4439	NCT00952588. "Study to Investigate the Efficacy, Safety and Tolerability of AZD1152 Alone and in Combination With Low Dose Cytosine Arabinoside (LDAC)in Acute Myeloid Leukaemia (AML) Patients." #journal# gov/show/NCT00952588. 2009. (2009///): #pages#. EBM Reviews - Cochrane Central Register of Controlled Trials	Population
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5049	ACTRN12611001112954. "Investigating the role of targeted therapy Sorafenib - the Fms-like tyrosine kinase 3 (FLT3) inhibitor, in combination with intensive chemotherapy, for previously untreated adult patients with Acute Myeloid Leukaemia (AML) with FLT3 mutations. A Phase II randomised placebo-controlled multi-centre study." #journal# who.int/trialsearch/Trial2.aspx?TrialID=ACTRN12611001112954. 2011. (2011///): #pages#. EBM Reviews - Cochrane Central Register of Controlled Trials	Population
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Ref ID	Citation	Reason for exclusion
5140	R. Schlenk, K. Dohner, J. Krauter, VI Gaidzik, P. Paschka, M. Heuser, F. Thol, T. Kindler, M. Lubbert, H. Martin, HR Salih, A. Kundgen, HA Horst, P. Brossart, K. Gotze, D. Nachbaur, M. Wattad, CH Kohne, W. Fiedler, M. Bentz, G. Wulf, G. Held, B. Hertenstein, H. Salwender, M. Rummel, A. Raghavachar, A. Benner, B. Schlegelberger, A. Ganser, H. Dohner. "All-trans retinoic acid as adjunct to intensive treatment in younger adult patients with acute myeloid leukemia-final results of the AMLSG 07-04 randomized treatment trial." Haematologica 99 (2014///): 222, 2014. EBM Reviews - Cochrane Central Register of Controlled Trials	Population
5775	J.-L. Harousseau, G. Martinelli, WW Jedrzejczak, J. Brandwein, D. Bourdessoule, T. Masszi, G. Ossenkoppele, YA Alexeeva, G. Beutel, YC Park, Porre P. De, AJ Howes. "A randomized phase 3 study of tipifarnib compared to best supportive care (including hydroxyurea) in the treatment of newly diagnosed acute myeloid leukemia (AML) in patients 70 years or older." Blood 110 (2007///): 135a. EBM Reviews - Cochrane Central Register of Controlled Trials	Population
6355	S. Oberoi, T. Lehrnbecher, B. Phillips, J. Hitzler, MC Ethier, J. Beyene, L. Sung. "Leukapheresis and low-dose chemotherapy do not reduce early mortality in acute myeloid leukemia hyperleukocytosis: a systematic review and meta-analysis." Leukemia Research 38 (2014///): 460. IN - NHS Centre for Reviews and Dissemination. University of York, York, UK	Population
2414	AB Halpern, M. Othus, K. Gardner, G. Alcorn, M.-E. Percival, EM Huebner, BL Scott, PS Becker, PC Hendrie, VG Oehler, EH Estey, RB Walter. "Mini-Vs. regular-dose CLAG-M (cladribine, cytarabine, G-CSF, and mitoxantrone) in medically less fit adults with newly-diagnosed acute myeloid leukemia (AML) and other high-grade myeloid neoplasms." Blood Conference: (2019///): #pages#. DB - Embase	Intervention/ comparator
4272	NCT00382590. "Azacytidine With Valproic Acid Versus Ara-C in Acute Myeloid Leukemia (AML)/ Myelodysplastic Syndrome (MDS) Patients." #journal# gov/show/NCT00382590. 2006. (2006///): #pages#. EBM Reviews - Cochrane Central Register of Controlled Trials	Intervention/ comparator
4386	NCT00180115. "AML96 - Risk-Adapted and Randomized Postremission-Therapy for Adult Acute Myeloid Leukemia Patients." #journal# gov/show/NCT00180115. 2005. (2005///): #pages#. EBM Reviews - Cochrane Central Register of Controlled Trials	Intervention/ comparator
6368	I. Levi, I. Grotto, R. Yerushalmi, I. Ben-Bassat, O. Shpilberg. "Meta-analysis of autologous bone marrow transplantation versus chemotherapy in adult patients with acute myeloid leukemia in first remission." Leukemia Research 28 (2004///): 605. IN - NHS Centre for Reviews and Dissemination. University of York, York, UK	Intervention/ comparator
84	TC Puty, JS Sarraf, TC Do Carmo Almeida, VCB Filho, LEW de Carvalho, FLA Fonseca, F. Adami. "Evaluation of the impact of single-nucleotide polymorphisms on treatment response, survival and toxicity with cytarabine and anthracyclines in patients with acute myeloid leukaemia: a systematic review protocol". #journal# 8 (2019/05/03/): 109. DB - Ovid MEDLINE(R) and Epub Ahead of Print, In-Process & Other Non-Indexed Citations and Daily Systematic Reviews. 8(1):109, 2019 05 03	Study design
299	P. Paschka, RF Schlenk, D. Weber, A. Benner, L. Bullinger, M. Heuser, VI Gaidzik, F. Thol, M. Agrawal, V. Teleanu, M. Lubbert, W. Fiedler, M. Radsak, J. Krauter, HA Horst, R. Greil, K. Mayer, A. Kundgen, U. Martens, G. Heil, HR Salih, B. Hertenstein, C. Schwanen, G. Wulf, E. Lange, M. Pfreundschuh, M. Ringhoffer, M. Girschikofsky, T. Heinicke, D. Kraemer, G. Gohring, A. Ganser, K. Dohner, H. Dohner. "Adding dasatinib to intensive treatment in core-binding factor acute myeloid leukemia-results of the AMLSG 11-08 trial". Leukemia 32 (2018/07//): 1621. DB - Ovid MEDLINE(R) and Epub Ahead of Print, In-Process & Other Non-Indexed Citations and Daily Leukemia. 32(7):1621-1630, 2018 07	Study design
338	PG Maslak, T. Dao, Y. Bernal, SM Chanel, R. Zhang, M. Frattini, T. Rosenblat, JG Jurcic, RJ Brentjens, ME Arcila, R. Rampal, JH Park, D. Douer, L. Katz, N. Sarlis, MS Tallman, DA Scheinberg. "Phase 2 trial of a multivalent WT1 peptide vaccine (galinpepimut-S) in acute myeloid leukemia". Blood Adv 2 (2018/02/13/): 224. DB - Ovid MEDLINE(R) and Epub Ahead of Print, In-Process & Other Non-Indexed Citations and Daily Blood Advances. 2(3):224-234, 2018 02 13	Study design

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403	JE Cortes, Smith B. Douglas, ES Wang, A. Merchant, VG Oehler, M. Arellano, DJ DeAngelo, DA Pollyea, MA Sekeres, T. Robak, WW Ma, M. Zeremski, Shaik M. Naveed, Laird A. Douglas, A. O'Connell, G. Chan, MA Schroeder. "Glasdegib in combination with cytarabine and daunorubicin in patients with AML or high-risk MDS: Phase 2 study results". #journal# 93 (2018/11//): 1301. DB - Ovid MEDLINE(R) and Epub Ahead of Print, In-Process & Other Non-Indexed Citations and Daily American Journal of Hematology. 93(11):1301-1310, 2018 11	Study design
506	JE Karp, BD Smith, I. Gojo, JE Lancet, J. Greer, M. Klein, L. Morris, MJ Levis, SD Gore, JJ Wright, E. Garrett-Mayer. "Phase II trial of tipifarnib as maintenance therapy in first complete remission in adults with acute myelogenous leukemia and poor-risk features". Clinical Cancer Research 14 (2008/05/15/): 3077. DB - Ovid MEDLINE(R) and Epub Ahead of Print, In-Process & Other Non-Indexed Citations and Daily Clinical Cancer Research. 14(10):3077-82, 2008 May 15	Study design
1101	TM Kadia, S. Faderl, F. Ravandi, E. Jabbour, G. Garcia-Manero, G. Borthakur, A. Ferrajoli, M. Konopleva, J. Burger, X. Huang, X. Wang, S. Pierce, M. Brandt, J. Feliu, J. Cortes, H. Kantarjian. "Final results of a phase 2 trial of clofarabine and low-dose cytarabine alternating with decitabine in older patients with newly diagnosed acute myeloid leukemia". Cancer 121 (2015/07/15/): 2375. DB - Ovid MEDLINE(R) and Epub Ahead of Print, In-Process & Other Non-Indexed Citations and Daily Cancer. 121(14):2375-82, 2015 Jul 15	Study design
1111	N. Boissel, A. Renneville, T. Leguay, PC Lefebvre, C. Recher, T. Lecerf, E. Delabesse, C. Berthon, O. Blanchet, T. Prebet, C. Pautas, P. Chevallier, S. Lepretre, S. Girault, C. Bonmati, R. Guieze, C. Himberlin, E. Randriamalala, C. Preudhomme, E. Jourdan, H. Dombret, N. Ifrah. "Dasatinib in high-risk core binding factor acute myeloid leukemia in first complete remission: a French Acute Myeloid Leukemia Intergroup trial". Haematologica 100 (2015/06//): 780. DB - Ovid MEDLINE(R) and Epub Ahead of Print, In-Process & Other Non-Indexed Citations and Daily Haematologica. 100(6):780-5, 2015 Jun	Study design
1459	G. Garcia-Manero, FP Tambaro, NB Bekele, H. Yang, F. Ravandi, E. Jabbour, G. Borthakur, TM Kadia, MY Konopleva, S. Faderl, JE Cortes, M. Brandt, Y. Hu, D. McCue, WM Newsome, SR Pierce, Lima M. de, HM Kantarjian. "Phase II trial of vorinostat with idarubicin and cytarabine for patients with newly diagnosed acute myelogenous leukemia or myelodysplastic syndrome". Journal of Clinical Oncology 30 (2012/06/20/): 2204. DB - Ovid MEDLINE(R) and Epub Ahead of Print, In-Process & Other Non-Indexed Citations and Daily Journal of Clinical Oncology. 30(18):2204-10, 2012 Jun 20	Study design
2293	MS Nilsson, A. Hallner, M. Brune, S. Nilsson, FB Thoren, A. Martner, K. Hellstrand. "Complete remission after the first cycle of induction chemotherapy determines the clinical efficacy of relapse-preventive immunotherapy in acute myeloid leukemia". Blood Conference: (2019///): #pages#. DB - Embase	Study design
3242	S. Anguille, AL Van de Velde, EL Smits, VF Van Tendeloo, G. Juliusson, N. Cools, G. Nijs, B. Stein, E. Lion, AV Driessche, I. Vandenbosch, A. Verlinden, AP Gadisseur, WA Schroyens, L. Muylle, K. Vermeulen, M.-B. Maes, K. Deiteren, R. Malfait, E. Gostick, M. Lammens, MM Couttenye, P. Jorens, H. Goossens, DA Price, K. Ladell, Y. Oka, F. Fujiki, Y. Oji, H. Sugiyama, ZN Berneman. "Dendritic cell vaccination as postremission treatment to prevent or delay relapse in acute myeloid leukemia". Blood 130 (2017///): 1713. DB - Embase	Study design
4435	NCT00931138. "Treatment of Acute Myeloid Leukemia (AML) in Adults 50 to 70 Years, Study of Two Anthracyclines and the Interest of Maintenance Treatment With Interleukin 2". #journal# gov/show/NCT00931138. 2009. (2009///): #pages#. EBM Reviews - Cochrane Central Register of Controlled Trials	Study design
4464	NCT01324063. "A Randomized Phase III Study of Intensive Consolidation With High Dose Cytosine Arabinoside in Acute Myelogenous Leukemia (AML-8B)". #journal# gov/show/NCT01324063. 2011. (2011///): #pages#. EBM Reviews - Cochrane Central Register of Controlled Trials	Study design
4889	ISRCTN62678383. "WT1 immunity via DNA vaccination in haematological malignancies by intramuscular injection and electroporation". #journal#	Study design

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5222	D. Niederwieser, VS Hoffmann, M. Pfirrmann, HK Al-Ali, S. Schwind, V. Vucinic, R. Krahl, C. Kahl, H.-H. Wolf, U. Kreibich, D. Hahling, U. Hegenbart, C. Hirt, N. Peter, A. Florschuetz, K. Reifenrath, A. Schulze, N. Zojer, S. Scholl, C. Junghanss, W. Ponisch, S. Heyn, HG Sayer, A. Hochhaus, T. Heinicke, T. Fischer, A. Kramer, P. Dreger, G. Maschmeyer, U. Krug, MC Sauerland, A. Heinecke, R. Hehlmann, E. Lengfelder, W. Hiddemann, H. Serve, C. Muller-Tidow, WE Berdel, T. Buchner. "Comparison of treatment strategies in patients over 60 years with AML: final analysis of a prospective randomized German AML intergroup study". Blood 128 (2016///): #pages#. EBM Reviews - Cochrane Central Register of Controlled Trials	Study design
5314	M. Cuzzola, C. Alati, Bartolomeo P. Di, P. Salutari, A. Candoni, E. Simeone, A. Cortelezzi, A. Freyrie, Raimondo F. Di, V. Calafiore, P. Niscola, D. Capelli, G. Irrera, C. Rigolino, MC Cannata, A. Marino, Angelis A. De, F. Ronco, EN Oliva. "Biological markers of relapse in elderly patients with AML in CR after induction-consolidation chemotherapy and maintenance with 5-azacitidine". Haematologica 101 (2016///): 370. EBM Reviews - Cochrane Central Register of Controlled Trials	Study design
5399	R. Schlenk, H. Dombret, S. Amadori, P. Montesinos, M. Levis, MA Sekeres, J. Cortes, A. Perl, O. Zernovak, D. Mires, N. Ge, H. Zhang, J. Hanyok, S. Macintyre, S. Gokmen, K. Kobayashi, H. Erba. "QuANTUM-First: phase 3, double-blind, placebo-controlled study of quizartinib in combination with induction and consolidation chemotherapy, and as maintenance therapy in patients (pts) with newly diagnosed (NDx) FLT3-ITD acute myeloid leukemia (AML)". Annals of Oncology 28 (2017///): v370. EBM Reviews - Cochrane Central Register of Controlled Trials	Study design
5412	T. Ouatas, V. Duval, K. Sinclair, N. Berkowitz. "Concomitant use of midostaurin with strong CYP3A4 inhibitors: an analysis from the ratify trial". Blood 130 (2017///): #pages#. EBM Reviews - Cochrane Central Register of Controlled Trials	Study design
5413	RM Stone, SJ Mandrekar, BL Sanford, K. Laumann, SM Geyer, CD Bloomfield, K. Dohner, C. Thiede, G. Marcucci, FL Coco, RB Klisovic, A. Wei, J. Sierra, MA Sanz, JM Brandwein, TMM De Witte, D. Niederwieser, FR Appelbaum, BC Medeiros, MS Tallman, J. Krauter, RF Schlenk, A. Ganser, H. Serve, G. Ehninger, S. Amadori, H. Dohner, RA Larson. "The addition of midostaurin to standard chemotherapy decreases cumulative incidence of relapse (CIR) in the international prospective randomized, placebo-controlled, double-blind trial (CALGB 10603/ratify) for newly diagnosed acute myeloid leukemia (AML) patients with FLT3 mutations". Blood 130 (2017///): #pages#. EBM Reviews - Cochrane Central Register of Controlled Trials	Study design
5423	RB Walter, M. Othus, KF Orlowski, EN McDaniel, BL Scott, PS Becker, M.-E. Percival, PC Hendrie, BC Medeiros, MT Chiarella, AC Louie, EH Estey. "Randomized study of CPX-351 for medically less-fit adults with newly diagnosed acute myeloid leukemia or other high-grade myeloid neoplasm". Blood 130 (2017///): #pages#. EBM Reviews - Cochrane Central Register of Controlled Trials	Study design
5425	GJ Roboz, SA Strickland, MR Litzow, A. Dalovisio, AE Perl, G. Bonifacio, K. Haines, A. Barbera, D. Purkayastha, K. Sweet. "RADIUS-X: an expanded treatment protocol of midostaurin in adults with newly diagnosed FLT3-mutation-positive acute myeloid leukemia eligible for standard chemotherapy". Blood 130 (2017///): #pages#. EBM Reviews - Cochrane Central Register of Controlled Trials	Study design
5455	N. Vey, P.-Y. Dumas, C. Recher, L. Gastaud, B. Lioure, C.-E. Bulabois, C. Pautas, J.-P. Marolleau, S. Lepretre, E. Raffoux, X. Thomas, Y. Hicheri, C. Bonmati, B. Quesnel, P. Rousselot, S. Castaigne, E. Jourdan, JV Malfuson, G. Guillerm, JH Bouhris, M. Ojeda, M. Hunault, N. Ifrah, C. Gardin, A. Delannoy, L. Beautier, C. Paturel, P. Andre, R. Zerbib, C. Preudhomme, A. Toubert, N. Dulphy, D. Olive, A. Pigneux, H. Dombret. "Randomized phase 2 trial of lirilumab (anti-KIR monoclonal antibody, mab) as maintenance treatment in elderly patients (pts) with acute myeloid leukemia (AML): results of the EFFIKIR trial". Blood 130 (2017///): #pages#. EBM Reviews - Cochrane Central Register of Controlled Trials	Study design
5460	RA Larson, SJ Mandrekar, BL Sanford, K. Laumann, SM Geyer, CD Bloomfield, C. Thiede, TW Prior, K. Dohner, G. Marcucci, FL Coco, RB Klisovic, A. Wei, J. Sierra, MA Sanz, JM Brandwein, TMM De Witte, D. Niederwieser, FR Appelbaum, BC Medeiros, MS Tallman, J. Krauter, RF Schlenk, A.	Study design

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	Ganser, H. Serve, G. Ehninger, S. Amadori, H. Dohner, RM Stone. "An analysis of maintenance therapy and post-midostaurin outcomes in the international prospective randomized, placebo-controlled, double-blind Trial (CALGB 10603/RATIFY) for newly diagnosed Acute Myeloid Leukemia (AML) Patients with FLT3 Mutations". Blood 130 (2017///): #pages#. EBM Reviews - Cochrane Central Register of Controlled Trials	
5464	K. Dohner, C. Thiede, RA Larson, TW Prior, G. Marcucci, D. Jones, J. Krauter, M. Heuser, Coco F. Lo, T. Ottone, J. Nomdedeu, SJ Mandrekar, BL Sanford, K. Laumann, SM Geyer, RB Klisovic, A. Wei, J. Sierra, MA Sanz, JM Brandwein, TMM De Witte, JH Jansen, D. Niederwieser, FR Appelbaum, BC Medeiros, MS Tallman, RF Schlenk, A. Ganser, H. Serve, G. Ehninger, S. Amadori, Y. Cheng, C. Pallaud, RM Stone, H. Dohner, CD Bloomfield. "Prognostic impact of NPM1/FLT3-ITD genotypes from randomized patients with acute myeloid leukemia (AML) treated within the international ratify study". Blood 130 (2017///): #pages#. EBM Reviews - Cochrane Central Register of Controlled Trials	Study design
5465	C. Rollig, H. Serve, A. Huttmann, R. Noppeney, C. Muller-Tidow, U. Krug, CD Baldus, CH Brandts, V. Kunzmann, H. Einsele, A. Kramer, K. Schafer-Eckart, A. Neubauer, A. Burchert, A. Giagounidis, SW Krause, A. Mackensen, WE Aulitzky, M. Hanel, R. Herbst, A. Kiani, N. Frickhofen, J. Kullmer, U. Kaiser, H. Link, T. Geer, A. Reichle, C. Junghanss, R. Repp, F. Heits, HA Durk, T. Illmer, M. Bornhauser, M. Schaich, SB Parmentier, M. Goerner, Bonin M. von, C. Thiede, J. Schetelig, M. Kramer, WE Berdel, G. Ehninger. "The addition of sorafenib to standard AML treatment results in a substantial reduction in relapse risk and improved survival. Updated results from long-term follow-up of the randomized- controlled soraml trial". Blood 130 (2017///): #pages#. EBM Reviews - Cochrane Central Register of Controlled Trials	Study design
5467	G. Huls, D. Chitu, V. Havelange, M. Jongen-Lavrencic, A. van de Loosdrecht, BJ Biemond, H. Sinnege, B. Hodossy, C. Graux, Kooij M. van Marwijk, Weerdt O. de, D. Breems, S. Klein, J. Kuball, GJ Ossenkoppele, B. Lowenberg, E. Vellenga. "Randomized maintenance therapy with azacitidine (Vidaza) in older patients (> = 60 years of age) with acute myeloid leukemia (AML) and refractory anemia with excess of blasts (RAEB, RAEB-t). results of the HOVON97 phase III randomized multicentre study (eudract 2008-001290-15)". Blood 130 (2017///): #pages#. EBM Reviews - Cochrane Central Register of Controlled Trials	Study design
5532	R. Nelson. "Postconsolidation immunotherapy in leukaemia remission". Lancet Oncology 7 (2006///): 367. EBM Reviews - Cochrane Central Register of Controlled Trials	Study design
5579	PG Maslak, T. Dao, Y. Bernal, SM Chanel, R. Zhang, MG Frattini, TL Rosenblat, JG Jurcic, R. Rampal, JH Park, D. Douer, L. Katz, AA Gutierrez, MS Tallman, DA Scheinberg. "Phase II trial of WT1 analog peptide vaccine in adults with acute myeloid leukemia (AML) in first complete remission (CR)". Journal of Clinical Oncology 34, 2016. (2016///): #pages#. EBM Reviews - Cochrane Central Register of Controlled Trials	Study design
5651	C. Alati, F. Ronco, A. Candoni, Bartolomeo P. Di, E. Simeone, A. Freyrie, A. Volpe, P. Musto, N. Cascavilla, D. Capelli, Raimondo F. Di, P. Niscola, A. Cortelezzi, P. Salutari, EN Oliva. "Quality of life at diagnosis in elderly patients with acute myeloid leukemia considered fit for induction of remission chemotherapy". Haematologica #volume# (2015///): 36. EBM Reviews - Cochrane Central Register of Controlled Trials	Study design
5683	Selina Luger, Xiaopan Yao, Elisabeth Paietta, Rhett Ketterling, Witold Rybka, Mark R. Litzow. "Tipifarnib is well tolerated as maintenance therapy in acute myeloid leukemia (AML). significant, but non-fatal, hematologic toxicity not ameliorated by dose reduction. preliminary results of the phase III Intergroup trial E2902". Blood 116 (2010///): 2010. EBM Reviews - Cochrane Central Register of Controlled Trials	Study design
5686	RH van der Jagt, K. Robinson, DP Sheridan, R. Delage, LM Larratt, L. Yetisir, G. Wells. "Long term follow-up of a randomized trial comparing response adapted (RA), non-cross resistant induction and consolidation with idarubicin/cytarabine (IDAC) followed by mitoxantone/etoposide (NOVE) compared with consolidation with high dose cytarabine (HDACc) in adult patients with aml. A study by the canadian leukemia studies group (CLSG)". Blood 108 (2006///): 565, 2006. EBM Reviews - Cochrane Central Register of Controlled Trials	Study design

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5742	RHC van der Jagt, KS Robinson, DP Sheridan, R. Delage, LM Larratt, E. Yetisir, GA Wells. "A multicenter randomized trial comparing response-adapted (RA), non-cross-resistant induction and consolidation with idarubicin/cytarabine (IDAC) followed by mitoxantrone/etoposide (NOVE) compared with consolidation with high dose cytarabine (HDAC) in adult patients with AML. A study by the Canadian Leukemia Studies Group (CLSG)". Blood 106 (2005///): 2005. EBM Reviews - Cochrane Central Register of Controlled Trials	Study design
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5797	A. Pigneux, C. Himberlin, M. Hunault-Berger, F. Witz, C. Recher, J.-L. Harousseau, O. Tournilhac, C. Berthou, M. Escoffre-Barbe, D. Guyotat, N. Fegueux, M. Delain, B. Lioure, F. Bauduer, E. Jourdan, D. Bouscary, L. Legros, F. Perry, N.-J. Milpied, M.-C. Bene, N. Ifrah, J.-J. Sotto. "A multicenter randomized comparison of maintenance treatment with androgens in elderly acute myeloid leukemia after ICL regimen as induction therapy: results of the Goelams-2002 study". Blood 108 (2006///): 561, 2006. EBM Reviews - Cochrane Central Register of Controlled Trials	Study design
5800	MR Baer, SL George, MA Caligiuri, BL Sanford, L. O'Loughlin, K. Mrozek, JE Kolitz, BL Powell, JO Moore, RM Stone, CD Bloomfeld, RA Larson. "Phase III study of immunotherapy with recombinant interleukin-2 (IL-2) versus no further therapy in acute myeloid leukemia (AML) patients 60 years in first complete remission (CALGB 9720)". Blood 108 (2006///): 129, 2006. EBM Reviews - Cochrane Central Register of Controlled Trials	Study design
5802	JE Kolitz, V. Hars, DJ DeAngelo, SL Allen, TC Shea, R. Vij. "Phase III trial of immunotherapy with recombinant interleukin-2 (rIL-2) versus observation in patients < 60 years with acute myeloid leukemia (AML) in first remission (CR1): preliminary results from cancer and leukemia group B (CALGB) 19808". Blood 110 (2007///): 53a. EBM Reviews - Cochrane Central Register of Controlled Trials	Study design
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6063	W. Blum, BL Sanford, R. Klisovic, DJ DeAngelo, G. Uy, BL Powell, W. Stock, MR Baer, JE Kolitz, ES Wang, E. Hoke, K. Mrozek, J. Kohlschmidt, CD Bloomfield, S. Geyer, G. Marcucci, RM Stone, RA Larson. "Maintenance therapy with decitabine in younger adults with acute myeloid leukemia in first remission: a phase 2 Cancer and Leukemia Group B Study (CALGB 10503)". Leukemia 31 (2017///): 34. EBM Reviews - Cochrane Central Register of Controlled Trials	Study design
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4561	NCT01686334. "Efficacy Study of Dendritic Cell Vaccination in Patients With Acute Myeloid Leukemia in Remission". #journal# gov/show/NCT01686334. 2012. (2012///): #pages#. EBM Reviews - Cochrane Central Register of Controlled Trials	Unavailable
4573	NCT02835729. "A Study of Indoximod in Combination With (7+3) Chemotherapy in Patients With Newly Diagnosed Acute Myeloid Leukemia". #journal# gov/show/NCT02835729. 2016. (2016///): #pages#. EBM Reviews - Cochrane Central Register of Controlled Trials	Unavailable
4578	NCT02085408. "Clofarabine or Daunorubicin Hydrochloride and Cytarabine Followed By Decitabine or Observation in Treating Older Patients With Newly Diagnosed Acute Myeloid Leukemia". #journal# gov/show/NCT02085408. 2014. (2014///): #pages#. EBM Reviews - Cochrane Central Register of Controlled Trials	Unavailable
4580	NCT01639456. "CD3/CD19 Depleted or CD3 Depleted/CD56 Selected Haploid Donor Natural Killer Cell Treatment in Older AML in First Complete Remission". #journal# gov/show/NCT01639456. 2012. (2012///): #pages#. EBM Reviews - Cochrane Central Register of Controlled Trials	Unavailable
4592	NCT01636609. "Combination Study of Cytarabine and Tosedostat in Acute Myeloid Leukemia (AML) or High Risk Myelodysplastic Syndromes (MDS)". #journal# gov/show/NCT01636609. 2012. (2012///): #pages#. EBM Reviews - Cochrane Central Register of Controlled Trials	Unavailable
4599	NCT01289457. "Clofarabine, Idarubicin, and Cytarabine (CIA) Versus Fludarabine, Idarubicin, and Cytarabine (FLAI) in Acute Myelogenous Leukemia (AML) and High-Risk Myelodysplastic Syndrome". #journal# gov/show/NCT01289457. 2011. (2011///): #pages#. EBM Reviews - Cochrane Central Register of Controlled Trials	Unavailable
4613	NCT02305563. "An Investigational Immuno-therapy Study of Ulocuplumab in Combination With Low Dose Cytarabine in Patients With Newly Diagnosed Acute Myeloid Leukemia". #journal# gov/show/NCT02305563. 2014. (2014///): #pages#. EBM Reviews - Cochrane Central Register of Controlled Trials	Unavailable
4616	NCT00121303. "Cytarabine and Daunorubicin With or Without Gemtuzumab Ozogamicin in Treating Older Patients With Acute Myeloid Leukemia or Myelodysplastic Syndromes". #journal# gov/show/NCT00121303. 2005. (2005///): #pages#. EBM Reviews - Cochrane Central Register of Controlled Trials	Unavailable
4621	NCT02432872. "Treatment of Older Adult Acute Myeloid Leukemia Patients Aged 55 to 65 Years". #journal# gov/show/NCT02432872. 2015. (2015///): #pages#. EBM Reviews - Cochrane Central Register of Controlled Trials	Unavailable
4636	NCT03417427. "A Clinical Trail of Demethylation Drug Combined With Chemotherapy in Intermediate-risk AML". #journal# gov/show/NCT03417427. 2017. (2017///): #pages#. EBM Reviews - Cochrane Central Register of Controlled Trials	Unavailable
4667	NCT03059485. "DC/AML Fusion Cell Vaccine vs DC/AML Fusion Cell Vaccine Plus Durvalumab vs Observation in Patients Who Achieve a Chemotherapy-induced Remission". #journal# gov/show/NCT03059485. 2017. (2017///): #pages#. EBM Reviews - Cochrane Central Register of Controlled Trials	Unavailable
4693	NCT03665480. "The Effect of G-CSF on MRD After Induction Therapy in Newly Diagnosed AML". #journal# gov/show/NCT03665480. 2018. (2018///): #pages#. EBM Reviews - Cochrane Central Register of Controlled Trials	Unavailable
4733	EUCTR2010-019710-24-IT. "A Randomized Study to Evaluate the Efficacy of 5-AZA for Post-Remission Therapy of Acute Myeloid Leukemia in Elderly Patients (QoLESS AZA-AMLE) - QoLESS-AZA-AMLE". #journal# who.int/trialsearch/Trial2.aspx?TrialID=EUCTR2010-019710-24-IT. 2010. (2010///): 019710. EBM Reviews - Cochrane Central Register of Controlled Trials	Unavailable
4736	EUCTR2008-001290-15-NL. "Study for the treatment of patients who have been successfully treated for leukemia before, to keep the patient leukemia free". #journal# who.int/trialsearch/Trial2.aspx?TrialID=EUCTR2008-001290-15-NL. 2008. (2008///): 001290. EBM Reviews - Cochrane Central Register of Controlled Trials	Unavailable

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Ref ID	Citation	Reason for exclusion
4767	EUCTR2004-001918-13-GB. "Randomised induction and post induction therapy in older patients (>=61 years of age) with acute myeloid leukaemia (AML) and refractory anaemia with excess blasts (RAEB, RAEB-t) - HOVON 43". #journal# who.int/trialsearch/Trial2.aspx?TrialID=EUCTR2004-001918-13-GB. 2005. (2005///): 001918. EBM Reviews - Cochrane Central Register of Controlled Trials	Unavailable
4817	EUCTR2004-004321-95-AT. "Randomized phase ii-study on valproic acid, all-trans retinoic acid and their combination in induction and consolidation therapy as well as pegfilgrastim after consolidation therapy in younger patients with newly diagnosed acute myeloid leukemia". #journal# who.int/trialsearch/Trial2.aspx?TrialID=EUCTR2004-004321-95-AT. 2005. (2005///): 004321. EBM Reviews - Cochrane Central Register of Controlled Trials	Unavailable
4819	EUCTR2011-001845-34-IT. "Liposomal amphotericin b (Ambisome) 10 Mg/kg once a week for 10 weeks as maintenance antifungal therapy for proven/probable invasive fungal infection in hematologic patients with acute myeloid leukaemia and/or in allogeneic hematopoietic stem cell transplant recipients". #journal# who.int/trialsearch/Trial2.aspx?TrialID=EUCTR2011-001845-34-IT. 2012. (2012///): 001845. EBM Reviews - Cochrane Central Register of Controlled Trials	Unavailable
4840	EUCTR2009-015720-28-BE. "Therapeutic efficacy of Wilms tumor gene (WT1) mRNA-electroporated autologous dendritic cell vaccination in patients with myeloid malignancies and multiple myeloma: a phase II trial". #journal# who.int/trialsearch/Trial2.aspx?TrialID=EUCTR2009-015720-28-BE. 2009. (2009///): 015720. EBM Reviews - Cochrane Central Register of Controlled Trial	Unavailable
4841	EUCTR2013-002730-21-GB. "The AML18 Trial is an intensive chemotherapy trial for patients primarily over the age of 60 with AML and High Risk Myelodysplastic disease. This randomised, up to 2000 patient trial will evaluate the effect of adding novel treatment combinations to standard chemotherapy". #journal# who.int/trialsearch/Trial2.aspx?TrialID=EUCTR2013-002730-21-GB. 2013. (2013///): 002730. EBM Reviews - Cochrane Central Register of Controlled Trials	Unavailable
4850	NTR1810. "Randomized maintenance therapy with Azacitidine (Vidaza) in older patients (> = 60 years of age) with acute myeloid leukemia (AML) and refractory anemia with excess of blasts (RAEB, RAEB-t)". #journal# who.int/trialsearch/Trial2.aspx?TrialID=NTR1810. 2009. (2009///): #pages#. EBM Reviews - Cochrane Central Register of Controlled Trials	Unavailable
4861	NTR291. "Risk adapted treatment of acute myelocytic leukemia (AML)". #journal# who.int/trialsearch/Trial2.aspx?TrialID=NTR291. 2005. (2005///): #pages#. EBM Reviews - Cochrane Central Register of Controlled Trials	Unavailable
4867	EUCTR2014-000319-15-ES. "Clinical trial comparing azacytidine (Vidaza(R)) versus fludarabine plus cytarabine in elderly patients with newly diagnosed acute myeloid leukemia". #journal# who.int/trialsearch/Trial2.aspx?TrialID=EUCTR2014-000319-15-ES. 2014. (2014///): 000319. EBM Reviews - Cochrane Central Register of Controlled Trials	Unavailable
4939	EUCTR2015-004856-24-HU. "A Clinical Trial Study of Quizartinib (AC220) Administered in Combination with Induction and Consolidation Chemotherapy, and Administered as Maintenance Therapy in Subjects 18 to 75 Years Old with Newly Diagnosed Acute Myeloid Leukemia". #journal# who.int/trialsearch/Trial2.aspx?TrialID=EUCTR2015-004856-24-HU. 2016. (2016///): 004856. EBM Reviews - Cochrane Central Register of Controlled Trials	Unavailable
4963	EUCTR2012-003457-28-PT. "The Efficacy and Safety of Oral Azacitidine Plus Best Supportive Care Versus Placebo and Best Supportive Care in Subjects with Acute Myeloid Leukemia (AML) no longer experiences symptoms of the disease". #journal# who.int/trialsearch/Trial2.aspx?TrialID=EUCTR2012-003457-28-PT. 2012. (2012///): 003457. EBM Reviews - Cochrane Central Register of Controlled Trials	Unavailable
4987	EUCTR2012-001494-91-BE. "Dendritic cell-based immunotherapy targeting the tumor protein WT1 to treat adult patients with acute myeloid leukemia". #journal# who.int/trialsearch/Trial2.aspx?TrialID=EUCTR2012-001494-91-BE. 2012. (2012///): 001494. EBM Reviews - Cochrane Central Register of Controlled Trials	Unavailable

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Ref ID	Citation	Reason for exclusion
5037	EUCTR2016-001643-39-CZ. "Effectiveness and safety of gilteritinib (ASP2215) as maintenance treatment (maintain the response achieved during the first course of treatment) for Acute myeloid leukemia patients who are in a first complete remission (no residual leukemia cells in your bone marrow), with mutations in the FLT3 gene compared to placebo given alone". #journal# who.int/trialsearch/Trial2.aspx?TrialID=EUCTR2016-001643-39-CZ. 2016. (2016///): 001643. EBM Reviews - Cochrane Central Register of Controlled Trials	Unavailable
5047	U.M.I.N. JPRN. "Phase 2 trial for hematological CR patients of AML after chemotherapy". #journal# who.int/trialsearch/Trial2.aspx?TrialID=JPRN-UMIN000015870. 2014. (2014///): #pages#. EBM Reviews - Cochrane Central Register of Controlled Trials	Unavailable
5055	EUCTR2006-005562-39-FR. "ALFA 0703: a Randomized Multicenter Phase III Study to Evaluate the Role of All-trans Retinoic Acid (ATRA) in Combination with Chemotherapy or azacitidine as salvage therapy and Azacitidine as Maintenance Therapy in Older Patients with Acute Myeloblastic Leukemia (AML) - ALFA 0703". #journal# who.int/trialsearch/Trial2.aspx?TrialID=EUCTR2006-005562-39-FR. 2008. (2008///): 005562. EBM Reviews - Cochrane Central Register of Controlled Trials	Unavailable
5070	IRCT2015072623349N1. "The effect of long-acting subcutaneous drug in increasing white blood cells in patients with leukemia after chemotherapy". #journal# who.int/trialsearch/Trial2.aspx?TrialID=IRCT2015072623349N1. 2016. (2016///): #pages#. EBM Reviews - Cochrane Central Register of Controlled Trials	Unavailable
5103	NTR4376. "Randomized study with a run-in dose-selection phase to assess the added value of lenalidomide in combination with standard remission-induction chemotherapy and post-remission treatment in patients aged 18-65 years with previously untreated acute myeloid leukemia (AML) or high risk myelodysplasia (MDS) (IPSS-R risk score > 4.5)". #journal# who.int/trialsearch/Trial2.aspx?TrialID=NTR4376. 2014. (2014///): #pages#. EBM Reviews - Cochrane Central Register of Controlled Trials	Unavailable
5118	EUCTR2013-002843-26-DE. "Randomized study with a run-in dose-selection phase to assess the added value of lenalidomide in combination with standard remission-induction chemotherapy and post-remission treatment in patients aged 18-65 years with previously untreated acute myeloid leukemia (AML) or high risk myelodysplasia (MDS) (IPSS-R risk score > 4.5)". #journal# who.int/trialsearch/Trial2.aspx?TrialID=EUCTR2013-002843-26-DE. 2015. (2015///): 002843. EBM Reviews - Cochrane Central Register of Controlled Trials	Unavailable
5124	ISRCTN31682779. "A trial for older patients with acute myeloid leukaemia and high risk myelodysplastic syndrome". #journal# who.int/trialsearch/Trial2.aspx?TrialID=ISRCTN31682779. 2013. (2013///): #pages#. EBM Reviews - Cochrane Central Register of Controlled Trials	Unavailable
5629	"E2902: a Phase III randomized study of farnesyl transferase inhibitor R115777 in acute myeloid leukemia patients in second or subsequent remission or in remission after primary induction failure or patients over age 60 in first remission". Clinical Advances in Hematology and Oncology 5 (2007///): 13. EBM Reviews - Cochrane Central Register of Controlled Trials	Unavailable

MA = meta-analysis; NMA = network meta-analysis; SLR = systematic literature review.

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Table A-10. Studies excluded at the full-text screening phase (updated review)

Excluded due to population (n = 1)
1. Wen B, You W, Yang S, Du X (2020) Indirect comparison of azacitidine and decitabine for the therapy of elderly patients with acute myeloid leukemia: A systematic review and network meta-analysis. Experimental Hematology and Oncology 9 (1): 3.
Excluded due to intervention/comparator (n = 1)
1. (2020) A prospective, randomized, open, multicenter clinical study of dexithabine combined with IA and IA alone in primary acute myeloid leukemia. http://wwwwhoint/trialsearch/Trial2aspx?TrialID=ChiCTR2000034253
Excluded due to study design (n = 5)
1. (2020) Molecular landscape and prognostic impact of FLT3 internal tandem duplication insertion site in acute myeloid leukemia (AML): results from the ratify study (alliance 10603). Molecular landscape and prognostic impact of FLT3 internal tandem duplication insertion site in acute myeloid leukemia (AML): results from the ratify study (alliance 10603) 4 26. 2. Advani AS, Tse W, Li H, Jia X, Elson P et al. (2021) A Phase II Trial of Imatinib Mesylate as Maintenance Therapy for Patients With Newly Diagnosed C-kit-positive Acute Myeloid Leukemia. Clinical Lymphoma, Myeloma and Leukemia. 3. Largeaud L, Cornillet-Lefebvre P, Hamel JF, Prade N, Dufrechou S et al. (2020) Lomustine is beneficial to older AML with ELN2017 adverse risk profile and intermediate karyotype: a FILO study. Leukemia. 4. Nilsson MS, Hallner A, Brune M, Nilsson S, Thoren FB et al. (2020) Immunotherapy with HDC/IL-2 may be clinically efficacious in acute myeloid leukemia of normal karyotype. Human Vaccines and Immunotherapeutics 16 (1): 109-111. 5. Marcucci G, Geyer S, Laumann K, Zhao W, Bucci D et al. (2020) Combination of dasatinib with chemotherapy in previously untreated core binding factor acute myeloid leukemia: CALGB 10801. Blood Advances 4 (4): 696-705.
Excluded SLRs/MA/NMA (n = 7)
1. Majothi S, Adams D, Loke J, Stevens SP, Wheatley K et al. (2020) FLT3 inhibitors in acute myeloid leukaemia: assessment of clinical effectiveness, adverse events and future research-a systematic nd meta-analysis. Systematic reviews 9 (1): 285. 2. Reljic T, Sehovic M, Lancet J, Kim J, Al-Ali N et al. (2020) Benchmarking treatment effects for patients over 70 with acute myeloid leukemia: A systematic review and meta-analysis. Journal of Geriatric Oncology 11 (8): 1293-1308. 3. Liu B, Guo Y, Deng L, Qiao Y, Jian J (2020) The efficacy and adverse events of venetoclax in combination with hypomethylating agents treatment for patients with acute myeloid leukemia and myelodysplastic syndrome: a systematic review and meta-analysis. Hematology (United Kingdom) 25 (1): 414-423. 4. Htut TW, Ball S, Khandelwal N, Wongsaengsak S, Mogollon-Duffo F et al. (2020) Efficacy of FMS-like Tyrosine Kinase 3 (FLT3) inhibitors in patients with acute myeloid leukemia. Br J Haematol 189 (Supplement 1): 52-53. 5. Golicki D, Jaskowiak K, Wojcik A, Mlynczak K, Dobrowolska I et al. (2020) EQ-5D-Derived Health State Utility Values in Hematologic Malignancies: A Catalog of 796 Utilities Based on a Systematic Review. Value in Health 23 (7): 953-968. 6. Wang H, Xiao X, Xiao Q, Lu Y, Wu Y (2020) The efficacy and safety of daunorubicin versus idarubicin combined with cytarabine for induction therapy in acute myeloid leukemia: A meta-analysis of randomized clinical trials. Medicine 99 (24): e20094. 7. Muhamad NA, Mohd Dali NS, Mohd Yacob A, Kassim MSA, Lodz NA et al. (2020) Effect and safety of gemtuzumab ozogamicin for the treatment of patients with acute myeloid leukaemia: a systematic review protocol. BMJ open 10 (6): e032503.
Exclude due to insufficient data (n = 2)
1. (2020) Investigator-initiated clinical trial (Phase II) of cancer vaccine "DSP-7888" for acute myeloid leukemia patients. Investigator-initiated clinical trial (Phase II) of cancer vaccine "DSP-7888" for acute myeloid leukemia patients - WT1-AM-05. 2. (2020) BLAST MRD AML-1: blockade of PD-1 added to standard therapy to target measurable residual disease in acute myeloid leukemia 1- a randomized phase 2 study of anti-PD-1 pembrolizumab in combination with intensive chemotherapy as frontline therapy in patients with acute myeloid leukemia. Blockade of PD-1 added to standard therapy to target measurable residual disease in acute myeloid leukemia 1 (BLAST MRD AML-1): a randomized phase 2 study of the anti-PD-1 antibody pembrolizumab in combination with conventional intensive chemotherapy as frontline therapy in patients with acute myeloid leukemia.

MA = meta-analysis; NMA = network meta-analysis; SLR = systematic literature review.

Table A-11 presents the RCTs included in the clinical SLR following screening of the titles and abstracts and full-text publications for the original and updated reviews.

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Table A-11. Randomised controlled trials identified in the clinical evidence review (original and update)

Author, year	Trial name	Trial number	Maintenance treatment
Main analysis is maintenance therapy			
Baer et al. (2008)[5]	CALGB 9720	NCT00003190	Recombinant IL-2 (rIL-2)
Foran et al. (2019)[6]	E-A E2906	NCT02085408	Decitabine
Huls et al. (2019)[7]	HOVON97	EUCTR2008-001290-15	Azacitidine (SC)
Hunault-Berger et al. (2017)[8]	LAMSA-maintenance Rev-5Aza	NCT01301820	Azacitidine (SC)/lenalidomide
Löwenberg et al. (2010)[9]	HOVON43	ISRCTN77039377	Gemtuzumab ozogamicin (GO)
Oliva et al. (2018)[10]; Oliva et al. (2019)[11]	QoLESS AZA-AMLE	EUCTR2010-019710-24	Azacitidine (SC/IV)
Pautas et al. (2010)[12]	ALFA-9801	NCT00931138	Recombinant IL-2 (rhIL-2)
Pigneux et al. (2017)[13]	LAM SA 2002	NCT00700544	Idarubicin, cytarabine, lomustine/ methotrexate + 6-mercaptopurine, norethandrolone
Usuki et al. (2007)[14]	NR	NR	Recombinant human IL-11 (rhIL-11)
Wei et al. (2019)[15]; Celgene data on file (2020)[16]; **Ravandi (2020)[31]; Ravandi et al. (2020)[32]; Roboz et al. (2020)[33]; Wei et al. (2020)[34]; Wei et al. (2020)[35]**	QUAZAR	NCT01757535	Oral azacitidine (Onureg)
Yamaguchi et al. (2018)[17]	NR	NCT01961882	OCV-501 (WT1 peptide vaccine)
Clinicaltrials.gov NCT01687387 (2012)[18]	EFFIKIR	NCT01687387	Lirilumab
Clinicaltrials.gov NCT00398983 (2006)[19]	NR	NCT00398983	Decitabine
Main analysis is consolidation therapy			
Hengeveld et al. (2012)[20]	AML 8B	NR	Daunorubicin, cytarabine
Schlenk et al. (2006)[21]	AML HD98-B	NR	Idarubicin, etoposide
Main analysis is induction therapy			
Burnett et al. (2017)[22]	AML 16	NCT00454480	Azacitidine (SC)
Latagliata et al. (2008)[23]	GSI 103-AMLE	NCT00589082	Cytarabine, ATRA
Petersdorf et al. (2013)[24]	S0106	NCT00085709	Gemtuzumab ozogamicin (GO)
Pigneux et al. (2007)[25]	BGMT95	NCT00480064	Idarubicin/cytarabine + methotrexate/ 6-mercaptopurine
Röllig et al. (2015)[26]; Rollig et al. (2017)[27]	SORAML	NCT00893373	Sorafenib
Schlenk et al. (2019)[28]	AMLSG 12-09	NCT01180322	Azacitidine (SC)
Stone et al. (2017)[29]; Voso et al. (2018)[30]; **Voso et al. (2020)[36]**	RATIFY	NCT00651261	Midostaurin
Pardee et al. (2020)[37]	**NR**	**NR**	**Selinexor**
Wei et al. (2020)[38]	**ALLG AML M16**	**ACTRN12611001112954**	**Sorafenib**

AML = acute myeloid leukaemia; ATRA = all-trans retinoic acid; IV = intravenous; NR = not reported; SC = subcutaneous; WT1 = Wilms' tumour gene 1.

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Note: articles / studies in bold were identified in the update searches.

To reflect DMC requirements, ClinicalTrials.gov and the EU Clinical Trials Register were reviewed for Onureg studies in the AML maintenance population that are active or not yet published. As discussed in Section 5.2.2, there is no standard of care in AML maintenance in Denmark; therefore, close monitoring is the predominant strategy in these patients and the appropriate comparator for Onureg. It should be noted that the patient population of interest for this submission are not candidates for haematopoietic stem cell transplant (HSCT). Two relevant ongoing studies of Onureg were identified as summarised in Table A-13.

Table A-12. Active Onureg trials in the AML maintenance population identified in ClinicalTrials.gov and EU Clinical Trials Register

Study/ID	Study title
2016-000069-22 https://www.clinicaltrialsregister.eu/ctr-search/trial/2016-000069-22/FR	A phase 2, open-label, single-arm rollover study to evaluate long-term safety in subjects who participated in other Celgene sponsored CC-486 (oral azacitidine) clinical trials in solid tumors and hematological disorders
2018-001012-30 https://www.clinicaltrialsregister.eu/ctr-search/trial/2018-001012-30/GB	A double-blind, phase III, randomised study to compare the efficacy and safety of oral azacitidine (CC-486) versus placebo in subjects with acute myeloid leukaemia or myelodysplastic syndromes as maintenance after allogeneic haematopoietic stem cell transplantation

Appendix A.4 Trials relevant to this submission

The SLR was conducted to identify all studies in maintenance treatment of AML. However, as noted in Section 5.2.2 of this dossier, close monitoring is the standard of care treatment in this setting in Denmark and, therefore, the only relevant comparator. Therefore, only 1 study relevant to this appraisal was identified—QUAZAR AML-001—and the other 23 studies were excluded at this stage for not including a relevant comparator.

Table 6 in the main submission dossier presents the trial methodology of QUAZAR AML-001.

Appendix A.5 Quality assessment

The Cochrane risk of bias assessment tool for RCTs was used to assess the included studies.[39] Table A-14 presents the results of the risk of bias assessment for the QUAZAR AML-001 study.

Table A-13. Risk of bias assessment for the QUAZAR AML-001 study

Author, year	Trial name	Random sequence generation	Allocation concealment	Blinding of participants and personnel	Blinding of outcome assessment	Incomplete outcome data	Selective reporting
Wei et al. (2019)[15]; Celgene data on file (2020)[16]; Ravandi (2020)[31]; Ravandi et al. (2020)[32];Roboz et al. (2020)[33] Wei et al. (2020)[34]; Wei et al. (2020)[35]	QUAZAR	+	+	+	+	+	+

A major strength of this SLR is that it adheres to best practices for the conduct and reporting of systematic reviews. Notably, all the searches were performed and peer-reviewed by experienced information specialists.

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Appropriate reporting was provided in alignment with PRISMA Guidelines through a detailed search strategy, PRISMA flow diagram, full included/excluded study lists, and a risk of bias assessment using appropriate tools.[40,41] A detailed assessment of patient/study characteristics among identified trials is also reported to assess the comparability of the studies.

A limitation of this systematic review is that the included studies were restricted to English language only at the study selection stage. This is likely a minor limitation, given most of the major trials are published in English journals. However, it is noteworthy that this restriction was applied at the study selection phase and we did not restrict the search to English only articles.

Appendix A.6 Unpublished data

The majority of evidence in this submission dossier is published and is only supplemented with information from the CSR for completeness. Updated OS/RFS data for the QUAZAR AML 001 study, based on the 2020 database lock, are planned for presentation at ASH 2021.

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Appendix B. Main characteristics of included studies

The only clinical trial relevant to this appraisal is QUAZAR AML-001, which is described in Table B-1.

Table B-1. QUAZAR AML-001: study characteristics

Trial name: QUAZAR AML-001	NCT number: NCT01757535
Objectives	**Primary:** To demonstrate if maintenance therapy with oral Onureg improves OS compared with placebo in patients with AML, age ≥ 55 years, who have achieved first CR or complete remission with CRi after induction with intensive chemotherapy with or without consolidation chemotherapy. **Secondary:** To determine RFS, safety, tolerability; and the effect of oral Onureg compared with placebo on HRQoL and healthcare resource utilisation.
Publications	**Full publications:** ▪ Oral azacytidine maintenance therapy for acute myeloid leukemia in first remission. Wei A, Dohner H, Pocock C, Montesinos P, Afanasyev B, et al. N Engl J Med 2020;383:2526-37. ▪ Design of the randomized, phase III, QUAZAR AML maintenance trial of CC-486 (oral azacitidine) maintenance therapy in acute myeloid leukemia. Roboz GJ, Montesinos D, Selleslag D, Jang J, Flantes J, et al. Future Oncol 2016; 12(3): 293-302. ▪ Oral azacytidine preserves favorable levels of fatigue and health-related quality of life for patients with acute myeloid leukamia in remission: results from the phase 3, placebo-controlled QUAZAR AML-001 trial. Roboz GJ, Dohner H, Pocock C, Dombret H, Ravandi F, Jang JH, et al. Haematologica, 2021; Sep 23. Doi: 10.3324/haematol.2021.279174. [Epub ahead of print]. **Abstracts:** ▪ The QUAZAR AML-001 maintenance trial: results of a phase III international, randomized, double-blind, placebo-controlled study of CC-486 (oral formulation of azacitidine) in patients with acute myeloid leukemia (AML) in first remission. Wei A, Dohner H, Pocock C, Montesinos P, Afanasyev B, et al. Blood 2019; 134 (Supplement_2): LBA-3-LBA-3. ▪ Escalated dosing schedules of CC-486 for patients experiencing first acute myeloid leukemia (AML) relapse: results from the phase III QUAZAR AML-001 maintenance trial. Dohner H, Wei A, Montesinos P, Dombret H, Ravandi F, et al. Journal of Clinical Oncology. Journal of Clinical Oncology 38 (no.15_suppl): 7513-7513; 2020. ▪ Oral azacitidine (CC-486) reduces hospitalization and associated estimated costs in patients with acute myeloid leukemia (AML) in first remission after intensive chemotherapy: results from the QUAZAR AML-001 trial. Olivia EN, Kambhampati S, Oriol A, La Torre I, Skikne B, et al. Blood 136 (Supplement 1): 14-15; 2020. ▪ Gastrointestinal events and management strategies for patients with acute myeloid leukemia in first remission receiving oral azacitidine (CC-486) maintenance therapy in the randomized, placebo-controlled, phase III QUAZAR®AML-001 trial. Ravandi F, Pocock C, Selleslag D, Montesinos P, Sayar H, et al. Blood 136 (Supplement 1): 22-23; 2020. ▪ CC-486 is safe and well-tolerated as maintenance therapy in elderly patients (≥ 75 years) with acute myeloid leukemia (AML) in first remission following induction chemotherapy: results from the phase III QUAZAR AML-001 trial. Journal of Clinical Oncology. Ravandi F, Wei A, Dohner H, Dombret H, Ossenkoppele GJ, et al. Journal of Clinical Oncology 38 (no.15_suppl): 7530-7530; 2020. ▪ Impact of subsequent allogeneic hematopoietic stem cell transplant (HSCT) on overall survival (OS) outcomes in the QUAZAR AML-001 trial of oral azacitidine (CC-486) maintenance therapy for patients with acute myeloid leukemia (AML) in First emission who were not eligible for HSCT at study entry. Ravandi F, Wei A, Pocock C, Montesinos P, Dombret H, et al. Transplantation and Cellular Therapy 27: S131-S132; 2021. ▪ Oral Azacitidine (CC-486) prolongs survival for patients with acute myeloid leukemia (AML) in remission after intensive chemotherapy (IC) independent of the presence of measurable residual disease (MRD) at study entry: results from the QUAZAR AML-001 trial. Roboz, GJ, Ravandi F, Wei AH, Dombret H, Dohner H, et al. Blood 136 (Supplement 1): 32-33; 2020. ▪ Health-related quality of life (HRQoL) in the phase III QUAZAR -AML-00l trial of CC-486 as maintenance therapy for patients with acute myeloid leukaemia (AML) in first remission

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	following induction chemotherapy (IC). Roboz GJ, Dohner H, Pocock C, Dombret H, Ravandi F, et al. J Clin Oncol 38 (Suppl; Abstract #7533); 2020. ▪ Oral azacitidine (CC-486) improves overall survival (OS) and relapse-free survival (RFS) for patients with acute myeloid leukemia (AML) in first remission after intensive chemotherapy (IC), regardless of amount of consolidation received: results from the phase III QUAZAR AML-001 trial. Wei A, Roboz GJ, Dombret H, Dohner H, Schuh A, et al. Blood 136 (Supplement 1): 38-40; 2020. ▪ Survival outcomes from the QUAZAR AML-001 trial with oral azacytidine for patients with acute myeloid leukemia in remission by NPM1 and FLT3 gene mutation status at diagnosis. Dohner H, Wei A, Roboz GJ, Montesinos P, Thol F, et al. Abstract presentation (No. S131) at: European Hematology Association Virtual Congress, 11 June 2021. ▪ Estimated hospitalisation-related costs with oral azacytidine vs. placebo for remission maintenance in patients with acute myeloid leukemia in Spain and United Kingdom. Pocock C, Montesinos P, Braun T, Kambhiampati S, Oriol A. et al. Abstract presentation (No. S311) at: European Hematology Association Virtual Congress, 11 June 2021. ▪ Hematologic adverse events and management strategies for patients with acute myeloid leukemia in first remission receiving oral azacitidine in the phase 3 QUAZAR AML-001 trial. Ravandi E, Roboz GJ, Wei AH, Dohner H, Pocock C, et al. Abstract presentation (No. EP445) at: European Hematology Association Virtual Congress, 11 June 2021. ▪ Prognostic factors of overall and relapse-free survival for patients with acute myeloid leukemia in remission: multivariate analyses from the QUAZAR AML-001 trial of oral azacytidine. Roboz GJ, Wei AH. Ravandi F, Pocock C, Montesinos P, et al. Abstract presentation (No. EP428) at: European Hematology Association Virtual Congress, 11 June 2021. ▪ The QUAZAR AML-001 maintenance trial: results of a phase III international, randomized, double-blind, placebo-controlled study of CC-486 (oral formulation of azacitidine) in patients with acute myeloid leukemia (AML) in first remission. Wei A, Dohner H, Pocock C, Montesinos P, Afanasyev B, et al. Presented at the American Society of Hematology (ASH) Annual Meeting and Exposition, 6-10 December 2019.
Study type and design	International, multicenter, placebo-controlled, phase III study with a double-blind, randomised, parallel-group design.[15,34] Patients were randomised in a 1:1 ratio to receive Onureg 300 mg or placebo using a central randomisation procedure with an Interactive Voice Response System. The block randomisation schedule (occurring within 4 months [± 7 days] of achieving first CR/CRi) stratified patients by key prognostic factors[34]: ▪ Age at the time of induction therapy (55 to 64 years or ≥ 65 years) ▪ Prior history of MDS or CMML (yes or no) ▪ Cytogenetic risk status at the time of induction therapy (intermediate or poor risk) ▪ Receipt of consolidation therapy (yes or no) After randomisation, no crossover between treatment groups was allowed. Patients who discontinued treatment but remained in the study were (or are being) followed for survival. Patients, investigators, study site staff and Celgene clinical and medical personnel were unaware of treatment assignments until study closure and database lock. Database cutoff for interim analyses was 15 July 2019; and 8 September 2020 for the 3-year updated analysis.
Sample size (n)	N = 472 randomised patients
Main inclusion and exclusion criteria	**Main inclusion criteria[42]:** ▪ Male or female patients ≥ 55 years of age ▪ Newly diagnosed, histologically confirmed de novo AML or AML secondary to prior myelodysplastic disease or CMML ▪ First CR/ CRi with induction therapy + consolidation therapy within 4 months (+/- 7 days of achieving CR or CRi) ▪ ECOG performance status: 0, 1, 2, 3 Inclusion Criteria in the extended phase of the study: At the Investigator's discretion and with approval of the sponsor, subjects meeting all of the following eligibility criteria are eligible to enter the extension phase:

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	▪ All patients randomised into the oral azacitidine or placebo arm and are continuing in either the treatment Phase or Follow-up Phase of the study; – Patients randomised to oral Onureg treatment arm and continuing in the Treatment Phase demonstrating clinical benefit as assessed by the Investigator are eligible to receive oral Onureg in the EP – Patients randomised into placebo arm of the study will not receive oral azacitidine in the EP, but will be followed for survival in the EP – Patients currently in the in the follow-up phase will continue to be followed for survival in the EP ▪ Patients who have signed the informed consent for the EP of the study ▪ Patients who do not meet any of the criteria for study discontinuation **Main exclusion criteria:** ▪ AML with inv(16), t(8;21), t(16;16), t(15;17), or t(9;22) or molecular evidence of such translocations ▪ Prior bone marrow or stem cell transplantation ▪ Have achieved CR/CRi following therapy with hypomethylating agents ▪ Diagnosis of malignant disease within the previous 12 months ▪ Proven Central Nervous System leukaemia
Intervention	Onureg (n = 238): 300 mg QD for the first 14 days of each 28-day cycle[34]
Comparator(s)	Placebo (n = 234): placebo for the first 14 days of each 28-days cycle [34]
Follow-up time	Median follow-up was 41.2 months at time of interim analysis
Is the study used in the health economic model?	Yes
Primary, secondary and exploratory endpoints	**Endpoints included in this application**: The primary endpoint was OS defined as time from randomisation to death from any cause. Secondary endpoints: were RFS, time to relapse from CR/CRi, time to discontinuation from treatment, HRQoL as measured by FACIT-Fatigue Scale and EQ-5D-3L, and safety (type, frequency, severity, and relationship of AEs to study treatments; physical examinations, vital signs; clinical laboratory evaluations, and concomitant medication/therapy). Exploratory endpoints included MRD assessed centrally by flow cytometry (≥ 0.1% MRD-positive threshold) and exploratory HRQoL analysis. **Other endpoints:** Health resource utilisation; flow cytometric analysis of haematopoietic cell immunophenotypes and analysis of genetic alterations, including gene sequencing for recurrent gene aberrations in AML were assessed as secondary and exploratory endpoints, respectively, but the results are not included in this application.
Method of analysis	Analysis sets included the ITT population, the safety population, and the mITT population All efficacy endpoints were analysed using the ITT population with supportive analysis of OS and RFS repeated for the mITT population. OS and RFS were estimated using Kaplan-Meier methods. The estimates were tested using a sequential gate-keeping approach. The equality of OS and RFS curves was compared between treatment arms using a log-rank test stratified for age, prior history of MDS/CMML, cytogenetic risk (per NCCN) at induction, and receipt of consolidation therapy. The assumption of proportional hazards was tested with a time-dependent Cox model with interaction terms of treatment and time and with a *P* value of 0.006. Confidence intervals for survival estimates at 6 months, 1 year, and 2 years were derived from Greenwood's variance estimate. Univariate analyses were performed for OS and RFS in predefined subgroups: age, sex, ECOG performance status score, cytogenetic risk status at diagnosis, prior history of MDS/CMML, geographic region, CR or CRi first achieved after induction, time to first achieving CR/CRi, CR/CRi status at randomisation, MRD status at randomisation, use of consolidation, number of consolidation cycles received, and platelet counts and ANC.
Subgroup analyses	Analyses were performed for the OS and RFS endpoints for the following subgroups: ▪ Age at induction therapy (< 65, ≥ 65, ≥ 75 years)

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	▪ Sex (male, female) ▪ Race (White, Asian, Black or Others) ▪ CR/CRi status at randomisation (CR, CRi) ▪ CR/CRi status at first achieving response (CR, CRi) ▪ CR/CRi status at randomisation and use of consolidation (CR with consolidation, CR without consolidation, CRi with consolidation, and CRi without consolidation) ▪ Prior history of MDS or CMML (yes, no) ▪ Cytogenetic risk category at induction therapy (intermediate, poor) ▪ MRD status at screening (prior to randomisation) (positive, negative) ▪ CR/CRi status at randomisation and MRD status at screening (prior to randomisation) (CR with MRD positive, CR with MRD negative, CRi with MRD positive, and CRi with MRD negative) ▪ Consolidation therapy following induction (yes, no) ▪ Consolidation therapy following induction (1 or 2 cycles, 3 or 4 cycles) ▪ Geographic region (North America, Europe, Asia and Australia) ▪ ECOG performance status (0 or 1, 2 or 3) ▪ WHO AML classification (AML with myelodysplasia-related changes, AML with recurrent genetic abnormalities, AML not otherwise specified) ▪ Types of first-line subsequent therapy – High-intensity, low-intensity chemotherapy – HMA monotherapy, other non-HMA subsequent therapy – Azacitidine monotherapy, other subsequent therapy (excluding decitabine monotherapy) Overall survival and RFS were analysed separately for each subgroup of adequate size using Kaplan-Meier and Cox proportional hazard methods previously described, but without stratification. The HRs from the subgroup analyses were displayed graphically in a Forest plot.

AE = adverse event; AML = acute myeloid leukaemia; ANC = absolute neutrophil count; CMML = chronic myelomonocytic leukaemia; CR = complete remission; CRi = complete remission with incomplete blood count recovery; ECOG = Eastern Cooperative Oncology Group; EP = extended phase; EQ-5D-3L = 3-level EQ-5D; FACIT = Functional Assessment of Chronic Illness Therapy; HMA = hypomethylating agent; HR = hazard ratio; HRQoL = health-related quality of life; ITT = intent to treat; MDS = myelodysplastic syndrome; mITT = modified intent to treat; MRD = minimal residual disease; NCCN = National Comprehensive Cancer Network; non-HMA = non-hypomethylating agent; OS = overall survival; QD = once daily; RFS = relapse-free survival; WHO = World Health Organization.

Notes: Throughout the treatment period patients in both the placebo and Onureg arms were permitted to receive best supportive care according to local practice, including blood product transfusions, erythropoiesis-stimulating agents, granulocyte colony-stimulating factors, nutritional support, and antibiotic, antiviral, antifungal, antiemetic, or antidiarrheal therapies. Best supportive care was included in the study design minimised the risk of providing patients with inadequate care and is consistent with current practice for many patients with AML who are in complete remission after induction/consolidation therapy.[16,43] Prophylactic therapy for gastrointestinal or haematologic adverse events was permitted at the discretion of the treating investigator.[34]

Source: Wei et al. (2020)[34]

Appendix C. Baseline characteristics of patients in studies used for the comparative analysis of efficacy and safety

Appendix C.1 QUAZAR AML-001: baseline characteristics

Table C-1 presents the baseline characteristics of patients included in the only relevant study, QUAZAR AML-001. The analysis was based on the intent-to-treat (ITT) population, which consisted of all 472 patients enrolled between the first patient visit on 10 May 2013 and the database cutoff date on 15 July 2019. The randomised patients were 87.5% White, 52% male, with a median age 68 years (range, 55-86 years). Overall, baseline characteristics were generally balanced between the groups and no clinically meaningful differences in baseline demographic and disease characteristics were observed between treatment groups.[15,34]

Table C-1. QUAZAR AML-001 (NCT number: NCT01757535): baseline patient characteristics

	Onureg (n = 238)	Placebo (n = 234)	Total (n = 472)
Age (year)			
Mean (SD)	[redacted]	[redacted]	[redacted]
Median (range)	68 (55-86)	68 (55-82)	68 (55-86)
Age category, n (%)			
≥ 55 to < 65 years	[redacted]	[redacted]	[redacted]
≥ 65 to < 75 years	[redacted]	[redacted]	[redacted]
≥ 75 years	[redacted]	[redacted]	[redacted]
≥ 85 years	[redacted]	[redacted]	[redacted]
Gender, n (%)			
Male	118 (50)	127 (54)	245 (52)
Female	120 (50)	107 (46)	227 (48)
Race, n (%)			
White	[redacted]	[redacted]	[redacted]
Black or African American	[redacted]	[redacted]	[redacted]
Asian	[redacted]	[redacted]	[redacted]
Other	[redacted]	[redacted]	[redacted]
Missing	[redacted]	[redacted]	[redacted]
Ethnicity, n (%)			
Hispanic/Latino	[redacted]	[redacted]	[redacted]
Non-Hispanic/Latino	[redacted]	[redacted]	[redacted]
Unknown	[redacted]	[redacted]	[redacted]
Geographical region, n (%) [a]			
North America	[redacted]	[redacted]	[redacted]
Europe	[redacted]	[redacted]	[redacted]
Asia	[redacted]	[redacted]	[redacted]
Australia	[redacted]	[redacted]	[redacted]
South America	[redacted]	[redacted]	[redacted]

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	Onureg (n = 238)	Placebo (n = 234)	Total (n = 472)
Time since original AML diagnosis (months)			
Mean (SD)	4.4 (1.3)	4.3 (1.2)	4.3 (1.3)
Median (min, max)	4.2 (1.5, 9.2)	4.2 (1.4, 10.9)	4.2 (1.4, 10.9)
AML WHO classification, n (%)			
AML with recurrent genetic abnormalities	39 (16)	46 (20)	85 (18)
AML with myelodysplasia - related changes	49 (21)	42 (18)	91 (19)
Therapy-related myeloid neoplasms	2 (1)	0	2 (0.4)
AML not otherwise specified	148 (62)	145 (62)	293 (62)
Missing	0	1 (0.4)	1 (0.2)
ECOG performance status, n (%)			
Grade 0	116 (49)	111 (47)	227 (48)
Grade 1	101 (42)	106 (45)	207 (44)
Grade 2-3	21 (9)	17 (7)	38 (8)
Prior history of MDS/CMML, n (%)			
Primary	20 (8)	17 (7)	37 (8)
Secondary	0	0	0
Missing	2 (1)	0	2 (0.4)
Reason ineligible for transplant, n (%)[b]			
Age	154 (65)	152 (65)	306 (65)
Comorbidities	52 (22)	50 (21)	102 (22)
Performance Status	14 (6)	9 (4)	23 (5)
Not acceptable or available donor	37 (16)	35 (15)	72 (15)
Patient decision	19 (8)	32 (14)	51 (11)
Unfavourable cytogenetics	6 (3)	10 (4)	16 (3)
Other	28 (12)	21 (9)	49 (10)
Received consolidation therapy following induction therapy, n (%)			
Yes	186 (78)	192 (82)	378 (80)
1 Cycle	110 (46)	102 (44)	212 (45)
2 Cycles	70 (29)	77 (33)	147 (31)
3 Cycles	6 (3)	13 (6)	19 (4)
No	52 (22)	42 (18)	94 (20)
Bone marrow blasts, %			
N	238	232	470
Mean (SD)	2.1 (1.5)	2.2 (1.5)	2.2 (1.5)
Median (min, max)	2.0 (0.0, 5.0)	2.0 (0.0, 6.5)	2.0 (0.0, 6.5)
Peripheral blood blasts, %			
N	230	222	452
Mean (SD)	0.1 (0.3)	0.0 (0.3)	0.1 (0.3)
Median (min, max)	0.0 (0.0, 2.0)	0.0 (0.0, 2.0)	0.0 (0.0, 2.0)

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	Onureg (n = 238)	Placebo (n = 234)	Total (n = 472)
Previous treatments in ≥ 10% of patient, n (%)			
At least 1 prior induction therapy for AML	[redacted]	[redacted]	[redacted]
Antineoplastic and immunomodulating agents	[redacted]	[redacted]	[redacted]
Cytarabine	[redacted]	[redacted]	[redacted]
Idarubicin	[redacted]	[redacted]	[redacted]
Daunorubicin	[redacted]	[redacted]	[redacted]
Fludarabine	[redacted]	[redacted]	[redacted]
Mitoxantrone	[redacted]	[redacted]	[redacted]

AML = acute myeloid leukaemia; CMML = chronic myelomonocytic leukaemia; ECOG = Eastern Cooperative Oncology Group; MDS = myelodysplastic syndrome; max = maximum; min = minimum; SD = standard deviation; WHO = World Health Organization.

Note: time interval in days was calculated as the difference between the randomisation date and the date of interest (e.g., date of original AML diagnosis) plus 1 day. Time interval presented in months is transformed from days to months by using the conversion formula: months = days/30.4375.

[a] North America includes Canada, Mexico, and the United States; Asia includes South Korea and Taiwan; Australia includes Australia; Europe includes Austria, Belgium, Czech Republic, Finland, France, Germany, Ireland, Israel, Italy, Lithuania, Poland, Portugal, the Russian Federation, Spain, and Turkey; South America includes Brazil.

[b] A patient may have had more than 1 reason.

Sources: Wei et al. (2020)[34]; Celgene data on file (2020)[16]; EMA (2021)[44]

Appendix C.2 Comparability of patients across studies

Not applicable as only the QUAZAR AML-001 study is relevant.

Appendix C.3 Comparability of the study populations with Danish patients eligible for treatment

[redacted] Although there were no sites in Demark, advice from Danish clinicians suggests that the trial population generally reflects the average patient with AML in first complete remission encountered in Danish clinical practice.

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Appendix D. Efficacy and safety results per study

Appendix D.1 Definition, validity, and clinical relevance of included outcome measures

The definition, validity and clinical relevance of the included outcome measures is provided in Table D-1.

Table D-1. Summary of endpoints in QUAZAR AML-001

Outcome measure	Definition	Validity	Clinical relevance
OS[a]	The number of days from the date of randomisation until the date of death from any cause, calculated as (date of death – date of randomisation + 1). Patients surviving at the end of the follow-up period or who were lost to follow-up were censored at the date last known to be alive. For patients who withdrew consent, the last date known alive was considered the date of consent withdrawal from the study.	OS is recognised as the gold standard measure of efficacy in oncology clinical trials and is required by drug regulatory agencies for the approval of new cancer treatments.[45-47]	OS is the most clinically relevant outcome, assessing how long a patient lives from the beginning of treatment.[45-47]
RFS[a,b]	The time from the date of randomisation to the date of documented relapse after CR or CRi or death from any cause, whichever occurred first. Patients who were still alive without documented relapse, or who were lost to follow-up or withdrew consent without documented relapse, were censored at the date of their last response assessment. Documented relapse was defined as the earliest date of any of the following (according to IWG for AML criteria): ▪ ≥ 5% BM blasts from the central pathology report; ▪ The appearance of > 0% blasts in the peripheral blood with a later BM confirmation (BM blasts ≥ 5%) within 100 days; or ▪ At least 2 peripheral blasts ≥ 5% within 30 days.	RFS is 1 of the most common survival measure used in assessing efficacy of cancer treatments. Its validity as a surrogate for OS has been investigated using individual patient data in a number of oncology clinical trials[48,49] For AML specifically, RFS is regarded by drug regulatory agencies such as the FDA and EMA as an acceptable outcome measure in trials of consolidation or maintenance treatment in patients with AML.[45,46]	Clinically relevant to measure the length of time a patient survives without signs, symptoms or recurrence of their cancer, or death after the completion of initial treatment because preventing or delaying relapse is an important goal of maintenance treatment in AML.[45,50,51] Additionally, RFS is crucial to long-term survival or cure, with some evidence indicating it is positively correlated with OS in AML.[52]
Time to relapse from CR/CRi[a]	The time from the date of randomisation to the date of documented relapse. Estimates of relapse rates at different times from randomisation were based on the cumulative incidence function from a competing risk analysis with death as a competing risk of relapse from CR/CRi; this differs from the censoring approach used for RFS.	This is linked to RFS but without the death from any cause element of the outcome.	Time to relapse from CR/CRi is a clinically relevant measure of the length of time a patient survives without signs, symptoms, or recurrence of their cancer.

Outcome measure	Definition	Validity	Clinical relevance
Time to discontinuation from treatment[a]	The time from the date of randomisation to the date of discontinuation from investigational product.	This is assessed as an estimate of treatment failure/tolerability with reasons for discontinuation (disease relapse, adverse event[s], became eligible for bone marrow or stem cell transplant, withdrawal of consent/lost to follow-up, protocol violation, and death) captured.	Relevant as a measure of tolerability to the treatment and used in the economic model to accurately cost treatment.
FACIT-Fatigue scale[c]	Analysed as both change from baseline and the proportion of patients with clinically meaningful improvement based on a prespecified MID. Clinically meaningful improvement was defined as ≥ 3 point change from baseline.[53]	The FACIT has undergone standard validation methodology (item generation, item-reduction, scale construction and psychometric evaluation) in a number of oncology studies.[54] The Fatigue subscale is validated for measuring disease-related fatigue and improved care in patient with cancer.[54,55] Treatments that reduce cancer disease-related fatigue are considered to have a positive effect on patients quality of life.[53,55]	In additional to being clinically important for capturing patients' own perspective of the impact a disease and its treatment on their health status, HRQoL outcomes are considered prognostics indicators for survival outcome in a wide range of cancers.[56] Quality of life and other patient-reported outcomes are becoming increasingly important consideration for approval new oncology treatments.[45]
EQ-5D-3L health utility index[c]	Analysed as both change from baseline and the proportion of patients with clinically meaningful improvement based on a prespecified MID. Clinically meaningful improvement was defined as 0.08- and 0.10-point or greater change from baseline.[57]	The EQ-5D is a standard validated generic preference-based health utility measurement instrument. Its reliability, validity and responsiveness in measuring HRQoL in cancer has been assessed via psychometric testing in several validation studies.[58]	The EQ-5D is a requirement of many HTA bodies, including DMC and as well as being a standard measure of health-related quality of life, and is used to calculate utilities for use in economic models.
Safety	Assessment of all adverse events including type, frequency, severity, and relationship of adverse events to study treatments; physical examination findings, vital signs measurements; clinical laboratory evaluations, and concomitant medication/therapy. Adverse events were recorded from the time the patient signed the ICF until 28 days after the last dose of study treatment or until the date of the last study visit, whichever was later.	Use of adverse events reporting as measures of drug safety has undergone experimental tests of reliability and validity in several studies. These include assessments of inter/intra-rater reliability, face validity and construct validity of adverse events measures,[59] as well as adverse events measurement instruments (including those specific to cancer).[60,61]	Safety assessment is clinically relevant to understand the overall adverse event profile of a treatment and the extent to which they are tolerable to patients. Safety is a key outcome currently used to establish regulatory approval for new cancer treatments.[45,47]

AML = acute myeloid leukaemia; BM = bone marrow; CR = complete remission; CRi = complete remission with incomplete blood count recovery; DMC = Danish Medicines Council; EQ-5D-3L = 3-level EQ-5D; FACIT = Functional Assessment of Chronic Illness Therapy; FDA = Food and Drug Administration; HRQoL = health-related quality of life; HTA = health technology assessment; ITT = intent to treat; IWG = International Working Group; MID = minimally important difference; OS = overall survival; RFS = relapse-free survival.

[a] Analysed using the ITT population.

[b] In AML trials, RFS is traditionally measured from the date of CR/CRi,[50] whereas in QUAZAR AML-001, RFS was measured from the date of randomisation, which occurred at a median of 85 days after CR/CRi. [34] Therefore, RFS should not be compared between QUAZAR AML-001 and other trials in AML.

[c] Analysed using the HRQoL-evaluable population, defined as all randomised patients who had a valid (i.e., not missing) assessment at baseline (i.e., Cycle 1 Day 1) and at least 1 valid post-baseline assessment.

Source: Wei et al. (2020)[62]

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Appendix D.2 Results per study: QUAZAR AML-001 (absolute and relative difference in effect)

The estimated absolute and relative difference in effect for the main outcomes in the QUAZAR AML-001 trial are presented in Table D-2.

Table D-2. Results of QUAZAR AML-001 (NCT number: NCT01757535)

Outcome	Study arm	N	Result (95% CI)	Estimated absolute difference in effect			Estimated relative difference in effect			Description of methods used for estimation	References
				Difference	95% CI	*P* value	Difference	95% CI	*P* value		
Median overall survival	Onureg	238	24.7 months (18.7-30.5)	9.9 months	4.6-15.3	0.0009	HR, 0.69	0.55-0.86	-	The median OS is based on the Kaplan-Meier estimates. The HR is based on a Cox proportional hazards model stratified by age, cytogenetic risk category, and receipt of consolidation	Wei et al. (2020)[34]; Wei et al. (2019)[15]
	Placebo	234	14.8 months (11.7-17.6)								
1-year overall survival rate	Onureg	238	173 (72.8%) patients (67.0-78.0)	17.0%	8.4-25.6	0.0009	HR, 0.69	0.55-0.86	NR	1-year survival was based on Kaplan-Meier methods. The HR is based on a Cox proportional hazards model stratified by age, cytogenetic risk category, and receipt of consolidation	Wei et al. (2020)[34]; Wei et al. (2019)[15]
	Placebo	234	131 (55.8%) patients (49.0-62.0)								
2-year overall survival rate	Onureg	238	120 (50.6%) patients (44.0-57.0)	13.5%	4.5-22.5	0.0009	HR, 0.69	0.55-0.86	NR	2-year survival was based on Kaplan-Meier methods. The HR is based on a Cox proportional hazards model stratified by age, cytogenetic risk category, and receipt of consolidation	Wei et al. (2020)[34]; Wei et al. (2019)[15]
	Placebo	234	87 (37.1%) patients (30.9-43.4)								
3-year overall survival rate	Onureg	238	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	The HR is based on a Cox proportional hazards model stratified by age,	Bristol Myers Squibb data on file (2021)[63]

Outcome	Study arm	N	Result (95% CI)	Estimated absolute difference in effect			Estimated relative difference in effect			Description of methods used for estimation	References
				Difference	95% CI	*P* value	Difference	95% CI	*P* value		
	Placebo	234	[redacted]							cytogenetic risk category, and receipt of consolidation	
Median relapse-free survival	Onureg	238	10.2 months (7.9-12.9)	5.3 months	3.1-7.5	0.0001	HR, 0.65	0.52-0.81	NR	Median relapse-free survival was based on Kaplan-Meier method. The HR is based on a Cox proportional hazards model stratified by age, cytogenetic risk category, and receipt of consolidation	Wei et al. (2020)[34]; Wei et al. (2019)[15]
	Placebo	234	4.8 months (4.6-6.4)								
1-year relapse-free survival rate	Onureg	238	107 (44.9%) patients (38.1-51.4)	17.5%	8.5-26.4	0.0001	HR, 0.65	0.52-0.81	NR	1-year relapse-free survival was based on Kaplan-Meier method. The HR is based on a Cox proportional hazards model stratified by age, cytogenetic risk category, and receipt of consolidation	Wei et al. (2019)[15], Wei et al. (2020)[34], EMA (2021)[44], Wei et al. (2020)[62]
	Placebo	234	64 (27.4%) patients (21.6-33.5)								
2-year relapse-free survival rate	Onureg	238	63 (26.6%) patients (20.7-32.8)	9.2%	1.1-17.2	0.0001	HR, 0.65	0.52-0.81	NR	2-year relapse-free survival was based on Kaplan-Meier method. The HR is based on a Cox proportional hazards model stratified by age, cytogenetic risk category, and receipt of consolidation	EMA (2021)[44]
	Placebo	234	41 (17.4%) (12.5-23.0) patients								
Median time to relapse	Onureg	238	10.2 (8.3-13.4) months	5.3 months	-	NR	HR, 0.53	0.43-0.66	NR	Median time to relapse was based on unstratified Kaplan-Meier method. HR is unstratified and based on log-rank test	Wei et al. (2020)[34]
	Placebo	234	4.9 (4.6-6.4) months								

Outcome	Study arm	N	Result (95% CI)	Estimated absolute difference in effect			Estimated relative difference in effect			Description of methods used for estimation	References
				Difference	95% CI	*P* value	Difference	95% CI	*P* value		
1-year relapse rate	Onureg	238	126 (53.0%) patients (46.0-59.0)	−19%	-	NR	HR, 0.47	0.38-0.60	NR	Relapse rate are based on the cumulative incidence function from a competing risk analysis with death as a competing risk of relapse from CR/CRi. HR is unstratified and based on log-rank test	Wei et al. (2020)[34]
	Placebo	234	167 (72.0%) (65.0-77.0) patients								
2-year relapse rate	Onureg	238	164 (69.0%) patients (62.0-75.0)	−13%	-	NR	HR, 0.53	0.43-0.66	NR	Relapse rate are based on the cumulative incidence function from a competing risk analysis with death as a competing risk of relapse from CR/CRi. HR is unstratified and based on log-rank test	Wei et al. (2020)[34]
	Placebo	234	192 (82.0%) patients (76.0-86.0)								
Median time to treatment discontinuation	Onureg	238	11.4 (9.8-13.6) months	5.4 months	3.1-7.8	NR	HR, 0.57	0.47-0.70	NR	Median time to treatment discontinuation was based on unstratified Kaplan-Meier method. The CIs for differences were derived from Kosorok's method. HR is unstratified and based on log-rank test	Wei et al. (2020)[34]
	Placebo	234	6.1 (5.1-7.4) months								
1-year treatment discontinuation rate	Onureg	238	124 (52.0%) patients (46.0-58.0)	−19%	−28.0 to −11.0	NR	HR, 0.49	0.39-0.62	NR	Treatment discontinuation was based on Kaplan-Meier method. The CIs for differences were derived from Greenwood's variance estimate. HR is unstratified and based on log-rank test	Wei et al. (2020)[34]
	Placebo	234	166 (71.0%) patients (65.0-77.0)								

Outcome	Study arm	N	Result (95% CI)	Estimated absolute difference in effect			Estimated relative difference in effect			Description of methods used for estimation	References
				Difference	95% CI	*P* value	Difference	95% CI	*P* value		
2-year treatment discontinuation rate	Onureg	238	169 (71.0%) patients (64.0-76.0)	−15%	−23.0 to −8	NR	HR, 0.52	0.42-0.64	NR	Treatment discontinuation was based on Kaplan-Meier method. The CIs for differences were derived from Greenwood's variance estimate. HR is unstratified and based on log-rank test	Wei et al. (2020)[34]
	Placebo	234	201 (86.0%) patients (81.0-90.0)								

CI = confidence interval; CR = complete remission; CRi = complete remission with incomplete blood count recovery; HR = hazard ratio; NR = not reported; OS = overall survival.

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Appendix E. Safety data for intervention and comparator(s)

Appendix E.1 Adverse events leading to dose modification

Table E-1 presents treatment-emergent adverse events (TEAEs) leading to dose interruption and dose reduction.

Treatment-emergent adverse events leading to dose interruption were reported for 43% in the Onureg group and 17% of patients in the placebo group. The most frequent TEAEs leading to dose interruption (reported for ≥ 1% of patients in the Onureg group) were neutropenia (20% for Onureg vs. 6.0% for placebo), thrombocytopenia (8% vs. 2%), nausea (6% vs. 0.4%), diarrhoea (4% vs. 1%), vomiting (4% vs. 0%), febrile neutropenia (2% vs. 0.4%), and alanine aminotransferase increased (2% vs. 1%).[34] Discontinuation of study treatment because of TEAEs was reported for 13.1% of patients in the Onureg group and 4.3% of patients in the placebo group. In the Onureg group, TEAEs leading to treatment discontinuation reported by more than 1 patient included nausea (2.1% for Onureg vs. 0% for placebo), diarrhoea (1.7% vs. 0%), vomiting (1.3% vs. 0%), abdominal pain upper (0.8% vs. 0%), and fatigue (0.8% vs. 0%).[15,34]

Treatment-emergent adverse events leading to dose reduction were reported for 16% of patients in the Onureg group and 3% of patients in the placebo group.[15,34] The most frequent TEAEs leading to dose reduction (reported for > 1% of patients in the Onureg group) were neutropenia (6% for Onureg vs. 0.4% for placebo), diarrhoea (3% vs. 0%), thrombocytopenia (2% vs. 1%), and nausea (2% vs. 0%).[15,34]

Table E-1. QUAZAR AML-001: treatment-emergent adverse events leading to drug interruption and dose reductions in ≥ 1% of patients (safety population)

TEAE, n (%)	Onureg (n = 236)	Placebo (n = 233)
≥ 1 TEAE leading to dose interruption	**102 (43)**	**40 (17)**
Neutropenia	47 (20)	14 (6)
Thrombocytopenia	20 (8)	5 (2)
Nausea	13 (6)	1 (0.4)
Diarrhoea	10 (4)	3 (1)
Vomiting	9 (4)	0
Leukopenia	6 (3)	1 (0.4)
Alanine aminotransferase increased	5 (2)	2 (1)
Febrile neutropenia	5 (2)	1 (0.4)
Abdominal pain	4 (2)	2 (1)
Pneumonia	4 (2)	1 (0.4)
Upper respiratory tract infection	3 (1)	4 (2)
Anaemia	3 (1)	0
Constipation	3 (1)	0
Herpes zoster	3 (1)	0
Influenza	3 (1)	0
Lung infection	3 (1)	0
Nasopharyngitis	3 (1)	0
≥ 1 TEAE leading to dose reduction	**37 (16)**	**6 (3)**
Neutropenia	13 (6)	1 (0.4)

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TEAE, n (%)	Onureg (n = 236)	Placebo (n = 233)
Diarrhoea	8 (3)	0
Thrombocytopenia	4 (2)	3 (1)
Nausea	4 (2)	0

MedDRA = Medical Dictionary for Regulatory Activities; TEAE = treatment-emergent adverse event.

Note: TEAEs coded using MedDRA version 22.0. A patient was counted only once for multiple events within preferred term/system organ class.

Source: Wei et al. (2020)[34]

Appendix E.2 Gastrointestinal adverse events

Gastrointestinal TEAEs generally occurred more frequently in the Onureg group (91.1%) than in the placebo group (61.8%).[15,34,64] These included nausea (64.8% for Onureg vs. [15,34,64] These included nausea (64.8% for Onureg vs. 23.6% for placebo), vomiting (59.7% vs. 9.9%), diarrhoea (50.4% vs. 21.5%), and constipation (38.6% vs. 24.0%).[64] However, the majority of these events were mild or moderate in severity; grade 3 or 4 gastrointestinal TEAEs only occurred in 14.4% of patients in the Onureg group and 5.6% of patients in the placebo group, and included diarrhoea (5.1% for Onureg vs. 1.3% for placebo), vomiting (3.0% vs. 0%), nausea (2.5% vs. 0.4%), and constipation (1.3% vs. 0%). In addition, most gastrointestinal AEs occurred in the first 2 treatment cycles, and the frequency decreased with continued treatment (Figure E-1).[15,34,64]

Use of prophylactic anti-emetics and antidiarrhea medication was not mandated given the double-blind nature of the study compared with real-world practice; such medications can be used to prevent and manage these events, as well as dose reduction and interruption.[64] Although gastrointestinal events were the most common TEAEs observed during maintenance therapy with Onureg, a relatively small percentage of patients who experienced these events required dose reduction (5.5% for Onureg vs. 0% for placebo), dose interruption (13.1% vs. 3.4%), or treatment discontinuation (4.7% vs. 0.4%).[15,34,64]0.4%).[15,34,64]

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Appendix E.3 Subgroup analysis for adverse events

Compared with younger patients, older patients with AML are more likely to relapse after achieving CR/CRi with intensive chemotherapy, less likely to be eligible for HSCT, and less likely to tolerate subsequent intensive salvage therapy.[32,64-66] Therefore, an effective, well tolerated maintenance therapy option may be especially important for older patients. A subgroup analysis was conducted to evaluate the safety and tolerability of Onureg compared with placebo among patients aged ≥ 75 years.

Fifty-one (10.9%) patients in the safety population (n = 28 [11.9%] for Onureg; n = 23 [9.9%] for placebo) were aged ≥ 75 years at study entry.[32] Similar to findings in the overall safety population, the median treatment duration among older patients was approximately twice as long in the Onureg group as in the placebo group (11.5 months vs. 6.0 months). Within each treatment group, the rates of TEAEs among patients aged ≥ 75 years were generally similar to those in the overall study population. Notable exceptions in the Onureg group included constipation (22%-points? more frequent among patients aged ≥ 75 years than among all patients) and thrombocytopenia (19% point? less frequent among patients aged ≥ 75 years than among all patients) (Table E-2). As observed in the overall study population, gastrointestinal events were the most common TEAEs associated with Onureg among older patients, and these events occurred at a higher frequency in the Onureg group than in the placebo group for the older patient population.[15,34]

The most common grade 3 or 4 TEAEs among patients aged ≥ 75 years were haematologic events, including neutropenia (46% for Onureg vs. 13% for placebo), anaemia (14% vs. 13%), febrile neutropenia (14% vs. 0%), and thrombocytopenia (11% vs. 30%).[32,64] Rates of TEAEs leading to dose reduction (11% for Onureg vs. 0% for placebo), dose interruption (54% vs. 13%), or treatment discontinuation (29% vs. 9%) were higher in the Onureg group than in the placebo group and were generally consistent with rates in the overall study population (Table E-3).[67]

Overall, these findings suggest that Onureg was generally well tolerated among older patients aged ≥ 75 years.[32,64]

Table E-2. QUAZAR AML-001: treatment-emergent adverse events reported for ≥ 20% of patients aged ≥ 75 years (safety population)

	Onureg		Placebo	
TEAE, %	Aged ≥ 75 years (n = 28)	All patients (n = 236)	Aged ≥ 75 years (n = 23)	All patients (n = 233)
Nausea	64	65	17	24
Vomiting	64	60	4	10
Constipation	61	39	30	24
Diarrhoea	61	50	26	21
Neutropenia	46	44	13	26
Fatigue	36	30	17	19
Asthenia	29	19	4	6
Decreased appetite	25	13	0	6
Thrombocytopenia	14	33	30	27

MedDRA = Medical Dictionary for Regulatory Activities; TEAE = treatment-emergent adverse event.

Note: TEAEs coded using MedDRA version 22.0. A patient was counted only once for multiple events within preferred term/system organ class.

Source:Ravandi et al. (2020)[68]

Table E-3. QUAZAR AML-001: grade 3-4 treatment-emergent adverse events reported for ≥ 10% of patients aged ≥ 75 years (safety population)

	Onureg		Placebo	
TEAE, %	Aged ≥ 75 years (n = 28)	All patients (n = 236)	Aged ≥ 75 years (n = 23)	All patients (n = 233)
Neutropenia	43	41	13	24
Anaemia	14	14	13	13
Febrile neutropenia	14	11	0	7
Thrombocytopenia	11	22	30	21
Diarrhoea	11	5	4	1

MedDRA = Medical Dictionary for Regulatory Activities; TEAE = treatment-emergent adverse event.
Note: TEAEs coded using MedDRA version 22.0. A patient was counted only once for multiple events within preferred term/system organ class.
Source:Ravandi et al. (2020)[68]

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Appendix F. Comparative analysis of efficacy and safety

As QUAZAR AML-001 is the only relevant trial, so a comparative analysis is not applicable.

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Appendix G. Extrapolation

The clinical trial survival data used to inform cost-utility models is often incomplete. Thus, survival extrapolations over longer periods of time are required to estimate the full therapeutic benefit of an intervention across the patient's life. However, the appropriateness of these extrapolations in estimating the long-term survival adds uncertainty and may be perceived as a limitation of cost-utility models. Therefore, it is important to detail and justify the methods informing the selected survival extrapolations to increase decision makers' confidence in the results of the economic analysis.

The main objectives of this analysis were: (1) to systematically apply non-parametric/semi-parametric models and parametric models in the estimation and extrapolation of overall survival (OS) and relapse-free survival (RFS) to ITT populations from the QUAZAR AML-001 trial, and (2) provide guidance on the most appropriate extrapolations for use in the cost-utility model based on predefined selection criteria.

Appendix G.1 Methods

Appendix G.1.1 QUAZAR AML-001

The safety and efficacy of Onureg as a maintenance therapy for patients with AML is currently supported by evidence from the QUAZAR AML-001 trial (CC-486-AML-001; Clinicaltrials.gov identifier: NCT01757535; EudraCT number: 2012-003457-28). QUAZAR AML-001 is an ongoing phase III, international, multicentre, randomised, double-blind, placebo-controlled study that compares the efficacy and safety of Onureg plus best supportive care (BSC) versus placebo plus BSC as maintenance therapy among patients with AML who are in complete remission/complete remission with incomplete blood count recovery (CR/CRi) after intensive chemotherapy and who are ineligible for HSCT. The primary efficacy endpoint in the QUAZAR AML-001 trial is OS, which is evaluated from the time of randomisation to death from any cause. One of the key secondary endpoints is RFS, defined as the date of randomisation to the date of documented relapse or death from any cause, whichever occurred first.

This report uses data from the September 2020 database cutoff of the QUAZAR AML-001 trial.

Appendix G.1.2 Populations and outcomes

The full ITT population of the QUAZAR AML-001 trial is assessed. This report focusses on extrapolations of OS and RFS. OS was defined as the time from randomisation to the date of death due to any cause. Patients surviving at the end of the follow-up period or who were lost to follow-up were censored at the date last known to be alive. Patients who were lost to follow-up were censored at the date last known to be alive. For patients who withdrew consent during the study, the last date known alive was considered the date of consent withdrawal from the study. For all other patients, the last date known alive was derived by searching through all valid assessment dates in all study datasets to identify the last valid assessment date available for each patient.

RFS was defined as the interval from the date of randomisation to the date of documented relapse or death from any cause, whichever occurred first. Patients who were still alive without documented relapse, or who were lost to follow-up or withdrew consent without documented relapse were censored at the date of their last response assessment. Patients who withdrew for any reason or received another therapy for AML without documented relapse were censored on the date of the last bone marrow assessment, prior to receiving any

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other therapy for AML. Patients still on treatment at the time of study closure without documented relapse were censored on the date of the last response assessment.

Appendix G.1.3 Statistical analyses

Two classes of survival models, non-parametric/semi-parametric and parametric, were fit to the individual patient-level data from the QUAZAR AML-001 trial for each outcome (OS and RFS). Survival analyses and assessments conducted and presented in this report followed the structure outlined by Tremblay et al. (2016)[69] and were supported by the metrics and criteria described in the National Institute for Health and Care Excellence (NICE) Technical Support Document (TSD) 14.[70]

Non-parametric/semi-parametric models were fit to estimate the probability of survival from event within the bounds of trial follow-up without strict distributional assumptions. KM survival estimators were fit to each treatment arm and plotted. Mean and median survival time were calculated. Cox proportional hazards models with a treatment covariate were used to estimate the hazard ratio (HR) between Onureg and placebo. Cox proportional hazards models were fit both with ("stratified") and without ("unstratified") stratification for QUAZAR AML-001 trial randomisation strata per the QUAZAR AML-001 trial clinical summary report (i.e., age at informed consent, cytogenetic risk assessment, and prior consolidation therapy). The proportional hazards assumption upon which the Cox proportional hazards model depends was assessed using log-cumulative hazard plots, Schoenfeld residual plots, and the Grambsch-Therneau global Schoenfeld residual.[71]

Appendix G.2 Results

Appendix G.2.1 Overall survival: non-parametric and semi-parametric model fits within trial data

Figure G-1 presents the probability of survival over time by treatment arm as estimated by the KM method. The median survival time for Onureg and placebo was 24.7 (95% CI, 18.7-30.5) and 14.8 (95% CI, 11.7-17.6) months, respectively.

The unstratified Cox proportional hazards model estimated Onureg to result in a reduced rate of mortality compared with placebo (HR, 0.73; 95% CI, 0.59-0.90). The log-cumulative hazard plot and Schoenfeld residual

plot showed violation of the proportional hazards assumption. A visual inspection of the log-cumulative hazard plot suggested that the 2 lines were not parallel (Figure G-2). Similarly, the Schoenfeld residual plot displayed a non-horizontal line and the Grambsch-Therneau global Schoenfeld residual test value was statistically significant (*P* = 0.0008) (Figure G-3). Therefore, the proportional hazards assumption was shown to be violated.

Similarly, the stratified Cox proportional hazards model estimated Onureg to result in a reduced rate of mortality compared with placebo (HR, 0.69; 95% CI, 0.56-0.86). According to the Schoenfeld residual plot and Grambsch-Therneau global Schoenfeld residual test, the proportional hazards assumption was violated since the line on the plot was not horizontal and the *P* value was statistically significant (*P* = 0.0017) (Figure G-4). Given the shape of the KM-estimated hazard functions and suspected violations of the proportional hazards assumption, individual model fits and joint AFT models (log-normal, log-logistic, generalised gamma) may be preferred over joint proportional hazards models (exponential, Weibull, Gompertz) because they do not assume hazards between treatment arms to be proportional.[69,70]

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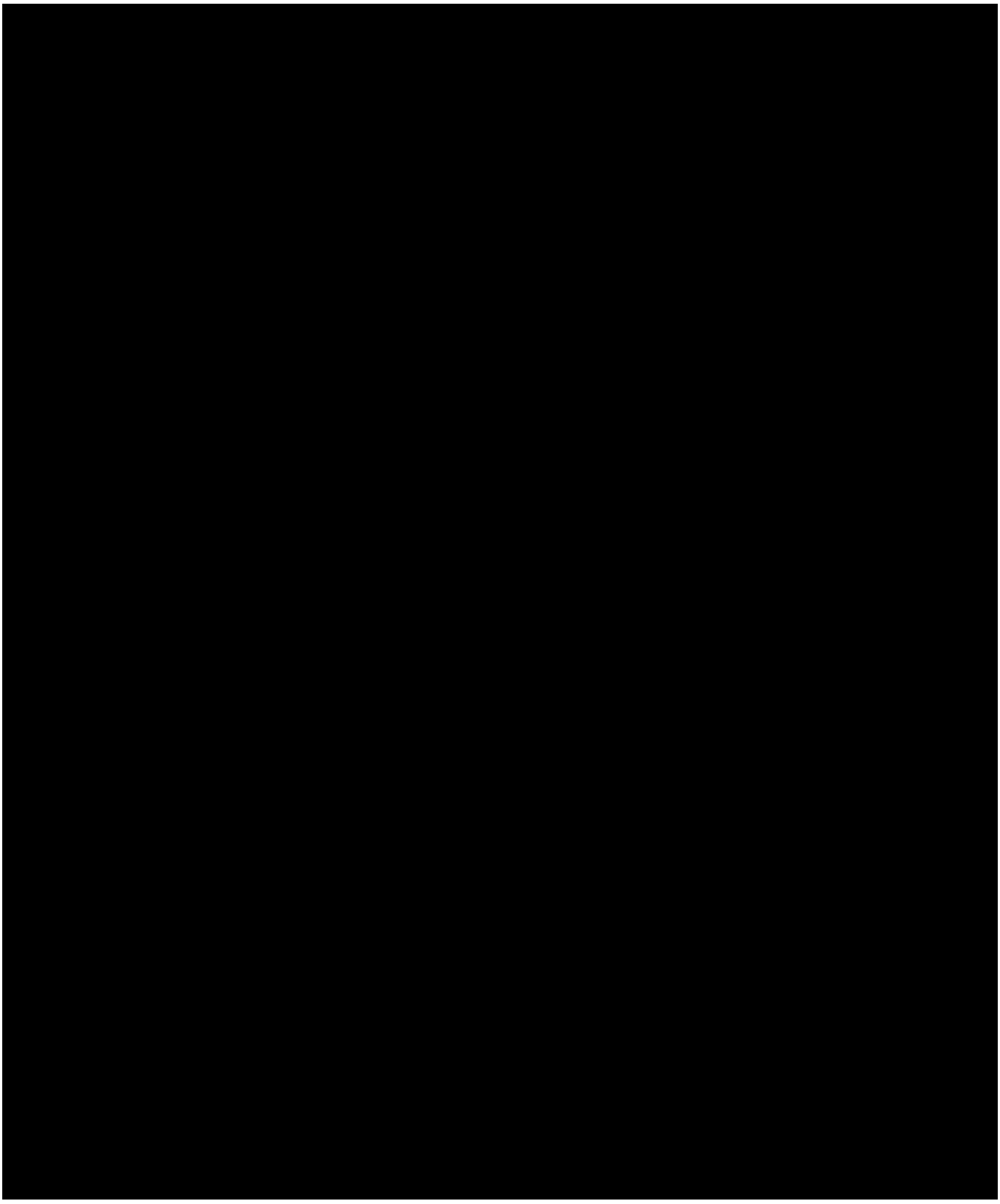

Appendix G.2.2 Overall survival: parametric model fits and extrapolation beyond trial data

Parametric curves are shown in Figure G-5 to Figure G-16. In these figures, KM curves are drawn with a solid line; parametric curves are drawn with a dashed line. Model fit statistics (Akaike information criterion [AIC], Bayesian information criterion [BIC]) for all parametric distributions are presented in Table G-1.

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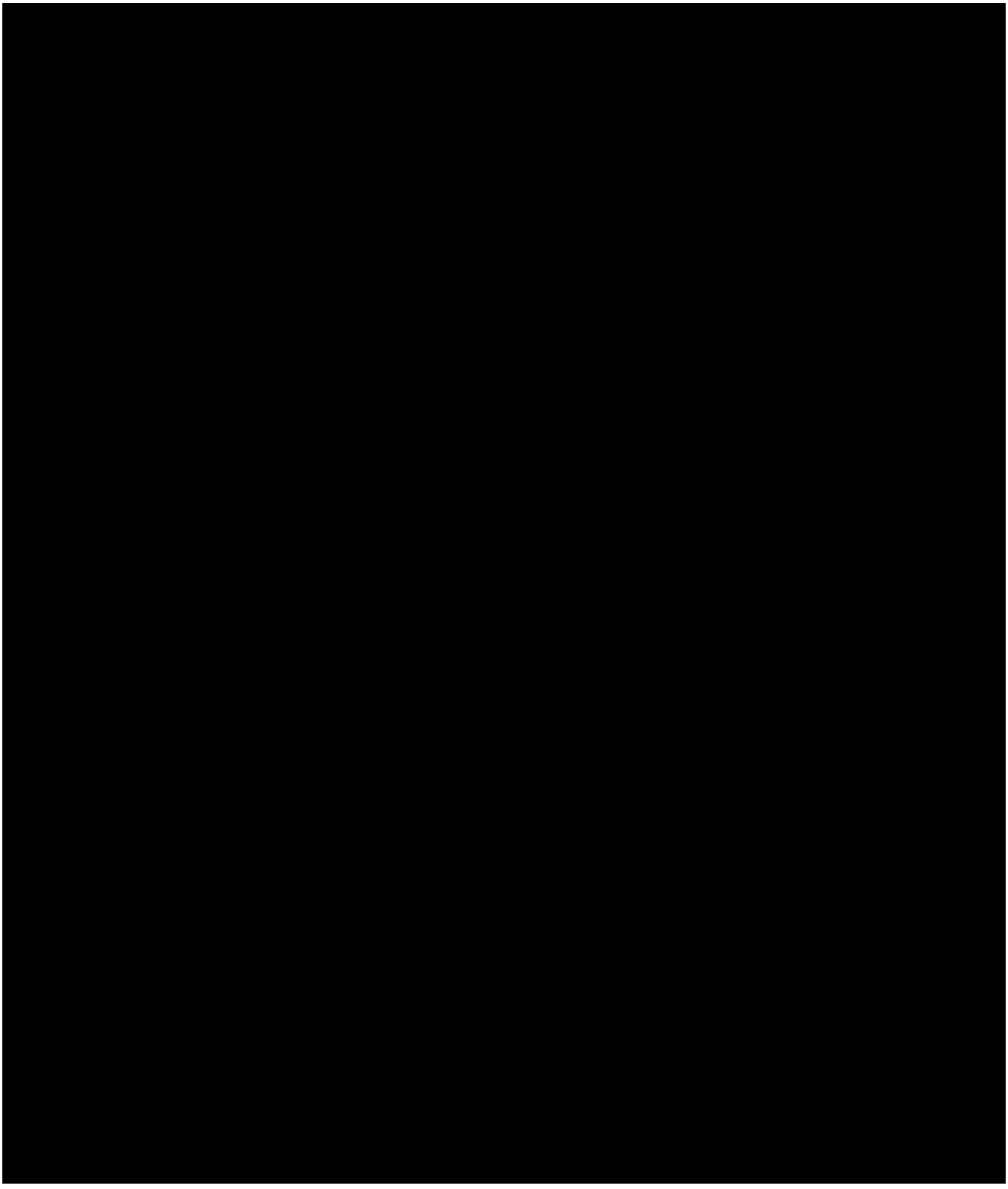
The generalised gamma distribution had the lowest AIC and BIC values among all distributions, indicating it had the best statistical fit to the observed data. Visual inspection of the individual generalised gamma survival function in Figure G-9 shows that the curves appear to fit well in the early part of the observed data, but do not fit well to the longer term observed data and have tails that may not be clinically plausible. In fact, a number of the distributions display implausible long-term projections showing Onureg absolute survival falling below that of patients on placebo. This is likely because the hazard function of Onureg is complex and standard parametric functions are not able to fully reflect this. Therefore, alternative approaches were explored using time-varying spline models.



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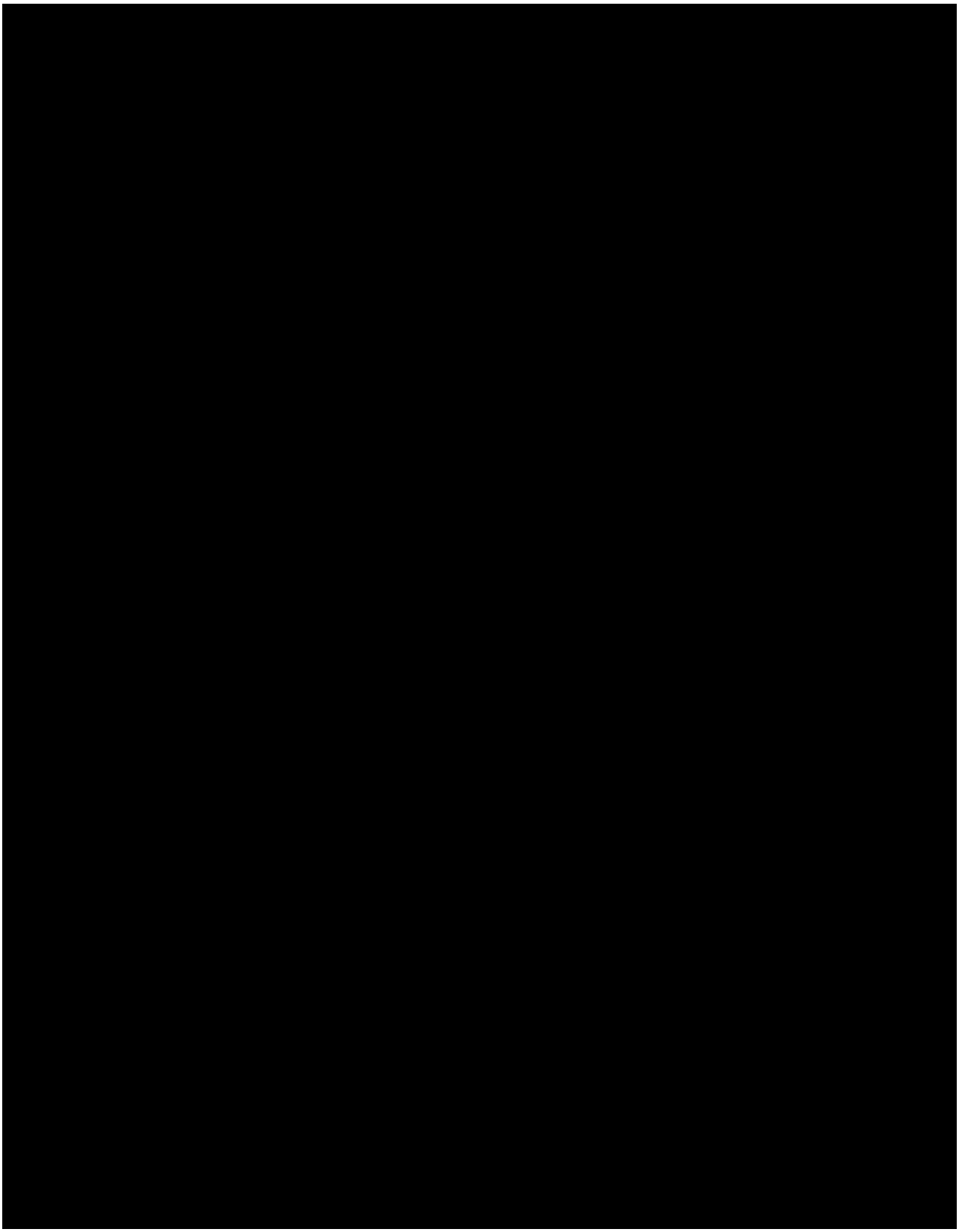

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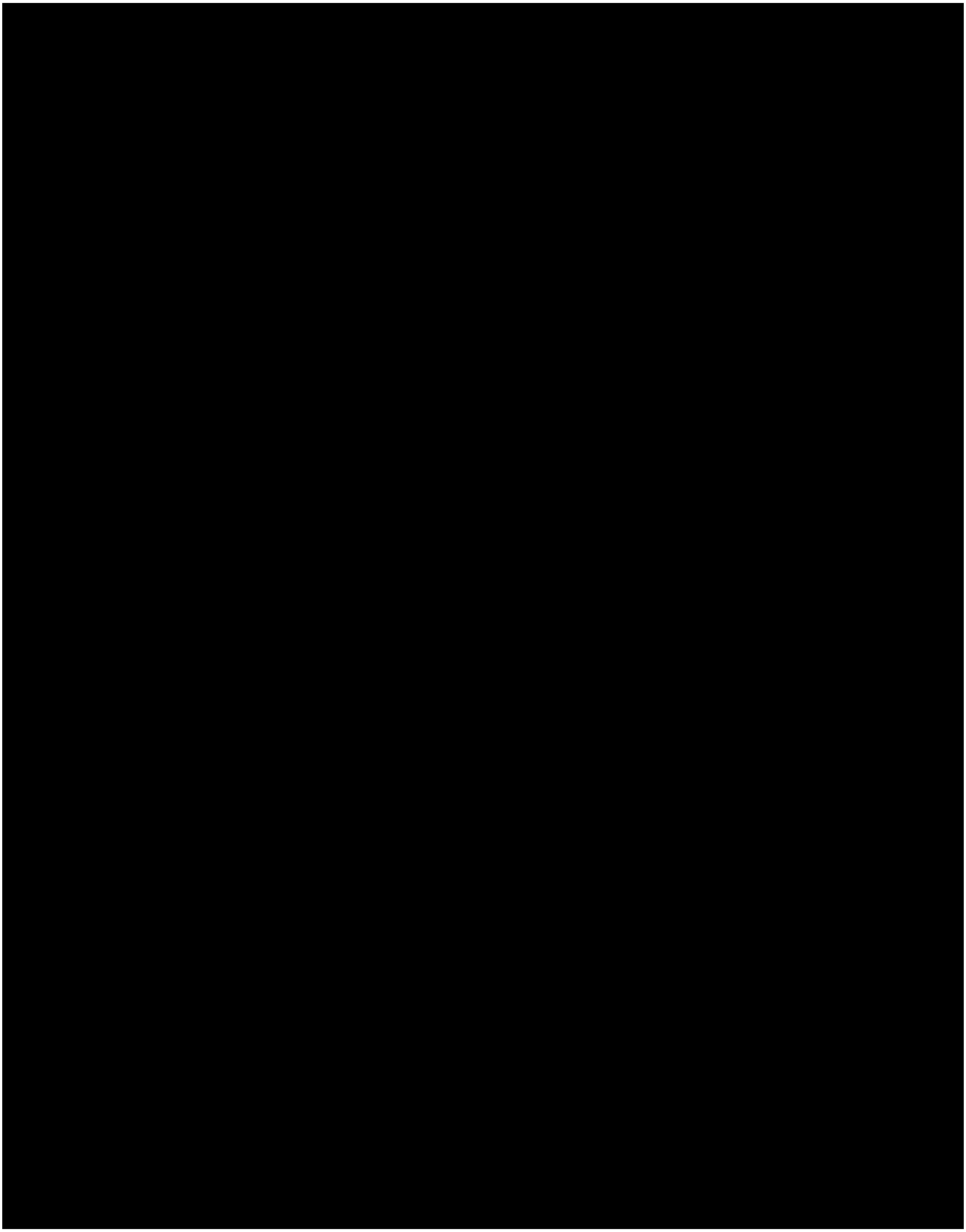

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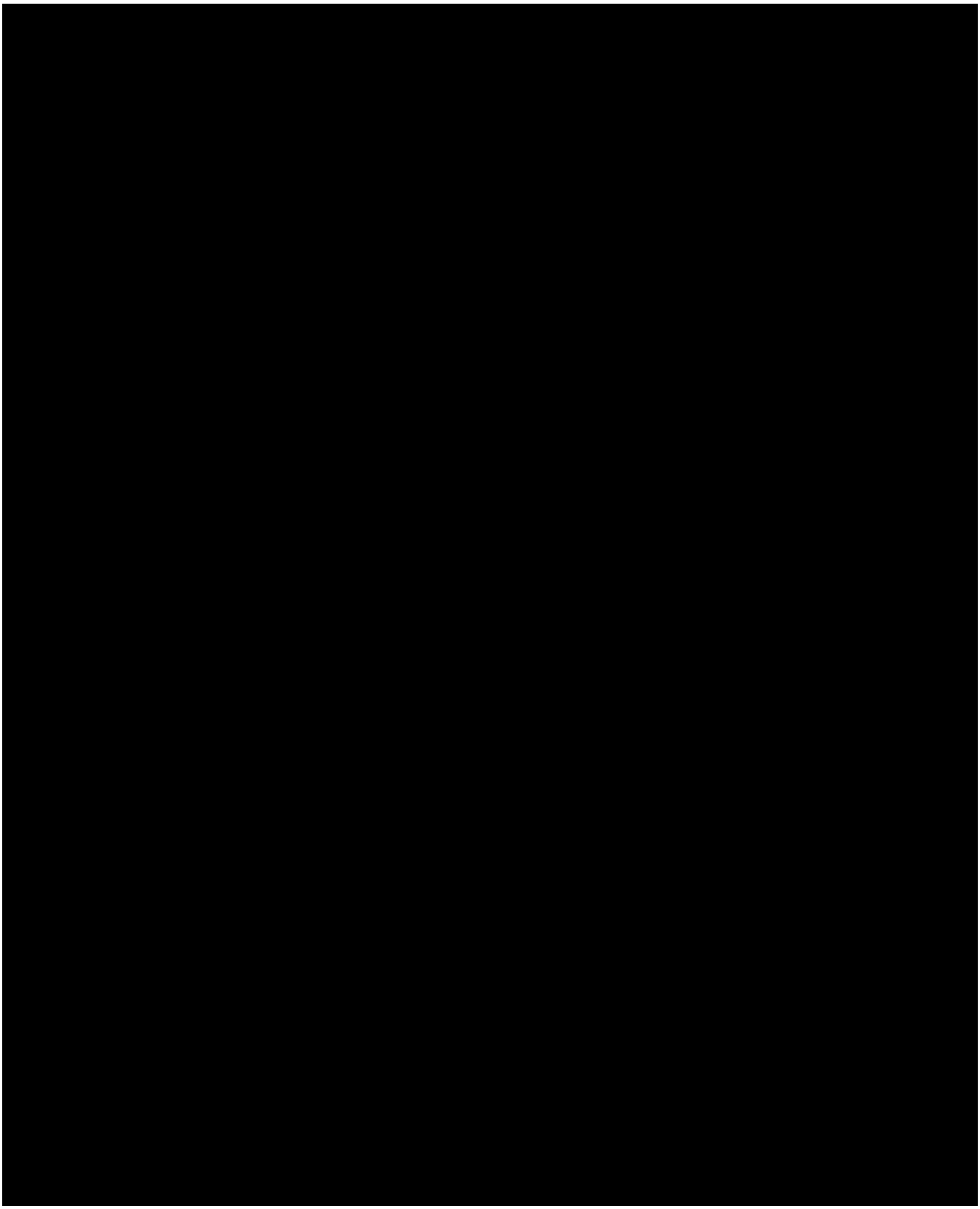

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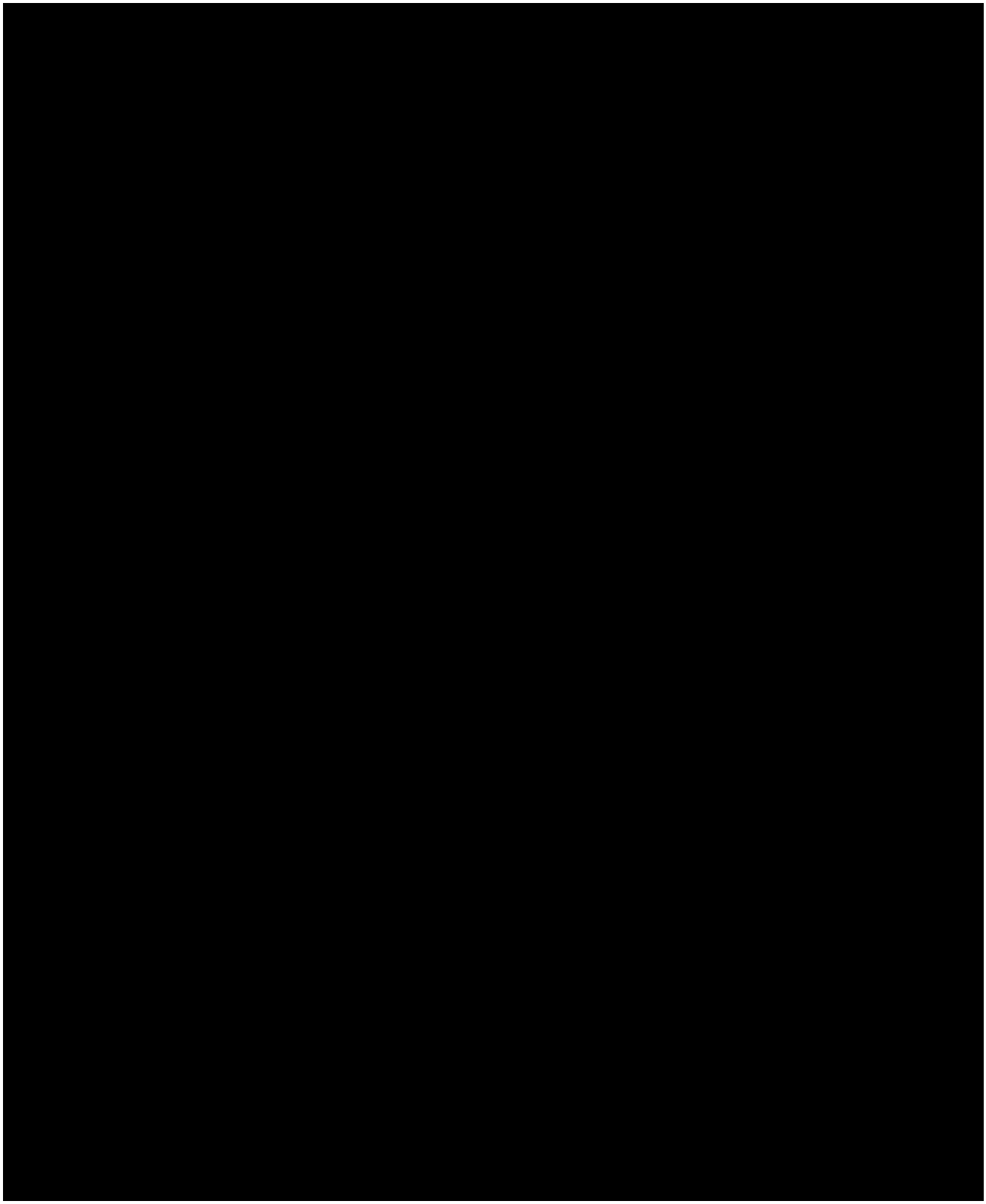

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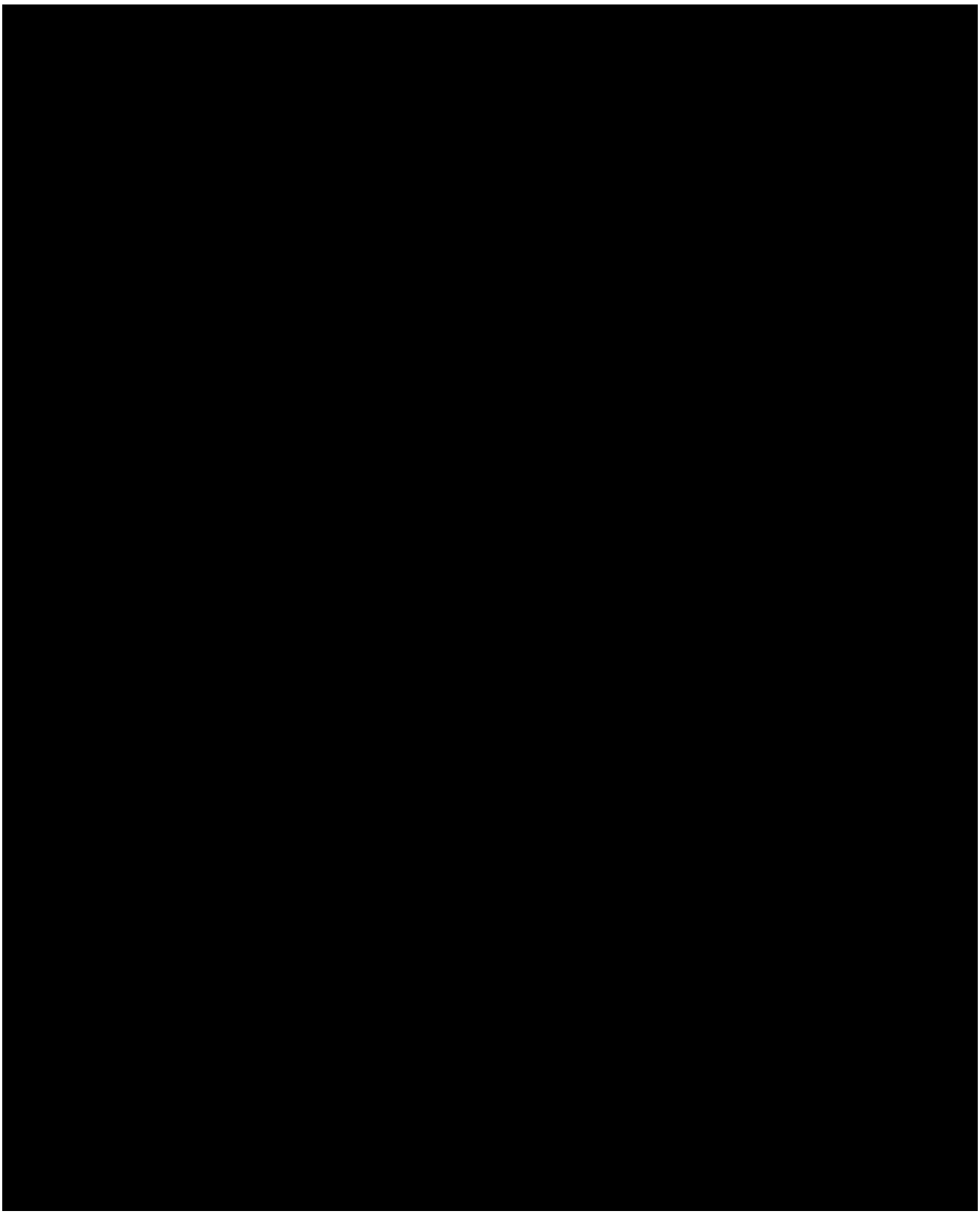

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Table G-1. Model fit statistics (AIC and BIC) for parametric models of the overall survival outcome in the ITT population

Parametric model	AIC	Ranks based on AIC	BIC	Ranks based on BIC
Individual models				
Exponential	3,117.23	6	3,124.16	5
Weibull	3,117.18	5	3,131.04	6
Log-logistic	3,065.56	3	3,079.41	3
Log-normal	3,057.57	2	3,071.43	2
Generalised Gamma	3,049.88	1	3,070.65	1
Gompertz	3,093.52	4	3,107.38	4
Joint models				
Exponential	3117.23	5	3125.55	5
Weibull	3118.51	6	3130.98	6
Log-logistic	3065.01	3	3077.48	3
Log-normal	3056.97	2	3069.44	2
Generalized Gamma	3049.21	1	3065.84	1
Gompertz	3096.39	4	3108.86	4

AIC = Akaike's information criteria; BIC = Bayesian information criterion; ITT = intention-to-treat.

The difference in mean time to event between treatment arms for OS was estimated via both the KM method over the duration of trial follow-up (87.1 months; the minimum of the last observations across treatment arms) and via parametric models restricted to 40 years (Table G-2). The 95% bootstrapped CIs for parametric curves are presented to assist with the inspection of uncertainty. The KM-estimated difference in mean time to mortality between Onureg and placebo was 7.32 months. Most parametric models estimated a larger increase in mean time to mortality for Onureg compared with placebo than did the KM estimator. The generalised gamma distribution estimates a small increase in mean time to mortality across the 40 year time horizon (difference in means: 0.87; 95% CI, −22.25 to 26.83). All models estimate a non-significant increase (or decrease in the case of the Gompertz distribution). The decrease in time to mortality observed for the Gompertz distribution when using individual models is likely the result of clinically implausible tails which plateau in both treatment arms leading to unrealistic survival projections (Figure G-10).

Table G-2. Difference in mean time to event for overall survival between Onureg and placebo arms in the ITT population

Model	Difference in mean OS, months (Onureg – placebo)	Difference in mean OS, months, lower bound of 95% CI	Difference in mean OS, months, upper bound of 95% CI
KM	7.32	NA	NA
Individual models			
Exponential	11.34	3.85	19.02
Weibull	8.94	−0.59	17.13
Log-Logistic	11.68	−1.95	25.86
Log-Normal	12.13	−0.78	26.50
Generalised Gamma	0.87	−22.25	26.83
Gompertz	−19.38	−60.89	31.21

CI = confidence interval; ITT = intention-to-treat; KM = Kaplan-Meier; NA = not applicable; OS = overall survival.

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Log-cumulative hazard plots are presented in Figure G-17 and Figure G-18, respectively. According to a visual assessment of the log-cumulative hazard plots, generalised gamma appears to be the best fit followed by log-normal. It should be noted, events early in time have created the stretching effect seen in the graphs but they represent a small number of events as the x-axis is on a log scale.

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The marginal survival gain both pre- and post-extrapolation for each model is presented in Table G-3. The cut-point to distinguish pre- and post-extrapolation time periods for the OS outcome was 87.1 months (the minimum of the last observations across treatment arms). According to the results, all models satisfied Criterion 5 in terms of having rate of survival gain in the extrapolated tail being lower than the rate of gain observed in the KM curve. In addition, for all models, the extrapolated tail rate of gain was lower compared with the pre-extrapolation rate of gain. However, in all instances except for the generalised gamma and Gompertz models, the pre-extrapolation rate of gain was higher than the KM rate of survival gain. For these models, a negative rate of survival gain occurred in the post-extrapolation tail, indicating the estimated Onureg and placebo curves cross at some point (see Figure G-9 and Figure G-10); these models should be interpreted with caution.

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Table G-3. Evaluation of Criterion 5: estimated rate of overall survival gain per month by receiving Onureg instead of placebo in the ITT population, before and after the trial cutoff

Model	Pre-extrapolation	Extrapolated tail
KM	0.084	-
Individual models		
Exponential	0.092	0.009
Weibull	0.088	0.003
Log-Logistic	0.092	0.009
Log-Normal	0.091	0.011
Generalised Gamma	0.082	−0.016
Gompertz	0.080	−0.067
Joint models		
Exponential	0.092	0.009
Weibull	0.088	0.003
Log-Logistic	0.092	0.009
Log-Normal	0.091	0.011
Generalized Gamma	0.082	-0.016
Gompertz	0.080	-0.067

ITT = intention-to-treat; KM = Kaplan-Meier.

Notes: The rate of survival gain in the pre-extrapolation period is defined as the difference in survival between Onureg and placebo at 87.1 months divided by the number of months in the pre-extrapolation period (i.e., 87.1 months). The rate of survival gain in the post-extrapolation period is defined as the marginal relative difference in the extrapolated period (after cutoff) divided by the number of months after cutoff. Negative values represent the rate of survival loss for Onureg (i.e., gain for placebo), which in the case of most fitted models indicate a crossing of curves.

Appendix G.2.3 Overall survival: Time-varying spline model fits and extrapolation beyond trial data

Time-varying spline curves are shown in Figure G to Figure G. In these figures, KM curves are drawn with a solid line; time-varying spline curves are drawn with a dashed line. Model fit statistics (AIC, BIC) for all parametric distributions are presented in Table G-4. To avoid overfitting the data, time-varying spline models were limited to 2 internal knots.

The 1 internal knot, odds linear predictor distribution, had the lowest AIC and BIC values among all distributions for both joint and individual models, indicating it had the best statistical fit to the observed data. Visual inspection of the time-varying spline curves confirmed that the long-term predictions are more clinically plausible when compared with standard parametric curves. However, functions still cross long-term, which has been adjusted for in the model to ensure that Onureg patients do not have an increased probability of death when compared with patients receiving no active therapy.

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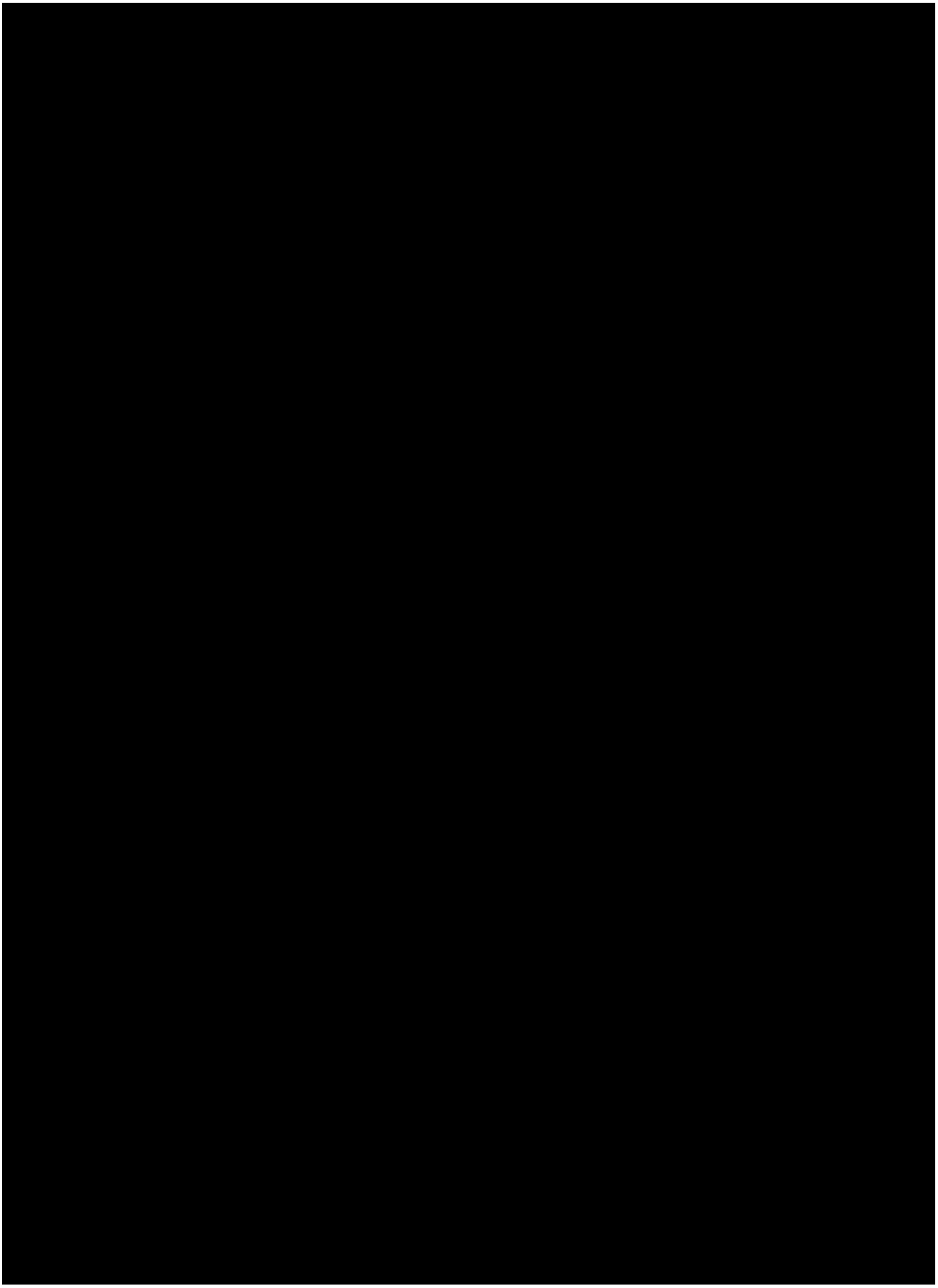

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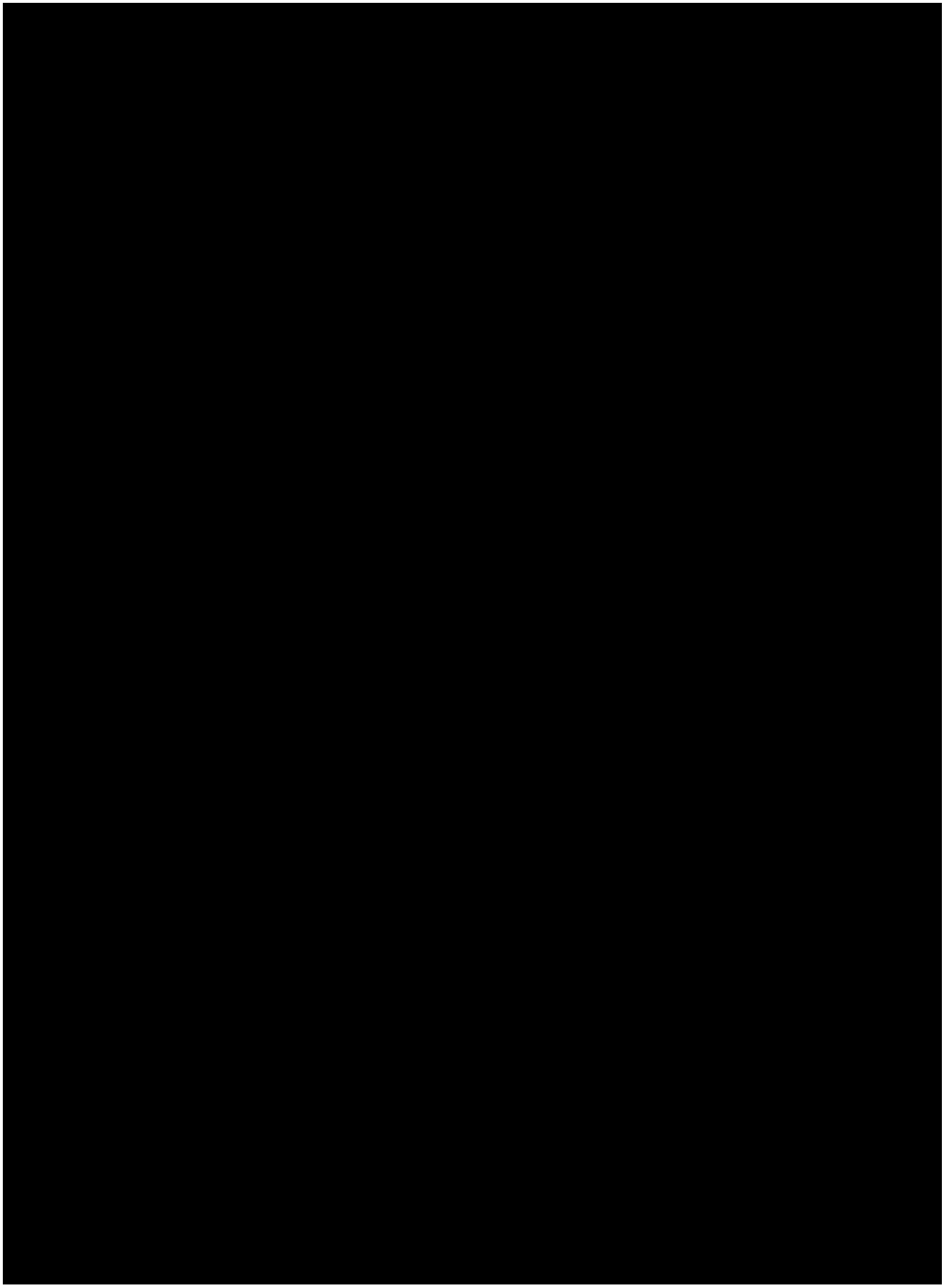

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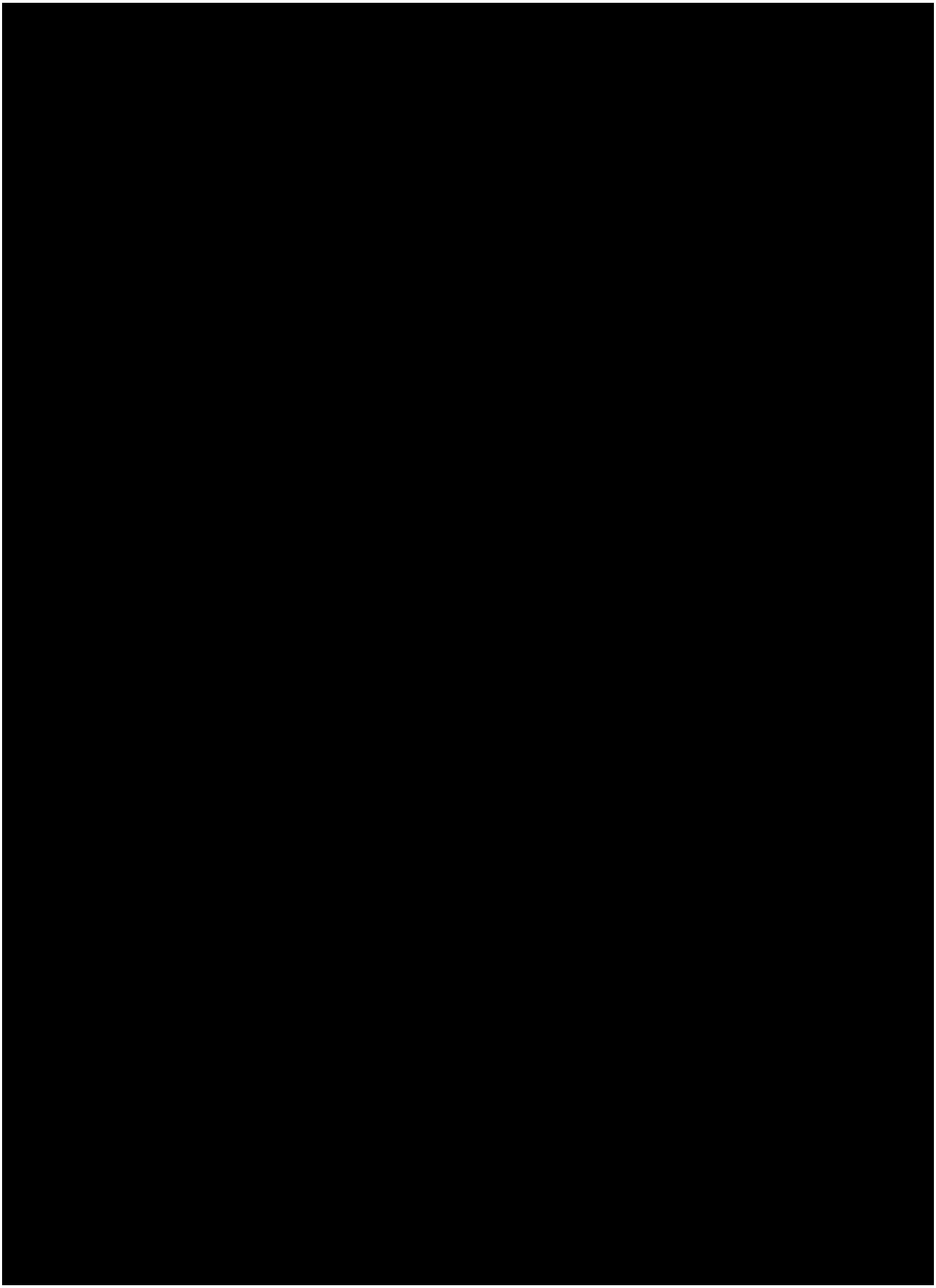

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Table G-4. Model fit statistics (AIC and BIC) for time-varying spline models of the overall survival outcome in the ITT population

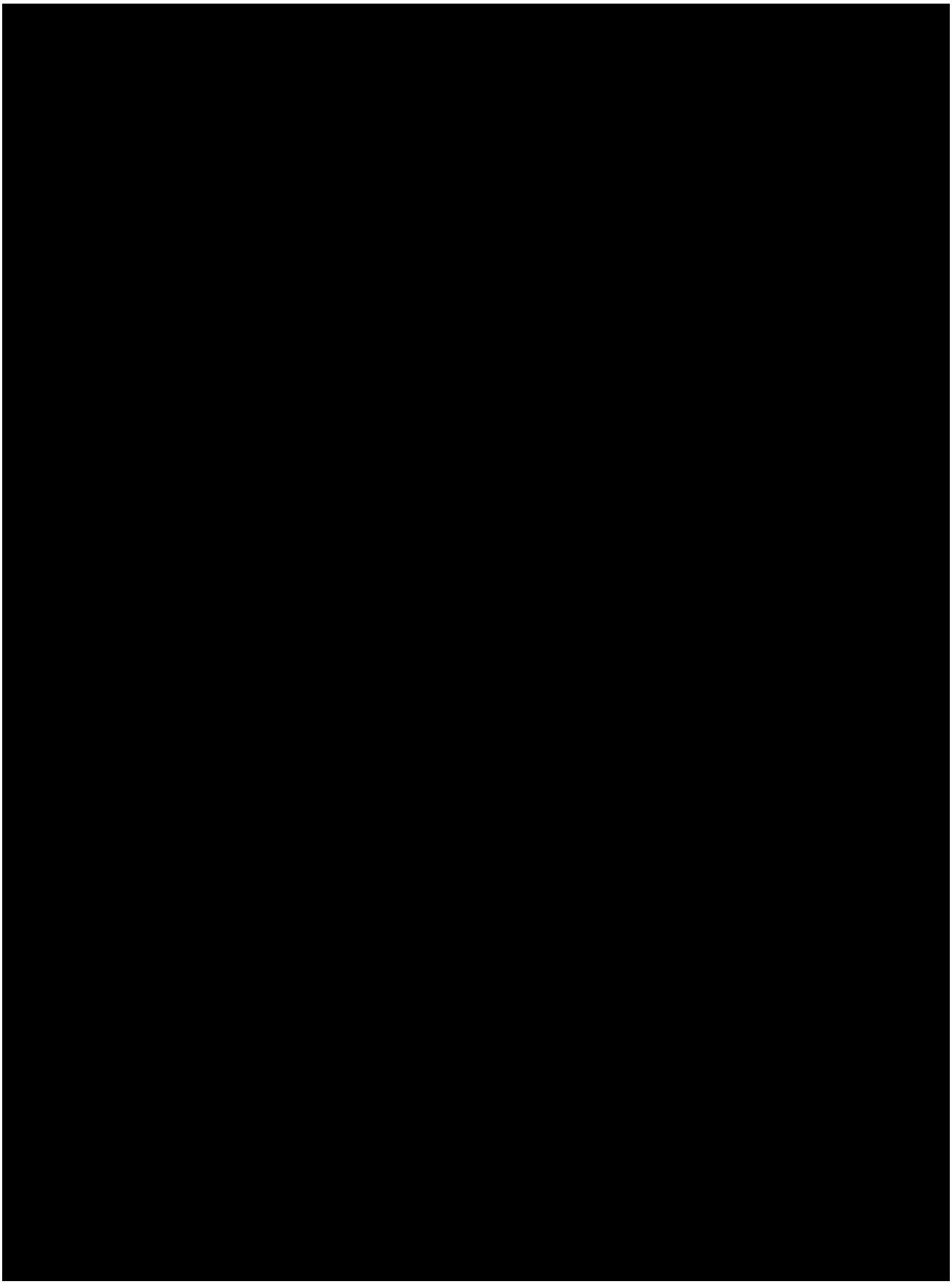
Parametric model	AIC	Ranks based on AIC	BIC	Ranks based on BIC
1 internal knot, odds linear predictor	3,044.229	1	3,069.171	1
1 internal knot, hazard linear predictor	3,044.547	2	3,069.489	2
2 internal knots, normal linear predictor	3,045.324	3	3,078.58	4
2 internal knots, odds linear predictor	3,047.058	4	3,080.314	5
2 internal knots, hazard linear predictor	3,047.504	5	3,080.76	6
1 internal knot, normal linear predictor	3,049.166	6	3,074.108	3

AIC = Akaike's information criteria; BIC = Bayesian information criterion; ITT = intention-to-treat.

Appendix G.2.4 Relapse-free survival: non-parametric and semi-parametric model fits within trial data

The probability of RFS over time by treatment arm as estimated by the KM method is shown with KM curves in Figure G. The median survival time for Onureg and placebo was 10.2 (95% CI, 7.9-12.9) and 4.8 (95% CI, 4.6-6.4) months, respectively.

The unstratified Cox proportional hazards model estimated Onureg to result in a reduced rate of relapse or mortality compared with placebo (HR, 0.66; 95% CI, 0.53-0.81). The log-cumulative hazard plot and Schoenfeld residual plots showed violation of the proportional hazards assumption. A visual inspection of the log-cumulative hazard plot suggested that the 2 lines were not parallel (Figure G). Similarly, the Schoenfeld residual plot displayed a non-horizontal line and the Grambsch-Therneau global Schoenfeld residual test value was statistically significant (P = 0.001) (Figure G).



The stratified Cox proportional hazards model estimated Onureg to be more beneficial compared with placebo (HR, 0.65; 95% CI, 0.52-0.80). According to the Schoenfeld residual plot and Grambsch-Therneau global Schoenfeld residual test, the proportional hazards assumption was violated since the line on the plot was not

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horizontal and the *P* value was statistically significant (*P* = 0.0012) (Figure G). Given the shape of the KM-estimated hazard functions and suspected violations of the proportional hazards assumption, individual model fits may be preferred over joint proportional hazards models because they do not assume hazards between treatment arms to be proportional.

Appendix G.2.5 Relapse-free survival: parametric model fits and extrapolation beyond trial data

Parametric curves are shown in Figure G to Figure G. In these figures, KM curves are drawn with a solid line; parametric curves are drawn with a dashed line. Model fit statistics (AIC, BIC) for all parametric distributions are presented in Table G-5.

According to the AIC and BIC, it appears that log-logistic distribution is the best fitting joint model and second-best fitting individual model, behind the Gompertz distribution. However, based on visual inspection of the survival functions, the Gompertz model lacks clinical plausibility as the probability of RFS stays well above zero for either treatment arm while the log-logistic model demonstrates a more clinically plausible extrapolation (see Figure G, and Figure G).

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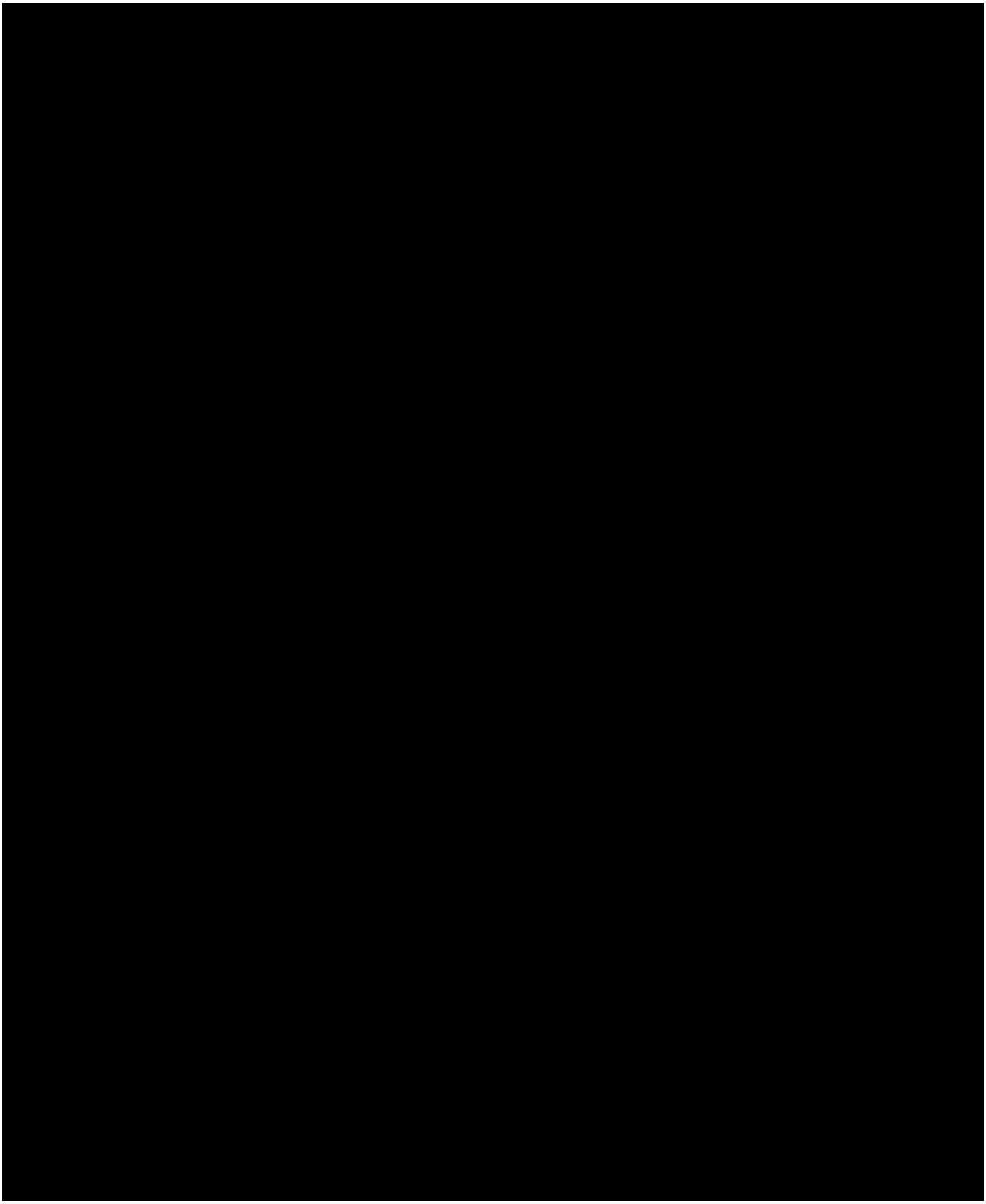

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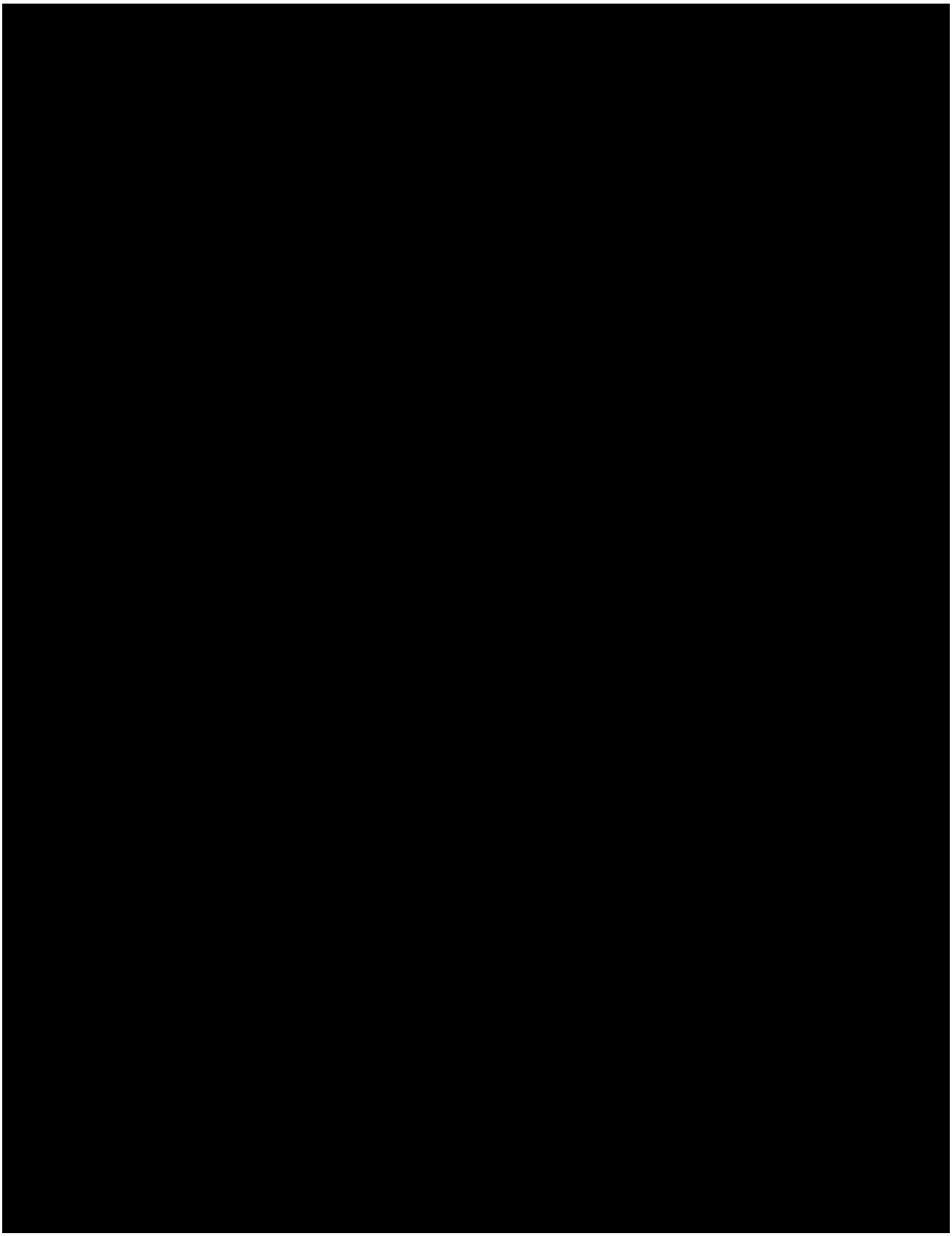

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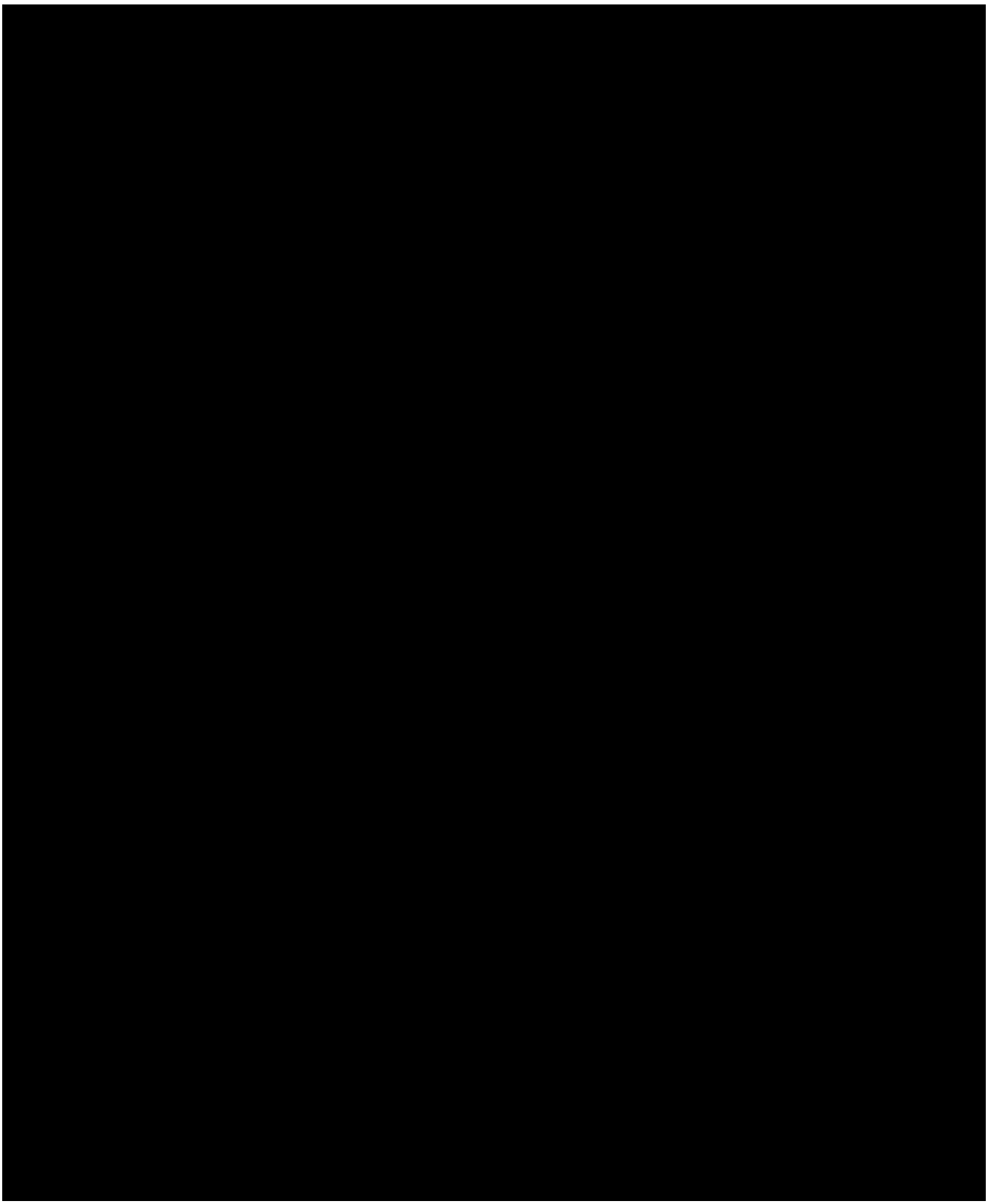

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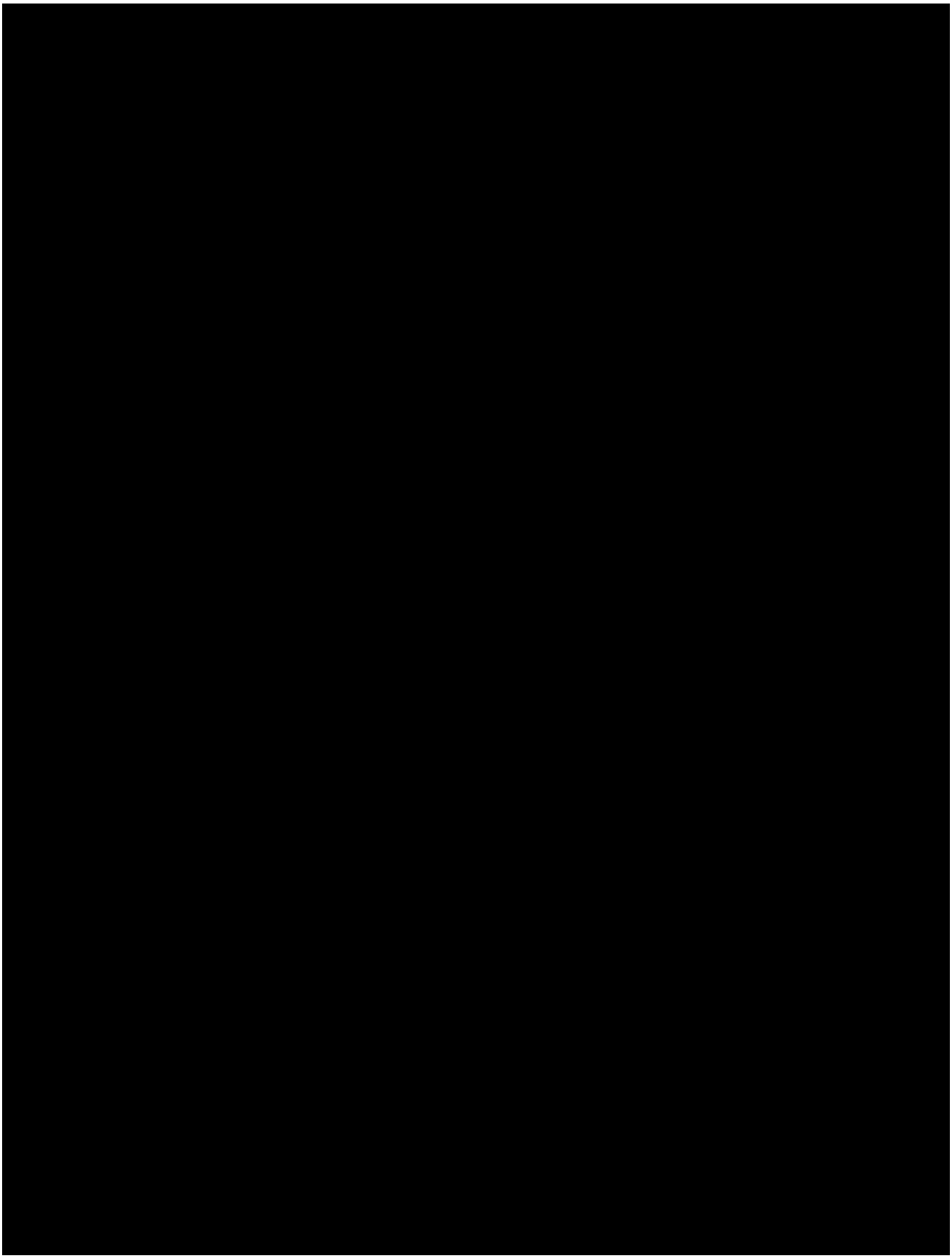

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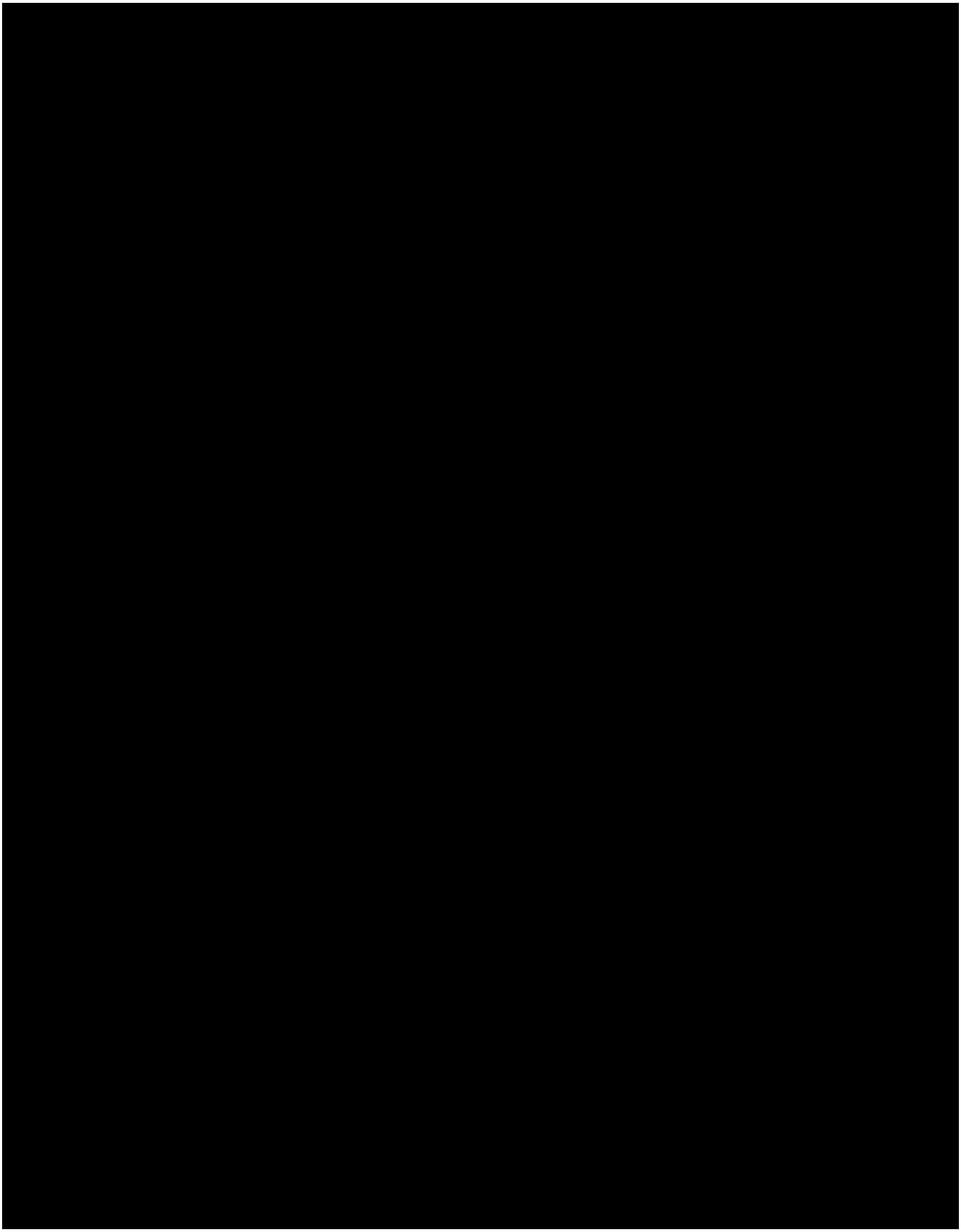

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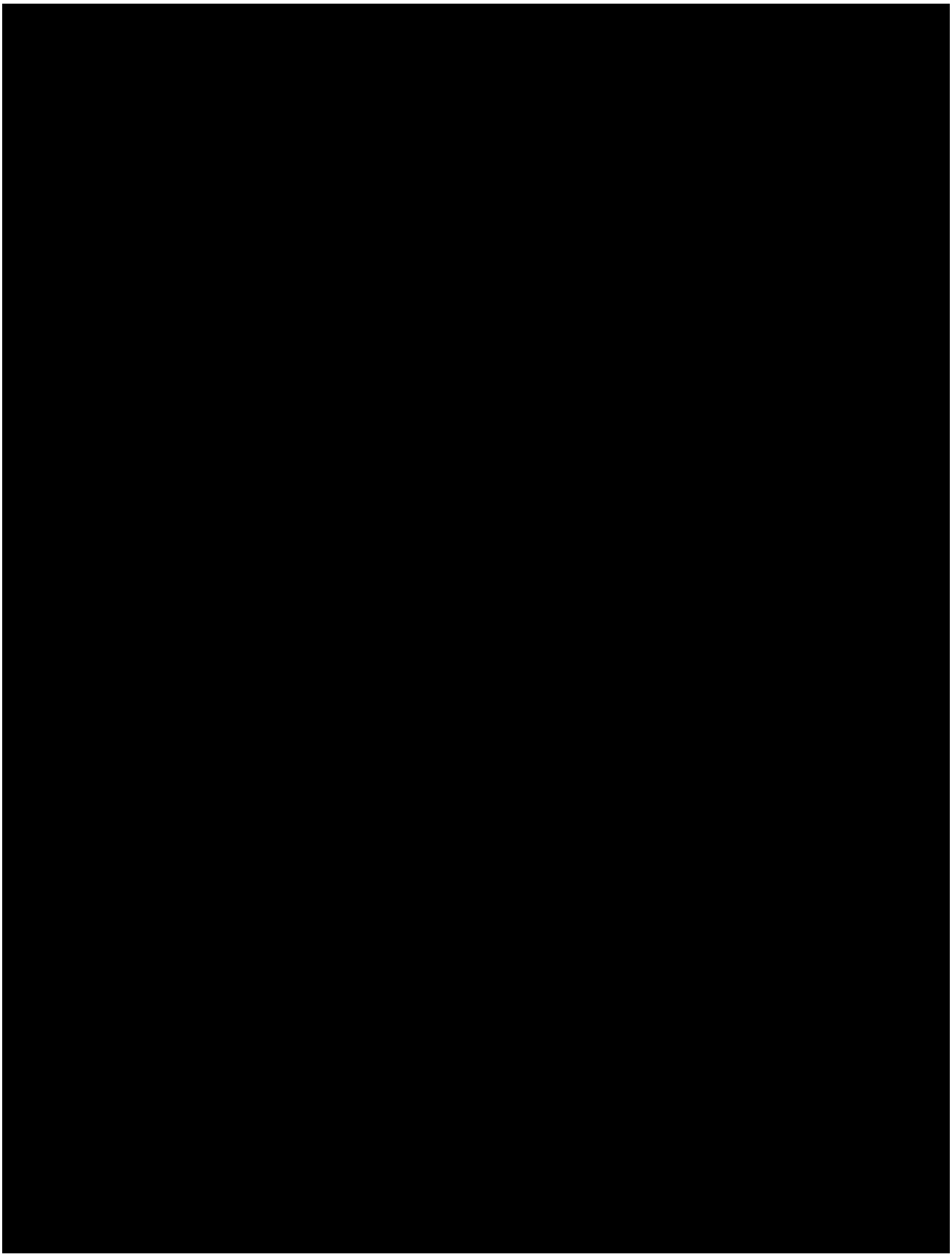

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Table G-5. Model fit statistics (AIC and BIC) for parametric models of the relapse-free survival outcome in the ITT population

Parametric model	AIC	Ranks based on AIC	BIC	Ranks based on BIC
Individual models				
Exponential	2,587.25	6	2,594.18	6
Weibull	2,548.55	5	2,562.40	5
Log-logistic	2,490.41	2	2,504.27	2
Log-normal	2,505.22	4	2,519.07	3
Generalised gamma	2,505.09	3	2,525.87	4
Gompertz	2,481.30	1	2,495.15	1
Joint models				
Exponential	2587.25	6	2594.18	6
Weibull	2548.55	5	2562.40	5
Log-logistic	2490.41	2	2504.27	2
Log-normal	2505.22	4	2519.07	3
Generalized Gamma	2505.09	3	2525.87	4
Gompertz	2481.30	1	2495.15	1

AIC = Akaike's information criteria; BIC = Bayesian information criterion; ITT = intent to treat.

The estimated difference in mean time to event between treatment arms for RFS was estimated via both the KM method over the duration of trial follow-up (67.8 months; the minimum of the last observations across treatment arms) and via parametric models restricted to 40 years (Table G-6). The 95% bootstrapped CIs for parametric curves are presented to assist with the inspection of uncertainty. The KM-estimated difference in mean time to relapse or mortality between Onureg and placebo was 5.18 months. Except for Gompertz, all parametric models estimated a larger increase in mean time to mortality for Onureg compared with placebo than did the KM estimator. The log-logistic distribution estimates a significant increase in time to relapse or mortality for Onureg compared with placebo (difference in means: 14.01; 95% CI, 4.36-24.41. All models estimate a significant increase in time to relapse or mortality for Onureg compared with placebo, except for the generalised gamma and Gompertz distributions.

Table G-6. Difference in mean time to event for relapse-free survival between Onureg and placebo arms in the ITT population

Model	Difference in mean RFS, months (Onureg – placebo)	Difference in mean RFS, months, lower bound of 95% CI	Difference in mean RFS, months, upper bound of 95% CI
KM	5.18	NA	NA
Individual models			
Exponential	7.23	4.09	10.63
Weibull	7.58	2.62	12.77
Log-logistic	14.01	4.36	24.41
Log-normal	14.66	4.71	26.01
Generalised gamma	5.58	−8.52	17.44
Gompertz	−0.12	−44.00	40.23
Joint models			
Exponential	7.23	3.86	10.85

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Model	Difference in mean RFS, months (Onureg – placebo)	Difference in mean RFS, months, lower bound of 95% CI	Difference in mean RFS, months, upper bound of 95% CI
Weibull	9.22	4.35	15.05
Log-Logistic	14.14	8.18	20.75
Log-Normal	14.03	7.85	21.23
Generalized Gamma	13.71	6.68	21.55
Gompertz	53.49	25.41	81.42

CI = confidence interval; ITT = intention-to-treat; KM = Kaplan-Meier; NA = not applicable; RFS = relapse-free survival.

Log-cumulative hazard plots for joint models and individual models for RFS are presented in Figure G, respectively. According to a visual assessment of the log-cumulative hazard plots, log-logistic appears to be the best fit. In comparison, the model fit for Gompertz is less optimal. These findings are consistent with the evidence presented above regarding model fit, AIC, BIC, and clinical plausibility.

Figure G-41. Log-cumulative hazard versus log time plots for the relapse-free survival outcome in the ITT population: parametric model fits (dashed line) compared with Kaplan-Meier fits (solid line) by treatment arm;

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Figure G-42. Log-cumulative hazard versus log time plots for the relapse-free survival outcome in the ITT population: parametric model fits (dashed line) compared with Kaplan-Meier fits (solid line) by treatment arm; joint models

The marginal survival gain both pre- and post-extrapolation for each model is presented in Table G-7. The cut-point to distinguish pre- and post-extrapolation time periods for the RFS outcome was 67.8 months (the minimum of the last observations across treatment arms). According to the results, all the models, satisfied Criterion 5 in terms of having rate of gain in the extrapolated tail being lower than the rate of gain observed in the KM curve. In addition, for all models, the extrapolated tail rate of gain was lower compared with the pre-extrapolation rate of gain. However, in all instances, the pre-extrapolation rate of gain was higher than the KM rate of survival gain.

Table G-7. Evaluation of Criterion 5: estimated rate of relapse-free survival gain per month by receiving Onureg instead of placebo in the ITT population, before and after the trial cutoff

Model	Pre-extrapolation	Extrapolated tail
KM	0.076	-
Individual models		
Exponential	0.099	0.001
Weibull	0.096	0.003
Log-logistic	0.110	0.016
Log-normal	0.108	0.018
Generalised gamma	0.091	–0.001
Gompertz	0.080	–0.014
Joint models		
Exponential	0.099	0.001
Weibull	0.105	0.005
Log-Logistic	0.110	0.016

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Model	Pre-extrapolation	Extrapolated tail
Log-Normal	0.106	0.017
Generalized Gamma	0.107	0.016
Gompertz	0.122	0.110

ITT = intent to treat; KM = Kaplan-Meier.

Notes: The rate of survival gain in the pre-extrapolation period is defined as the difference in RFS between Onureg and placebo at 67.8 months divided by the number of months in the pre-extrapolation period (i.e., 67.8 months). The rate of survival gain in the post-extrapolation period is defined as the marginal relative difference in the extrapolated period (after cutoff) divided by the number of months after cutoff. Negative values represent the rate of survival loss for Onureg (i.e., gain for placebo), which in the case of most fitted models indicate a crossing of curves.

Appendix G.2.6 Relapse-free survival: time-varying spline model fits and extrapolation beyond trial data

Time-varying spline curves are shown in Figure G to Figure G. In these figures, KM curves are drawn with a solid line; time-varying spline curves are drawn with a dashed line. Model fit statistics (AIC, BIC) for all parametric distributions are presented in . In order to avoid overfitting the data, time-varying spline models were limited to 2 internal knots.

The 2 internal knots, hazard linear predictor distribution had the lowest AIC value and second-lowest BIC value among all distributions, indicating it had very good statistical fit to the observed data. Visual inspection of the time-varying spline curves confirmed that the within trial fit is improved when compared with standard parametric curves and long-term extrapolations are more plausible.

Figure G-43. Time-varying spline curves fit to the relapse -free survival outcome in the ITT population: time-varying, 1 internal knot, hazard linear predictor

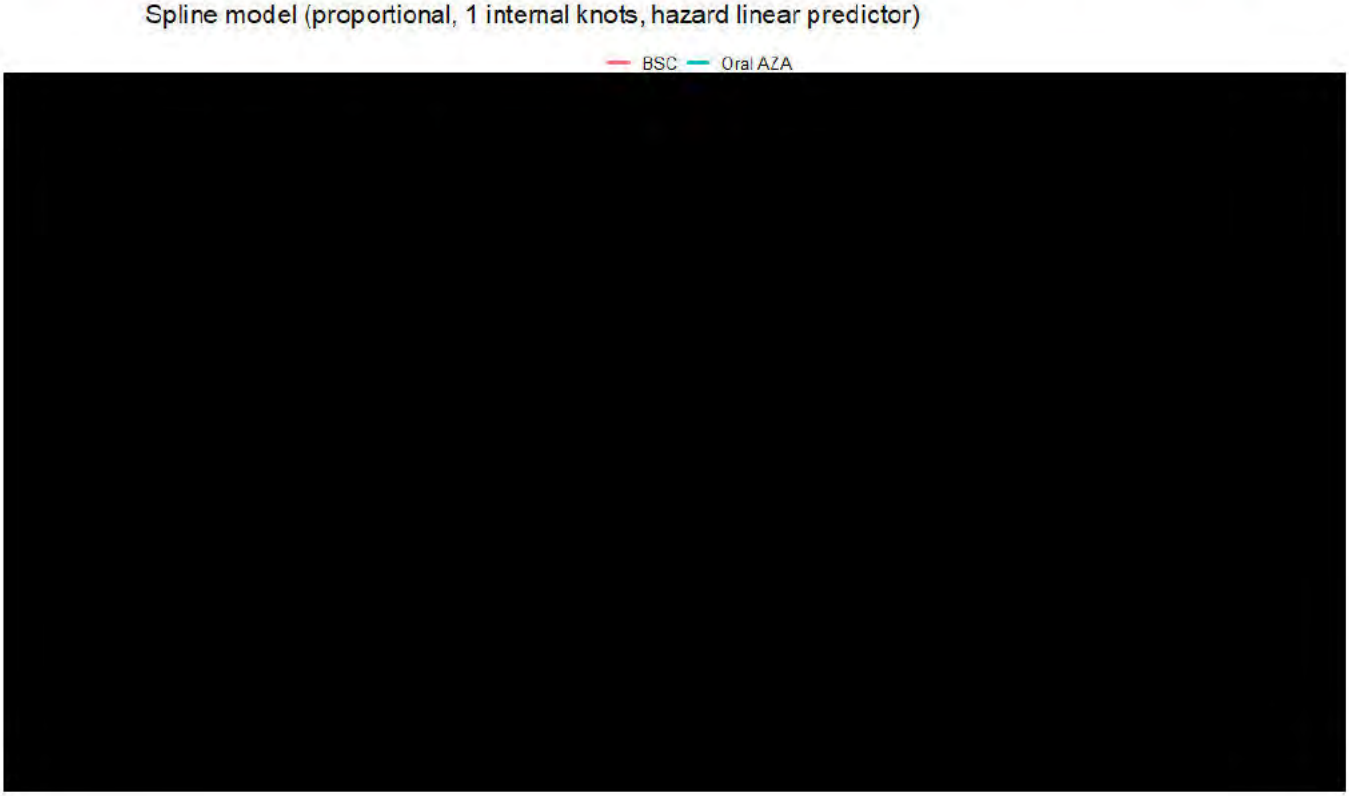

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Figure G-44. Time-varying spline curves fit to the relapse-free survival outcome in the ITT population: time-varying, 0 internal knots, normal linear predictor

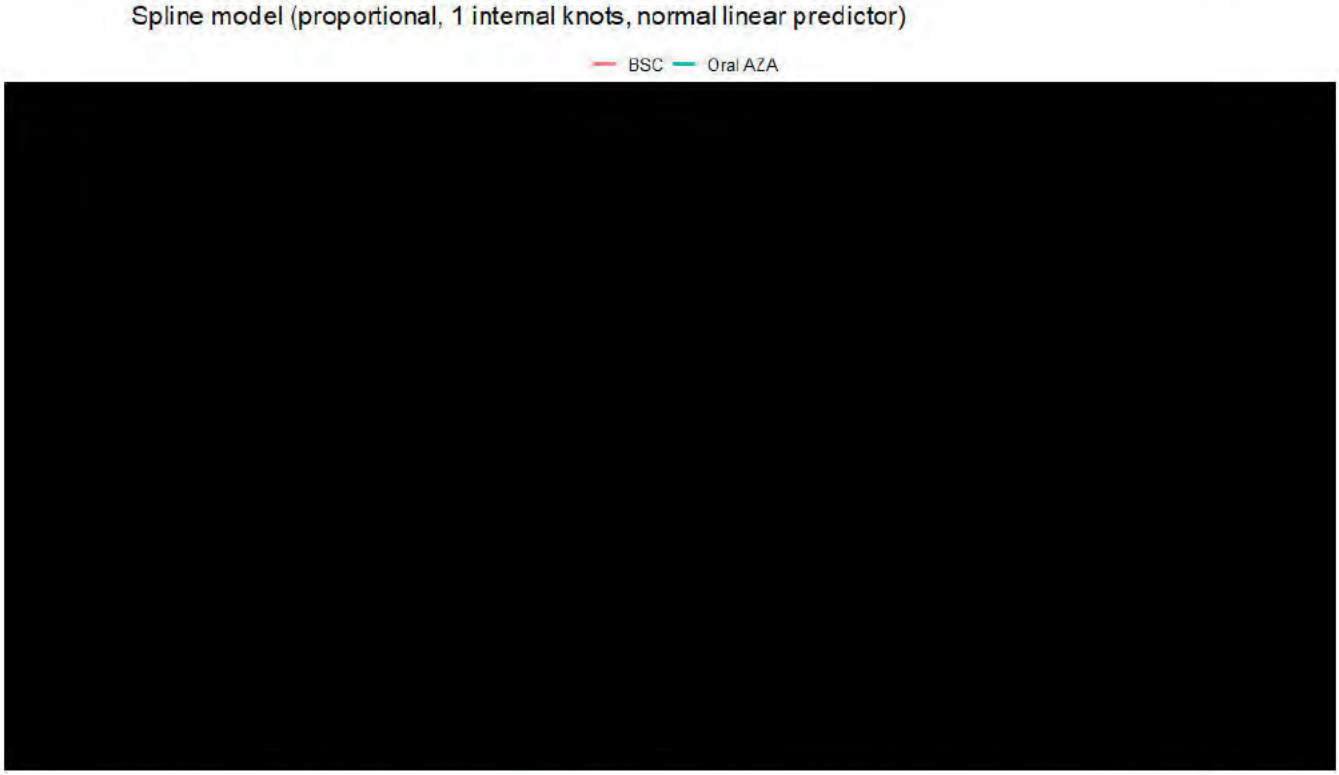

Figure G-45. Time-varying spline curves fit to the relapse-free survival outcome in the ITT population: time-varying, 0 internal knots, odds linear predictor

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Figure G-46. Time-varying spline curves fit to the relapse-free survival outcome in the ITT population: time-varying, 2 internal knots, hazard linear predictor

Spline model (proportional, 2 internal knots, hazard linear predictor)

Figure G-47. Time-varying spline curves fit to the relapse-free survival outcome in the ITT population: time-varying, 2 internal knots, normal linear predictor

Spline model (proportional, 2 internal knots, normal linear predictor)

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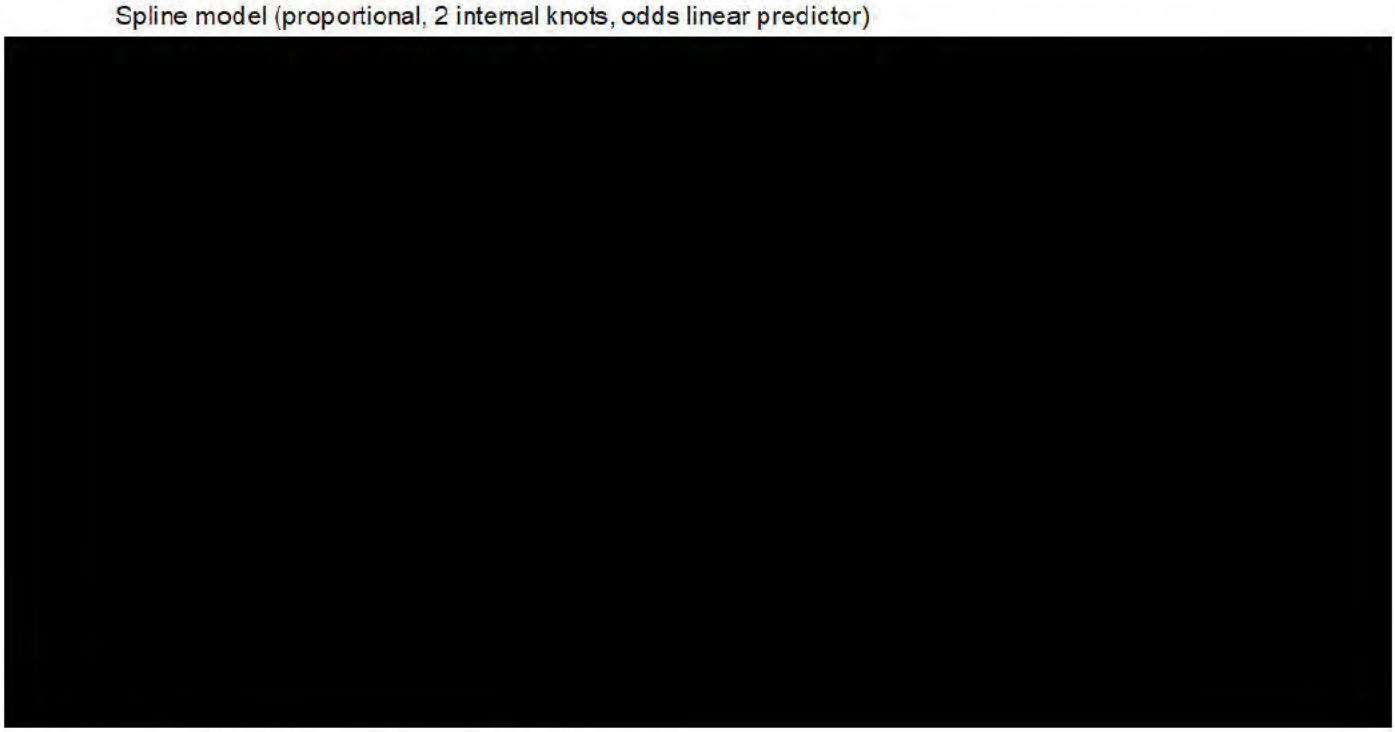
Figure G-48. Time-varying spline curves fit to the relapse-free survival outcome in the ITT population: time-varying, 2 internal knots, odds linear predictor



AZA = azacytidine; BSC = best supportive care; ITT = intent to treat.

Table G-8. Model fit statistics (AIC and BIC) for time-varying spline models of the relapse-free survival outcome in the ITT population

Parametric model	AIC	Ranks based on AIC	BIC	Ranks based on BIC
2 internal knots, hazard linear predictor	2,477.973	1	2,511.229	2
2 internal knots, odds linear predictor	2,478.536	2	2,511.792	3
2 internal knots, normal linear predictor	2,479.574	3	2,512.83	4
1 internal knot, odds linear predictor	2,486.125	4	2,511.066	1
1 internal knot, hazard linear predictor	2,491.043	5	2,515.985	5
1 internal knot, normal linear predictor	2,502.748	6	2,527.69	6

AIC = Akaike's information criteria; BIC = Bayesian information criterion; ITT = intent to treat.

Appendix G.2.7 Survival Curves included in the cost-effectiveness model

Standard parametric and time-varying splines for OS and RFS are included in the model and can be explored on the 'Efficacy' worksheet. Presented below are OS and RFS parametric extrapolations and time-varying spline extrapolations for Onureg and No Active Therapy in Figure G-49 to Figure G-52.

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Figure G-49. Overall Survival Extrapolations: Onureg

Figure G-50. Overall Survival Extrapolations: No Active Therapy

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Figure G-51 Relapse Free Survival Extrapolations: Onureg

Figure G-52 Relapse Free Survival Extrapolations: No Active Therapy

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Appendix H. Literature search for HRQoL data

The objective of the SLR was to identify and summarise health utility values for adults (aged ≥ 18 years) with AML receiving high-intensity first-line therapy (induction with or without consolidation) with or without maintenance therapy.

The design of the SLR protocol was based on the PRISMA-P (Preferred Reporting Items for Systematic Reviews and Meta-Analysis Protocols) guidelines. The literature search was conducted by an experienced medical information specialist on 12 February 2020 and updated on 11 June 2021. The searches were also peer-reviewed independently by a second information specialist using the PRESS Checklist.[3]

Details for the databases searched in the original and updated SLRs are presented in Table H-1 and Table H-2.

Table H-1. Bibliographic databases included in the literature search (original review)

Database	Platform	Relevant period for the search	Date of search completion
MEDLINE[a]	Ovid	2005 to current	12 February 2020
Embase	Ovid	2005 to current	12 February 2020
Cochrane Central Register of Controlled Trials	Ovid EBMR	2005 to current	12 February 2020

EBMR = Evidence-Based Medicine Reviews.

[a] Including Epub Ahead of Print and In-Process & Other Non-Indexed Citations.

Table H-2. Bibliographic databases included in the literature search (review update)

Database	Platform	Relevant period for the search	Date of search completion
MEDLINE[a]	Ovid	2020 to current	11 June 2021
Embase	Ovid	2020 to current	11 June 2021
Cochrane Central Register of Controlled Trials	Ovid EBMR	2020 to current	11 June 2021

EBMR = Evidence-Based Medicine Reviews.

[a] Including Epub Ahead of Print and In-Process & Other Non-Indexed Citations.

A supplementary search of the ScHARRHUD (health utilities database) was also conducted using the following search terms: "acute myeloid leukemia," "acute myelogenous leukemia," "AML," "acute myeloid leukaemia," and "acute myelogenous leukaemia." In addition, the bibliographies of relevant systematic review articles were reviewed to obtain any additional, relevant references.

Appendix H.1 Study selection

Eligibility criteria were established using the PICOS framework (Table H-3). This review captured studies of adults (≥ 18 years) with de novo AML or AML secondary to prior myelodysplastic disease, treated with conventional interventions. Studies that reported baseline utility values, changes in utility values (utility increments or decrements), and generic and disease-specific HRQoL (health-related quality of life) measures that can be mapped to utility values were included. The search was not limited by language; however, non-English publications were screened at the title and abstract phase and excluded if the language of publication was known.

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Table H-3. Inclusion and exclusion criteria

Item	Inclusion criteria	Exclusion criteria
Primary considerations		
Population	▪ Male and female adults (≥ 18 years) ▪ De novo AML or AML secondary to prior myelodysplastic disease receiving high-intensity first-line (induction with or without consolidation), with or without maintenance therapy	▪ Patients < 18 years ▪ Relapsed or refractory AML
Intervention	▪ Any nontransplant therapy	▪ Stem cell transplant
Comparators	▪ See intervention	▪ See intervention
Outcomes (considered at full-text review)	▪ Direct utility values at baseline and utility increments or decrements by health state ▪ Generic Measures of HRQoL: – EQ-5D-5L index score – EQ-5D-3L index score – Health Utility Index (HUI mark 2, HUI2 or mark 3, HUI3) – Quality of Wellbeing (QWB) index – Assessment of Quality of Life (AQoL) – 15D – SF-36 (using SF-6D) ▪ Disease-specific measures of HRQoL: – FACIT-Fatigue Scale – European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire (EORTC QLQ-C30) – Functional Assessment of Cancer Therapy (FACT) – AML-QOL	▪ Studies that do not report any relevant outcomes
Study design	▪ Any study type (e.g., clinical trials, observational studies, surveys, registries, economic evaluations)	▪ Conference abstracts
Additional considerations		
Language	▪ English	▪ Any other languages
Publication types	▪ All full-text articles from 2005-Present	▪ Full-text articles pre-2005 ▪ Conference abstracts
Date	▪ 2005-Present	▪ Pre-2005

AML = acute myeloid leukaemia; AML-QOL = Acute Myeloid Leukemia – Quality of Life; AQoL = assessment of quality of life; EQ-3D-3L = 3-level EQ-5D; EQ-5D-5L = 5-level EQ-5D; FACIT-Fatigue = Functional Assessment of Chronic Illness Therapy–Fatigue; HRQoL = health-related quality of life; HUI = Health Utility Index; QWB = Quality Of Wellbeing; SF-6D = Short-Form Six Dimensions Questionnaire; SF-36 = SF-36 Health Survey.

Note: the search was not restricted to English language studies, but any non-English studies were excluded in the study selection phase.

Two reviewers independently reviewed the study records, article titles, and abstracts identified in the literature search to assess study eligibility. Citations considered to describe potentially eligible articles were independently reviewed in full-text form for formal inclusion in the final review. Disagreements between reviewers were resolved during a consensus meeting. Any discrepancies between the 2 reviewers that could not be resolved by consensus were referred to and resolved by a third reviewer. Screening was performed in DistillerSR (Evidence Partners, Ontario, Canada) at both the title and abstract screening phase and full-text screening phase.

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Appendix H.2 Search strategy

The search strategies for the original and review update are presented in Table H-4 to Table H-7.

Table H-4. MEDLINE search strategy (original review): Ovid MEDLINE(R) and Epub Ahead of Print, In-Process, and Other Non-Indexed Citations and Daily

#	Searches	Results
1	exp Leukemia, Myeloid, Acute/	54,278
2	(acute adj2 myelo* adj2 leu#?emi*).tw,kf.	44,998
3	(acute adj2 (nonlympho* or non-lympho*) adj2 leu#?emi*).tw,kf.	3,175
4	(acute adj2 granulocytic adj2 leu#?emi*).tw,kf.	168
5	((AML or ANLL) and (leu#?emi* or myelo* or nonlympho* or non-lympho*)).tw,kf.	29,756
6	(AML or ANLL).tw,kf. and exp Leukemia, Myeloid/	22,738
7	(acute adj2 basophilic adj2 leu#?emi*).tw,kf.	66
8	(acute adj2 eosinophilic adj2 leu#?emi*).tw,kf.	35
9	(acute adj2 erythroblastic adj2 leu#?emi*).tw,kf.	19
10	(erythroleu#?emi* or erythro-leu#?emi* or erythr?emic myelosis or diguglielmo* or diguglielmo*).tw,kf.	6,546
11	((mast-cell* or mastcell*) adj2 leu#?emia*).tw,kf.	397
12	((megakaryocytic or mega-karyocytic) adj2 leu#?emi*).tw,kf.	392
13	((megakaryoblastic or mega-karyoblastic) adj2 leu#?emi*).tw,kf.	1,006
14	(acute adj2 monoblastic adj2 leu#?emi*).tw,kf.	366
15	(acute adj2 monocytic adj2 leu#?emi*).tw,kf.	1,134
16	(acute adj2 promyelocytic adj2 leu#?emi*).tw,kf.	7,077
17	(acute adj2 progranulocytic adj2 leu#?emi*).tw,kf.	14
18	(Schilling-Type adj1 myelo* adj2 leu#?emi*).tw,kf.	0
19	or/1-18 [AML-Medline]	83,434
20	"Value of Life"/ or Quality of Life/ or Quality-Adjusted Life Years/ or exp health status indicators/	470,172
21	quality of life.ti,kf,kw. or ((instrument or instruments) adj3 quality of life).ab. or quality adjusted life.ti,ab,kf,kw. or (qaly* or qald* or qale* or qtime* or life year or life years).ti,ab,kf,kw. or disability adjusted life.ti,ab,kf,kw. or daly*.ti,ab,kf,kw.	102,279
22	(sf36 or sf 36 or short form 36 or shortform 36 or short form36 or shortform36 or sf thirtysix or sfthirtysix or sfthirty six or sf thirty six or shortform thirtysix or shortform thirty six or short form thirtysix or short form thirty six or (sf6 or sf 6 or short form 6 or shortform 6 or sf six or sfsix or shortform six or short form six or shortform6 or short form6) or (sf8 or sf 8 or sf eight or sfeight or shortform 8 or shortform 8 or shortform8 or short form8 or shortform eight or short form eight) or (sf12 or sf 12 or short form 12 or shortform 12 or short form12 or shortform12 or sf twelve or sftwelve or shortform twelve or short form twelve) or (sf16 or sf 16 or short form 16 or shortform 16 or short form16 or shortform16 or sf sixteen or sfsixteen or shortform sixteen or short form sixteen) or (sf20 or sf 20 or short form 20 or shortform 20 or short form20 or shortform20 or sf twenty or sftwenty or shortform twenty or short form twenty)).ti,ab,kf,kw.	33,390
23	(hql or hqol or h qol or hrqol or hr qol or (hye or hyes) or (health* adj2 year* adj2 equivalent*) or (pqol or qls) or (quality of wellbeing or quality of well being or index of wellbeing or index of well being or qwb) or nottingham health profile* or sickness impact profile).ti,ab,kf,kw.	19,687
24	((health adj3 (utilit* or status)) or (utilit* adj3 (valu* or measur* or health or life or estimat* or elicit* or disease or score* or weight)) or (preference* adj3 (valu* or measur* or health or life or estimat* or elicit* or disease or score* or instrument or instruments)) or disutilit* or rosser or willingness to pay or standard gamble* or (time trade off or time tradeoff) or tto or (hui or hui1 or	105,618

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#	Searches	Results
	hui2 or hui3) or (eq or euroqol or euro qol or eq5d or eq 5d or euroqual or euro qual) or duke health profile or functional status questionnaire or dartmouth coop functional health assessment*).ti,ab,kf,kw.	
25	or/20-24 [Filter-Utilities-QoL-CADTH-Medline]	586,295
26	(aqol or "assessment of quality of life").ti,ab,kw,kf.	1,867
27	(facit or facitf or facit-f).ti,ab,kw,kf.	747
28	(fatigue? adj2 (scale? or score?)).ti,ab,kw,kf.	4,910
29	"European Organization for Research and Treatment of Cancer Quality of Life".ti,ab,kw,kf.	914
30	(EORTC QLQ-C30 or eortc qlq c30).ti,ab,kw,kf.	2,799
31	"Functional Assessment of Cancer Therap$ ".ti,ab,kw,kf.	2,126
32	((fact adj3 (assess$ or questionnai$ or questionai$ or survey? or tool?)) or (factg or fact-g)).ti,ab,kw,kf.	1,550
33	((Rotterdam Symptom adj1 (Checklist? check list? or questionai$ or questionnai$ or survey?)) or RSCL?).ti,ab,kw,kf.	116
34	Functional Assessment of Chronic Illness Therapy.ti,ab,kw,kf.	700
35	AML-QOL.ti,ab,kw,kf.	2
36	(sf-36 or sf-6D).ti,ab,kw,kf.	20,502
37	(symptom? distress adj2 (scale? or instrument? or survey or questionai$ or questionnai$)).ti,ab,kw,kf.	264
38	quality of life adj3 (measur$ or survey? or questionn$ or questionai$)).ti,ab,kw,kf. [Not in CADTH filter]	30,252
39	or/26-38 [additional utility terms per protocol; and specific to cancer]	57,716
40	(2005 $ or 2006 $ or 2007 $ or 2008 $ or 2009 $ or $201 or $202).dp,yr.	14,365,582
41	19 and (or/25,39)	678
42	and/40-41 [Results-Medline-Utilities-2005-]	524

Table H-5. Embase search strategy (original review)

#	Searches	Results
1	exp acute myeloid leukemia/	35,807
2	acute leukemia/ and myeloid leukemia/	347
3	(acute adj2 myelo* adj2 leu#?emi*).tw,kw.	66,433
4	(acute adj2 (nonlympho* or non-lympho*) adj2 leu#?emi*).tw,kw.	1,845
5	(acute adj2 granulocytic adj2 leu#?emi*).tw,kw.	28
6	((AML or ANLL) and (leu#?emi* or myelo* or nonlympho* or non-lympho*)).tw,kw.	54,916
7	(AML or ANLL).tw,kw. and exp myeloid leukemia/	19,898
8	(acute adj2 basophilic adj2 leu#?emi*).tw,kw.	60
9	(acute adj2 eosinophilic adj2 leu#?emi*).tw,kw.	21
10	(acute adj2 erythroblastic adj2 leu#?emi*).tw,kw.	24
11	(erythroleu#?emi* or erythro-leu#?emi* or erythr?emic myelosis or diguglielmo* or di guglielmo*).tw,kw.	5,024
12	((mast-cell* or mastcell*) adj2 leu#?emia*).tw,kw.	562
13	((megakaryocytic or mega-karyocytic) adj2 leu#?emi*).tw,kw.	430
14	((megakaryoblastic or mega-karyoblastic) adj2 leu#?emi*).tw,kw.	1,181

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#	Searches	Results
15	(acute adj2 monoblastic adj2 leu#?emi*).tw,kw.	325
16	(acute adj2 monocytic adj2 leu#?emi*).tw,kw.	1,136
17	(acute adj2 promyelocytic adj2 leu#?emi*).tw,kw.	9,024
18	(acute adj2 progranulocytic adj2 leu#?emi*).tw,kw.	19
19	(Schilling-Type adj1 myelo* adj2 leu#?emi*).tw,kw.	0
20	or/1-19 [AML-EMBASE]	102,748
21	socioeconomics/ or exp Quality of Life/ or Quality-Adjusted Life Year/ or nottingham health profile/ or sickness impact profile/ or health status indicator/ [EMTREE]	588,784
22	quality of life.ti,kw. or ((instrument or instruments) adj3 quality of life).ab. or quality adjusted life.ti,ab,kw. or (qaly* or qald* or qale* or qtime* or life year or life years).ti,ab,kw. or disability adjusted life.ti,ab,kw. or daly*.ti,ab,kw.	165,296
23	(sf36 or sf 36 or short form 36 or shortform 36 or short form36 or shortform36 or sf thirtysix or sfthirtysix or sfthirty six or sf thirty six or shortform thirtysix or shortform thirty six or short form thirtysix or short form thirty six or (sf6 or sf 6 or short form 6 or shortform 6 or sf six or sfsix or shortform six or short form six or shortform6 or short form6) or (sf8 or sf 8 or sf eight or sfeight or shortform 8 or shortform 8 or shortform8 or short form8 or shortform eight or short form eight) or (sf12 or sf 12 or short form 12 or shortform 12 or short form12 or shortform12 or sf twelve or sftwelve or shortform twelve or short form twelve) or (sf16 or sf 16 or short form 16 or shortform 16 or short form16 or shortform16 or sf sixteen or sfsixteen or shortform sixteen or short form sixteen) or (sf20 or sf 20 or short form 20 or shortform 20 or short form20 or shortform20 or sf twenty or sftwenty or shortform twenty or short form twenty)).ti,ab,kw.	52,586
24	(hql or hqol or h qol or hrqol or hr qol or (hye or hyes) or (health* adj2 year* adj2 equivalent*) or (pqol or qls) or (quality of wellbeing or quality of well being or index of wellbeing or index of well being or qwb) or nottingham health profile* or sickness impact profile).ti,ab,kw.	31,032
25	((health adj3 (utilit* or status)) or (utilit* adj3 (valu* or measur* or health or life or estimat* or elicit* or disease or score* or weight)) or (preference* adj3 (valu* or measur* or health or life or estimat* or elicit* or disease or score* or instrument or instruments)) or disutilit* or rosser or willingness to pay or standard gamble* or (time trade off or time tradeoff) or tto or (hui or hui1 or hui2 or hui3) or (eq or euroqol or euro qol or eq5d or eq 5d or euroqual or euro qual) or duke health profile or functional status questionnaire or dartmouth coop functional health assessment*).ti,ab,kw.	140,587
26	or/21-25 [Filter: CADTH: Health Utilities/Quality of Life – OVID Embase]	722,879
27	(aqol or "assessment of quality of life").ti,ab,kw.	2,991
28	(facit or facitf or facit-f).ti,ab,kw.	2,115
29	(fatigue? adj2 (scale? or score?)).ti,ab,kw.	9,464
30	"European Organization for Research and Treatment of Cancer Quality of Life".ti,ab,kw.	1,218
31	(EORTC QLQ-C30 or eortc qlq c30).ti,ab,kw.	6,001
32	"Functional Assessment of Cancer Therap$ ".ti,ab,kw.	3,435
33	((fact adj3 (assess$ or questionnai$ or questionai$ or survey? or tool?)) or (factg or fact-g)).ti,ab,kw.	3,066
34	((Rotterdam Symptom adj1 (Checklist? check list? or questionai$ or questionnai$ or survey?)) or RSCL?).ti,ab,kw.	190
35	Functional Assessment of Chronic Illness Therapy.ti,ab,kw.	1,257
36	AML-QOL.ti,ab,kw.	3
37	(sf-36 or sf-6D).ti,ab,kw.	34,209
38	(symptom? distress adj2 (scale? or instrument? or survey or questionai$ or questionnai$)).ti,ab,kw.	319
39	(quality of life adj3 (measur$ or survey? or questionn$ or questionai$)).ti,ab,kw. [Not in CADTH filter]	46,259

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#	Searches	Results
40	"quality of life index"/	2,720
41	"quality of life assessment"/	8,779
42	or/27-41 [HRQoL--Additional terms per protcol; additional EMTREE & Instruments--MF]	102,416
43	20 and 26 [AML & CADTH FILTER-EMBASE]	1,552
44	(20 and 42) not 43 [AML & ADDITIONAL UTIL HRQOL TERMS]	34
45	or/43-44	1,586
46	45 not (CONFERENCE ABSTRACT or CONFERENCE REVIEW).pt.	904
47	limit 46 to yr="2005 -Current" [RESULTS -EMBASE-AML-UTIL-HRQOL]	737

Table H-6. Evidence-Based Medicine Reviews and Cochrane Central Register of Controlled Trials search strategy (original review)

#	Searches	Results
1	exp Leukemia, Myeloid, Acute/	1,504
2	(AML or ANLL).tw,kw. and exp Leukemia, Myeloid/	1,065
3	(acute adj2 myelo* adj2 leu#?emi*).tw,kw.	4,349
4	(acute adj2 (nonlympho* or non-lympho*) adj2 leu#?emi*).tw,kw.	231
5	(acute adj2 granulocytic adj2 leu#?emi*).tw,kw.	267
6	((AML or ANLL) and (leu#?emi* or myelo* or nonlympho* or non-lympho*)).tw,kw.	3,435
7	(AML or ANLL).tw,kw. and exp Leukemia, Myeloid/	1,065
8	(acute adj2 basophilic adj2 leu#?emi*).tw,kw.	0
9	(acute adj2 eosinophilic adj2 leu#?emi*).tw,kw.	0
10	(acute adj2 erythroblastic adj2 leu#?emi*).tw,kw.	0
11	(erythroleu#?emi* or erythro-leu#?emi* or erythr?emic myelosis or diguglielmo* or di guglielmo*).tw,kw.	16
12	((mast-cell* or mastcell*) adj2 leu#?emia*).tw,kw.	10
13	((megakaryocytic or mega-karyocytic) adj2 leu#?emi*).tw,kw.	8
14	((megakaryoblastic or mega-karyoblastic) adj2 leu#?emi*).tw,kw.	6
15	(acute adj2 monoblastic adj2 leu#?emi*).tw,kw.	4
16	(acute adj2 monocytic adj2 leu#?emi*).tw,kw.	13
17	(acute adj2 promyelocytic adj2 leu#?emi*).tw,kw.	436
18	(acute adj2 progranulocytic adj2 leu#?emi*).tw,kw.	1
19	(Schilling-Type adj1 myelo* adj2 leu#?emi*).tw,kw.	0
20	or/1-19 [AML-central]	5,687
21	"Value of Life"/ or Quality of Life/ or Quality-Adjusted Life Years/ or exp health status indicators/ [MeSH]	41,334
22	quality of life.ti,kw. or ((instrument or instruments) adj3 quality of life).ab. or quality adjusted life.ti,ab,kw. or (qaly* or qald* or qale* or qtime* or life year or life years).ti,ab,kw. or disability adjusted life.ti,ab,kw. or daly*.ti,ab,kw.	46,680
23	(sf36 or sf 36 or short form 36 or shortform 36 or short form36 or shortform36 or sf thirtysix or sfthirtysix or sfthirty six or sf thirty six or shortform thirtysix or shortform thirty six or short form thirtysix or short form thirty six or (sf6 or sf 6 or short form 6 or shortform 6 or sf six or sfsix or shortform six or short form six or shortform6 or short form6) or (sf8 or sf 8 or sf eight or sfeight or shortform 8 or shortform 8 or shortform8 or short form8 or shortform eight or short form eight) or (sf12 or sf 12 or short form 12 or shortform 12 or short form12 or shortform12 or sf twelve or	15,234

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#	Searches	Results
	sftwelve or shortform twelve or short form twelve) or (sf16 or sf 16 or short form 16 or shortform 16 or short form16 or shortform16 or sf sixteen or sfsixteen or shortform sixteen or short form sixteen) or (sf20 or sf 20 or short form 20 or shortform 20 or short form20 or shortform20 or sf twenty or sftwenty or shortform twenty or short form twenty)).ti,ab,kw.	
24	(hql or hqol or h qol or hrqol or hr qol or (hye or hyes) or (health* adj2 year* adj2 equivalent*) or (pqol or qls) or (quality of wellbeing or quality of well being or index of wellbeing or index of well being or qwb) or nottingham health profile* or sickness impact profile).ti,ab,kw.	6,374
25	((health adj3 (utilit* or status)) or (utilit* adj3 (valu* or measur* or health or life or estimat* or elicit* or disease or score* or weight)) or (preference* adj3 (valu* or measur* or health or life or estimat* or elicit* or disease or score* or instrument or instruments)) or disutilit* or rosser or willingness to pay or standard gamble* or (time trade off or time tradeoff) or tto or (hui or hui1 or hui2 or hui3) or (eq or euroqol or euro qol or eq5d or eq 5d or euroqual or euro qual) or duke health profile or functional status questionnaire or dartmouth coop functional health assessment*).ti,ab,kw.	23,895
26	or/21-25 [Filter: CADTH: Health Utilities/Quality of Life]	103,774
27	(aqol or "assessment of quality of life").ti,ab,kw.	893
28	(facit or facitf or facit-f).ti,ab,kw.	861
29	(fatigue? adj2 (scale? or score?)).ti,ab,kw.	3,521
30	"European Organization for Research and Treatment of Cancer Quality of Life".ti,ab,kw.	578
31	(EORTC QLQ-C30 or eortc qlq c30).ti,ab,kw.	2,288
32	"Functional Assessment of Cancer Therap$ ".ti,ab,kw.	1,264
33	((fact adj3 (assess$ or questionnai$ or questionai$ or survey? or tool?)) or (factg or fact-g)).ti,ab,kw.	976
34	((Rotterdam Symptom adj1 (Checklist? check list? or questionai$ or questionnai$ or survey?)) or RSCL?).ti,ab,kw.	42
35	Functional Assessment of Chronic Illness Therapy.ti,ab,kw.	566
36	AML-QOL.ti,ab,kw.	0
37	(sf-36 or sf-6D).ti,ab,kw.	9,638
38	(symptom? distress adj2 (scale? or instrument? or survey or questionai$ or questionnai$)).ti,ab,kw.	120
39	(quality of life adj3 (measur$ or survey? or questionn$ or questionai$)).ti,ab,kw. [Not in CADTH filter]	22,584
40	or/27-39 [Additional HRQoL terms]	36,131
41	20 and (or/26,40)	251
42	("conference 4th pediatric allergy and asthma meeting paam berlin germany 15 17 october 2015" or conference abstract or conference abstract placebo controlled partly blinded crossover study in 12 sle patients or conference proceeding or "conference review").pt.	16,934
43	41 not 42	242
44	limit 43 to yr="2005 -Current"	215

Table H-7. Ovid search strategy (review update)

#	Searches	Results
1	exp Leukemia, Myeloid, Acute/	106,857
2	(acute adj2 myelo* adj2 leu#?emi*).tw,kf.	130,053
3	(acute adj2 (nonlympho* or non-lympho*) adj2 leu#?emi*).tw,kf.	6,847
4	(acute adj2 granulocytic adj2 leu#?emi*).tw,kf.	337
5	((AML or ANLL) and (leu#?emi* or myelo* or nonlympho* or non-lympho*)).tw,kf.	98,579

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#	Searches	Results
6	(AML or ANLL).tw,kf. and exp Leukemia, Myeloid/	51,086
7	(acute adj2 basophilic adj2 leu#?emi*).tw,kf.	139
8	(acute adj2 eosinophilic adj2 leu#?emi*).tw,kf.	70
9	(acute adj2 erythroblastic adj2 leu#?emi*).tw,kf.	50
10	(erythroleu#?emi* or erythro-leu#?emi* or erythr?emic myelosis or diguglielmo* or di guglielmo*).tw,kf.	13,629
11	((mast-cell* or mastcell*) adj2 leu#?emia*).tw,kf.	1,004
12	((megakaryocytic or mega-karyocytic) adj2 leu#?emi*).tw,kf.	881
13	((megakaryoblastic or mega-karyoblastic) adj2 leu#?emi*).tw,kf.	2,400
14	(acute adj2 monoblastic adj2 leu#?emi*).tw,kf.	829
15	(acute adj2 monocytic adj2 leu#?emi*).tw,kf.	2,695
16	(acute adj2 promyelocytic adj2 leu#?emi*).tw,kf.	17,963
17	(acute adj2 progranulocytic adj2 leu#?emi*).tw,kf.	32
18	(Schilling-Type adj1 myelo* adj2 leu#?emi*).tw,kf.	0
19	or/1-18 [AML-Medline]	216,972
20	"Value of Life"/ or Quality of Life/ or Quality-Adjusted Life Years/ or exp health status indicators/	1,258,664
21	quality of life.ti,kf,kw. or ((instrument or instruments) adj3 quality of life).ab. or quality adjusted life.ti,ab,kf,kw. or (qaly* or qald* or qale* or qtime* or life year or life years).ti,ab,kf,kw. or disability adjusted life.ti,ab,kf,kw. or daly*.ti,ab,kf,kw.	364,612
22	(sf36 or sf 36 or short form 36 or shortform 36 or short form36 or shortform36 or sf thirtysix or sfthirtysix or sfthirty six or sf thirty six or shortform thirtysix or shortform thirty six or short form thirtysix or short form thirty six or (sf6 or sf 6 or short form 6 or shortform 6 or sf six or sfsix or shortform six or short form six or shortform6 or short form6) or (sf8 or sf 8 or sf eight or sfeight or shortform 8 or shortform 8 or shortform8 or short form8 or shortform eight or short form eight) or (sf12 or sf 12 or short form 12 or shortform 12 or short form12 or shortform12 or sf twelve or sftwelve or shortform twelve or short form twelve) or (sf16 or sf 16 or short form 16 or shortform 16 or short form16 or shortform16 or sf sixteen or sfsixteen or shortform sixteen or short form sixteen) or (sf20 or sf 20 or short form 20 or shortform 20 or short form20 or shortform20 or sf twenty or sftwenty or shortform twenty or short form twenty)).ti,ab,kf,kw.	112,698
23	(hql or hqol or h qol or hrqol or hr qol or (hye or hyes) or (health* adj2 year* adj2 equivalent*) or (pqol or qls) or (quality of wellbeing or quality of well being or index of wellbeing or index of well being or qwb) or nottingham health profile* or sickness impact profile).ti,ab,kf,kw.	65,723
24	((health adj3 (utilit* or status)) or (utilit* adj3 (valu* or measur* or health or life or estimat* or elicit* or disease or score* or weight)) or (preference* adj3 (valu* or measur* or health or life or estimat* or elicit* or disease or score* or instrument or instruments)) or disutilit* or rosser or willingness to pay or standard gamble* or (time trade off or time tradeoff) or tto or (hui or hui1 or hui2 or hui3) or (eq or euroqol or euro qol or eq5d or eq 5d or euroqual or euro qual) or duke health profile or functional status questionnaire or dartmouth coop functional health assessment*).ti,ab,kf,kw.	312,239
25	or/20-24 [Filter-Utilities-QoL-CADTH-Medline]	1,622,974
26	(aqol or "assessment of quality of life").ti,ab,kw,kf.	6,382
27	(facit or facitf or facit-f).ti,ab,kw,kf.	4,539

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#	Searches	Results
28	(fatigue? adj2 (scale? or score?)).ti,ab,kw,kf.	20,956
29	"European Organization for Research and Treatment of Cancer Quality of Life".ti,ab,kw,kf.	3,453
30	(EORTC QLQ-C30 or eortc qlq c30).ti,ab,kw,kf.	12,973
31	"Functional Assessment of Cancer Therap$ ".ti,ab,kw,kf.	7,864
32	((fact adj3 (assess$ or questionnai$ or questionai$ or survey? or tool?)) or (factg or fact g)).ti,ab,kw,kf.	6,391
33	((Rotterdam Symptom adj1 (Checklist? check list? or questionai$ or questionnai$ or survey?)) or RSCL?).ti,ab,kw,kf.	356
34	Functional Assessment of Chronic Illness Therapy.ti,ab,kw,kf.	3,129
35	AML-QOL.ti,ab,kw,kf.	7
36	(sf-36 or sf-6D).ti,ab,kw,kf.	71,190
37	(symptom? distress adj2 (scale? or instrument? or survey or questionai$ or questionnai$)).ti,ab,kw,kf.	765
38	(quality of life adj3 (measur$ or survey? or questionn$ or questionai$)).ti,ab,kw,kf. [Not in CADTH filter]	114,047
39	or/26-38 [additional utility terms per protocol; and specific to cancer]	215,086
40	(2005 $ or 2006 $ or 2007 $ or 2008 $ or 2009 $ or $201 or $202).dp,yr.	39,084,071
41	19 and (or/25,39)	2,913
42	and/40-41 [Results-Medline-Utilities-2005-]	2,564
43	**42 use ppez [MEDLINE results]**	**604**
44	exp acute myeloid leukemia/	106,857
45	acute leukemia/ and myeloid leukemia/	521
46	(acute adj2 myelo* adj2 leu#?emi*).tw,kw.	131,012
47	(acute adj2 (nonlympho* or non-lympho*) adj2 leu#?emi*).tw,kw.	6,876
48	(acute adj2 granulocytic adj2 leu#?emi*).tw,kw.	605
49	((AML or ANLL) and (leu#?emi* or myelo* or nonlympho* or non-lympho*)).tw,kw.	99,488
50	(AML or ANLL).tw,kw. and exp myeloid leukemia/	51,391
51	(acute adj2 basophilic adj2 leu#?emi*).tw,kw.	139
52	(acute adj2 eosinophilic adj2 leu#?emi*).tw,kw.	70
53	(acute adj2 erythroblastic adj2 leu#?emi*).tw,kw.	49
54	(erythroleu#?emi* or erythro-leu#?emi* or erythr?emic myelosis or diguglielmo* or di guglielmo*).tw,kw.	13,691
55	((mast-cell* or mastcell*) adj2 leu#?emia*).tw,kw.	1,031
56	((megakaryocytic or mega-karyocytic) adj2 leu#?emi*).tw,kw.	894
57	((megakaryoblastic or mega-karyoblastic) adj2 leu#?emi*).tw,kw.	2,416
58	(acute adj2 monoblastic adj2 leu#?emi*).tw,kw.	835
59	(acute adj2 monocytic adj2 leu#?emi*).tw,kw.	2,702
60	(acute adj2 promyelocytic adj2 leu#?emi*).tw,kw.	18,033
61	(acute adj2 progranulocytic adj2 leu#?emi*).tw,kw.	35
62	(Schilling-Type adj1 myelo* adj2 leu#?emi*).tw,kw.	0
63	or/44-62 [AML-EMBASE]	218,173

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#	Searches	Results
64	socioeconomics/ or exp Quality of Life/ or Quality-Adjusted Life Year/ or nottingham health profile/ or sickness impact profile/ or health status indicator/ [EMTREE]	946,487
65	quality of life.ti,kw. or ((instrument or instruments) adj3 quality of life).ab. or quality adjusted life.ti,ab,kw. or (qaly* or qald* or qale* or qtime* or life year or life years).ti,ab,kw. or disability adjusted life.ti,ab,kw. or daly*.ti,ab,kw.	361,282
66	(sf36 or sf 36 or short form 36 or shortform 36 or short form36 or shortform36 or sf thirtysix or sfthirtysix or sfthirty six or sf thirty six or shortform thirtysix or shortform thirty six or short form thirtysix or short form thirty six or (sf6 or sf 6 or short form 6 or shortform 6 or sf six or sfsix or shortform six or short form six or shortform6 or short form6) or (sf8 or sf 8 or sf eight or sfeight or shortform 8 or shortform 8 or shortform8 or short form8 or shortform eight or short form eight) or (sf12 or sf 12 or short form 12 or shortform 12 or short form12 or shortform12 or sf twelve or sftwelve or shortform twelve or short form twelve) or (sf16 or sf 16 or short form 16 or shortform 16 or short form16 or shortform16 or sf sixteen or sfsixteen or shortform sixteen or short form sixteen) or (sf20 or sf 20 or short form 20 or shortform 20 or short form20 or shortform20 or sf twenty or sftwenty or shortform twenty or short form twenty)).ti,ab,kw.	112,589
67	(hql or hqol or h qol or hrqol or hr qol or (hye or hyes) or (health* adj2 year* adj2 equivalent*) or (pqol or qls) or (quality of wellbeing or quality of well being or index of wellbeing or index of well being or qwb) or nottingham health profile* or sickness impact profile).ti,ab,kw.	65,563
68	((health adj3 (utilit* or status)) or (utilit* adj3 (valu* or measur* or health or life or estimat* or elicit* or disease or score* or weight)) or (preference* adj3 (valu* or measur* or health or life or estimat* or elicit* or disease or score* or instrument or instruments)) or disutilit* or rosser or willingness to pay or standard gamble* or (time trade off or time tradeoff) or tto or (hui or hui1 or hui2 or hui3) or (eq or euroqol or euro qol or eq5d or eq 5d or euroqual or euro qual) or duke health profile or functional status questionnaire or dartmouth coop functional health assessment*).ti,ab,kw.	310,946
69	or/64-68 [Filter: CADTH: Health Utilities/Quality of Life – OVID Embase]	1,314,376
70	(aqol or "assessment of quality of life").ti,ab,kw.	6,378
71	(facit or facitf or facit-f).ti,ab,kw.	4,535
72	(fatigue? adj2 (scale? or score?)).ti,ab,kw.	20,932
73	"European Organization for Research and Treatment of Cancer Quality of Life".ti,ab,kw.	3,447
74	(EORTC QLQ-C30 or eortc qlq c30).ti,ab,kw.	12,966
75	"Functional Assessment of Cancer Therap$ ".ti,ab,kw.	7,854
76	((fact adj3 (assess$ or questionnai$ or questionai$ or survey? or tool?)) or (factg or fact-g)).ti,ab,kw.	6,379
77	((Rotterdam Symptom adj1 (Checklist? check list? or questionai$ or questionnai$ or survey?)) or RSCL?).ti,ab,kw.	356
78	Functional Assessment of Chronic Illness Therapy.ti,ab,kw.	3,129
79	AML-QOL.ti,ab,kw.	7
80	(sf-36 or sf-6D).ti,ab,kw.	71,107
81	(symptom? distress adj2 (scale? or instrument? or survey or questionai$ or questionnai$)).ti,ab,kw.	764
82	(quality of life adj3 (measur$ or survey? or questionn$ or questionai$)).ti,ab,kw. [Not in CADTH filter]	113,937

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#	Searches	Results
83	"quality of life index"/	2,880
84	"quality of life assessment"/	11,001
85	or/70-84 [HRQoL--Additional terms per protcol; additional EMTREE & Instruments--MF]	223,837
86	63 and 69 [AML & CADTH FILTER-EMBASE]	2,556
87	(63 and 85) not 86 [AML & ADDITIONAL UTIL HRQOL TERMS]	86
88	or/86-87	2,642
89	88 not (CONFERENCE ABSTRACT or CONFERENCE REVIEW).pt.	1,844
90	limit 89 to yr="2005 -Current" [RESULTS -EMBASE-AML-UTIL-HRQOL]	1,542
91	**90 use oemezd [EMBASE results]**	**910**
92	exp Leukemia, Myeloid, Acute/	106,857
93	(AML or ANLL).tw,kw. and exp Leukemia, Myeloid/	51,391
94	(acute adj2 myelo* adj2 leu#?emi*).tw,kw.	131,012
95	(acute adj2 (nonlympho* or non-lympho*) adj2 leu#?emi*).tw,kw.	6,876
96	(acute adj2 granulocytic adj2 leu#?emi*).tw,kw.	605
97	((AML or ANLL) and (leu#?emi* or myelo* or nonlympho* or non-lympho*)).tw,kw.	99,488
98	(AML or ANLL).tw,kw. and exp Leukemia, Myeloid/	51,391
99	(acute adj2 basophilic adj2 leu#?emi*).tw,kw.	139
100	(acute adj2 eosinophilic adj2 leu#?emi*).tw,kw.	70
101	(acute adj2 erythroblastic adj2 leu#?emi*).tw,kw.	49
102	(erythroleu#?emi* or erythro-leu#?emi* or erythr?emic myelosis or diguglielmo* or di guglielmo*).tw,kw.	13,691
103	((mast-cell* or mastcell*) adj2 leu#?emia*).tw,kw.	1,031
104	((megakaryocytic or mega-karyocytic) adj2 leu#?emi*).tw,kw.	894
105	((megakaryoblastic or mega-karyoblastic) adj2 leu#?emi*).tw,kw.	2,416
106	(acute adj2 monoblastic adj2 leu#?emi*).tw,kw.	835
107	(acute adj2 monocytic adj2 leu#?emi*).tw,kw.	2,702
108	(acute adj2 promyelocytic adj2 leu#?emi*).tw,kw.	18,033
109	(acute adj2 progranulocytic adj2 leu#?emi*).tw,kw.	35
110	(Schilling-Type adj1 myelo* adj2 leu#?emi*).tw,kw.	0
111	or/92-110 [AML-central]	217,935
112	"Value of Life"/ or Quality of Life/ or Quality-Adjusted Life Years/ or exp health status indicators/ [MeSH]	1,258,664
113	quality of life.ti,kw. or ((instrument or instruments) adj3 quality of life).ab. or quality adjusted life.ti,ab,kw. or (qaly* or qald* or qale* or qtime* or life year or life years).ti,ab,kw. or disability adjusted life.ti,ab,kw. or daly*.ti,ab,kw.	361,282
114	(sf36 or sf 36 or short form 36 or shortform 36 or short form36 or shortform36 or sf thirtysix or sfthirtysix or sfthirty six or sf thirty six or shortform thirtysix or shortform thirty six or short form thirtysix or short form thirty six or (sf6 or sf 6 or short form 6 or shortform 6 or sf six or sfsix or shortform six or short form six or shortform6 or short form6) or (sf8 or sf 8 or sf eight or sfeight or shortform 8 or shortform 8 or shortform8 or short form8 or shortform eight or short form eight) or (sf12 or sf 12 or short form 12 or shortform 12 or short form12 or shortform12 or sf twelve or sftwelve or shortform twelve or short form twelve) or (sf16 or sf 16 or short form 16	112,589

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#	Searches	Results
	or shortform 16 or short form16 or shortform16 or sf sixteen or sfsixteen or shortform sixteen or short form sixteen) or (sf20 or sf 20 or short form 20 or shortform 20 or short form20 or shortform20 or sf twenty or sftwenty or shortform twenty or short form twenty)).ti,ab,kw.	
115	(hql or hqol or h qol or hrqol or hr qol or (hye or hyes) or (health* adj2 year* adj2 equivalent*) or (pqol or qls) or (quality of wellbeing or quality of well being or index of wellbeing or index of well being or qwb) or nottingham health profile* or sickness impact profile).ti,ab,kw.	65,563
116	((health adj3 (utilit* or status)) or (utilit* adj3 (valu* or measur* or health or life or estimat* or elicit* or disease or score* or weight)) or (preference* adj3 (valu* or measur* or health or life or estimat* or elicit* or disease or score* or instrument or instruments)) or disutilit* or rosser or willingness to pay or standard gamble* or (time trade off or time tradeoff) or tto or (hui or hui1 or hui2 or hui3) or (eq or euroqol or euro qol or eq5d or eq 5d or euroqual or euro qual) or duke health profile or functional status questionnaire or dartmouth coop functional health assessment*).ti,ab,kw.	310,946
117	or/112-116 [Filter: CADTH: Health Utilities/Quality of Life]	1,620,856
118	(aqol or "assessment of quality of life").ti,ab,kw.	6,378
119	(facit or facitf or facit-f).ti,ab,kw.	4,535
120	(fatigue? adj2 (scale? or score?)).ti,ab,kw.	20,932
121	"European Organization for Research and Treatment of Cancer Quality of Life".ti,ab,kw.	3,447
122	(EORTC QLQ-C30 or eortc qlq c30).ti,ab,kw.	12,966
123	"Functional Assessment of Cancer Therap$ ".ti,ab,kw.	7,854
124	((fact adj3 (assess$ or questionnai$ or questionai$ or survey? or tool?)) or (factg or fact-g)).ti,ab,kw.	6,379
125	((Rotterdam Symptom adj1 (Checklist? check list? or questionai$ or questionnai$ or survey?)) or RSCL?).ti,ab,kw.	356
126	Functional Assessment of Chronic Illness Therapy.ti,ab,kw.	3,129
127	AML-QOL.ti,ab,kw.	7
128	(sf-36 or sf-6D).ti,ab,kw.	71,107
129	(symptom? distress adj2 (scale? or instrument? or survey or questionai$ or questionnai$)).ti,ab,kw.	764
130	(quality of life adj3 (measur$ or survey? or questionn$ or questionai$)).ti,ab,kw. [Not in CADTH filter]	113,937
131	or/118-130 [Additional HRQoL terms]	214,871
132	111 and (or/117,131)	2,944
133	("conference 4th pediatric allergy and asthma meeting paam berlin germany 15 17 october 2015" or conference abstract or conference abstract placebo controlled partly blinded crossover study in 12 sle patients or conference proceeding or "conference review").pt.	4,134,489
134	132 not 133	2,146
135	limit 134 to yr="2005 -Current"	1,792
136	**135 use cctr [CENTRAL results]**	**269**
137	("202001*" or "20200201" or "20200202" or "20200203" or "20200204" or "20200205" or "20200206" or "20200207" or "20200208" or "20200209" or "20200210" or "20200211").dt.	148,726

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#	Searches	Results
138	43 and ("2020*" or "2021*").dt.	66
139	138 not 137	53
140	limit 139 to yr="2020 -Current" [MEDLINE results - Feb 11, 2020 - Current]	52
141	("202001*" or "20200201" or "20200202" or "20200203" or "20200204" or "20200205" or "20200206" or "20200207" or "20200208" or "20200209" or "20200210" or "20200211").dc.	208,571
142	91 and ("2020*" or "2021*").dc.	197
143	142 not 141	186
144	limit 143 to yr="2020 -Current" [Embase results - Feb 11, 2020 - Current]	179
145	("202001*" or "20200201" or "20200202" or "20200203" or "20200204" or "20200205" or "20200206" or "20200207" or "20200208" or "20200209" or "20200210" or "20200211").up.	39,856
146	136 and ("2020*" or "2021*").up.	114
147	146 not 145	103
148	limit 147 to yr="2020 -Current" [CENTRAL results - Feb 11, 2020 - Current]	46
149	140 or 144 or 148	277
150	remove duplicates from 149 [All Results – deduplicated - Feb 11, 2020 - Current]	236

CENTRAL = Cochrane Central Register of Controlled Trials.

Appendix H.3 Systematic selection of studies

The original literature search for studies reporting health utilities identified 3,401 articles through database searches. After removing duplicates, there were 2,368 articles for title and abstract review. Of these, 2,205 were excluded at the title and abstract screening phase because they did not meet the prespecified inclusion criteria. Among the 163 articles remaining, 145 were excluded at the full-text screening phase. The remaining 18 articles were included in this review. The PRISMA flow diagram for the selection of these studies is presented in Figure H-1.

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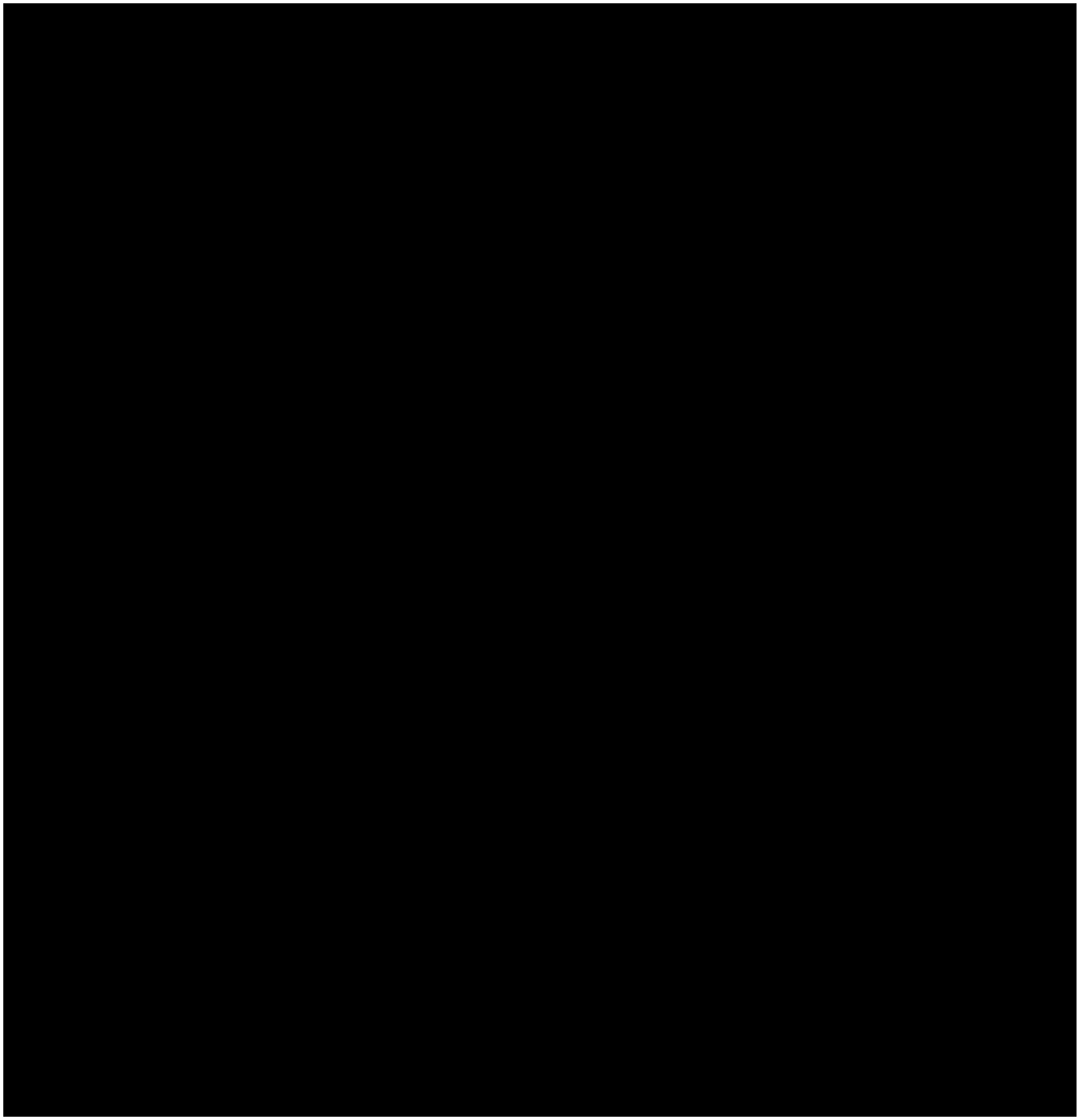

The literature search update identified 236 records after duplicates were removed. Eighteen additional citations were identified through the original systematic review. Of these, 192 records were excluded at the title and abstract screening phase because they did not meet the prespecified inclusion criteria. Of the 62 citations remaining, 42 were excluded at the full-text screening phase. The remaining 20 records were included in this review. The PRISMA flow diagram for the selection of these studies is presented in Figure H-2.

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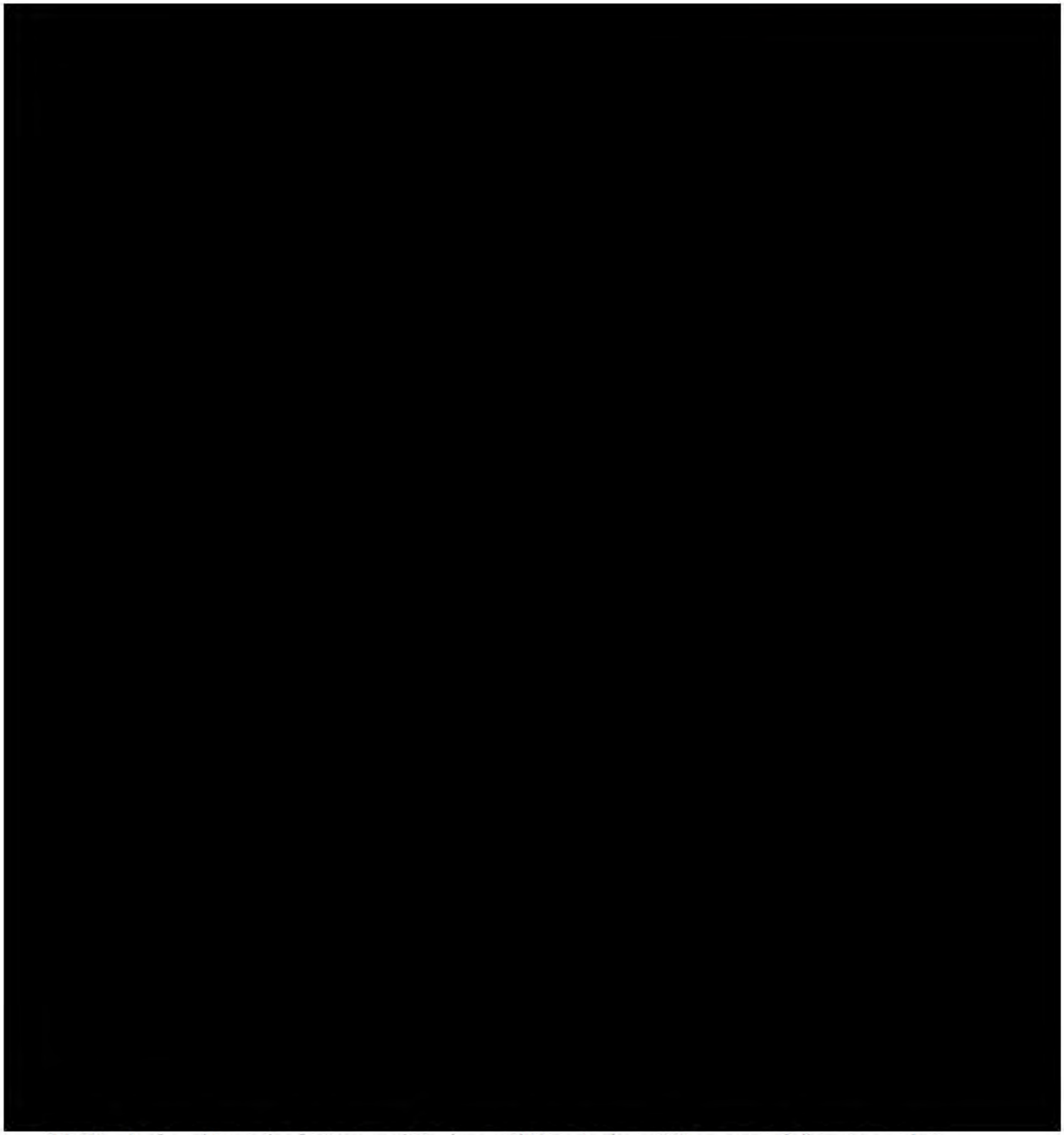

PRISMA = Preferred Reporting for Systematic Reviews and Meta-Analyses; SLR = systematic literature review.

A detailed list of the excluded studies at the full-text screening phase for the original and updated review is provided in Table H-8 and Table H-9, respectively.

Table H-8. Studies excluded at the full-text screening phase (original review)

Excluded due to population (N = 28)
1. (2010a) Acute Myeloid Leukaemia (AML) Patients Undergoing Induction Chemotherapy. https://clinicaltrialsgov/show/NCT01170598
2. (2010b) Individualised patient education as supportive lung infection protective technique among patients with acute leukaemia. http://wwwwhoint/trialsearch/Trial2aspx?TrialID=ISRCTN36674014
3. Alibhai SM, Durbano S, Breunis H, Brandwein JM, Timilshina N et al. (2015) A phase II exercise randomized controlled trial for patients with acute myeloid leukemia undergoing induction chemotherapy. Leukemia Research 28 28.
4. Alibhai SM, Neill SO, Fisher-Schlombs K, Breunis H, Timilshina N et al. (2014) A pilot phase II RCT of a home-based exercise intervention for survivors of AML. Supportive Care in Cancer 22 (4): 881-889.

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5. Bell JA, Galaznik A, Pompilus F, Strzok S, Bejar R et al. (2019) A pragmatic patient-reported outcome strategy for rare disease clinical trials: application of the EORTC item library to myelodysplastic syndromes, chronic myelomonocytic leukemia, and acute myeloid leukemia. Journal of Patientreported Outcomes 3 (1): 35.
6. Bryant AL, Coffman EM, Phillips B, Gray TF, Knafl GJ et al. (2018) Symptoms, Mobility and Function, and Quality of Life in Adults With Acute Leukemia During Initial Hospitalization. Oncology Nursing Forum 45 (5): 653-664.
7. Buchner T, Schlenk RF, Schaich M, Dohner K, Krahl R et al. (2012) Acute Myeloid Leukemia (AML): different treatment strategies versus a common standard arm--combined prospective analysis by the German AML Intergroup. Journal of Clinical Oncology 30 (29): 3604-3610.
8. Cheng MJ, Smith BD, Hourigan CS, Gojo I, Pratz KW et al. (2017) A Single Center Survey of Health-Related Quality of Life among Acute Myeloid Leukemia Survivors in First Complete Remission. Journal of Palliative Medicine 20 (11): 1267-1273.
9. Estcourt LJ, Malouf R, Trivella M, Fergusson DA, Hopewell S et al. (2017) Restrictive versus liberal red blood cell transfusion strategies for people with haematological malignancies treated with intensive chemotherapy or radiotherapy, or both, with or without haematopoietic stem cell support. Cochrane Database of Systematic Reviews 1 CD011305.
10. Goswami P, Oliva EN, Ionova T, Else R, Kell J et al. (2019) Paper and electronic versions of HM-PRO, a novel patient-reported outcome measure for hematology: An equivalence study. Journal of Comparative Effectiveness Research 8 (7): 523-533.
11. Kenealy M, Patton N, Filshie R, Nicol A, Ho SJ et al. (2017) Results of a phase II study of thalidomide and azacitidine in patients with clinically advanced myelodysplastic syndromes (MDS), chronic myelomonocytic leukemia (CMML) and low blast count acute myeloid leukemia (AML). Leukemia and Lymphoma 58 (2): 298-307.
12. Kurosawa S, Yamaguchi H, Yamaguchi T, Fukunaga K, Yui S et al. (2016) Decision Analysis of Postremission Therapy in Cytogenetically Intermediate-Risk Acute Myeloid Leukemia: The Impact of FLT3 Internal Tandem Duplication, Nucleophosmin, and CCAAT/Enhancer Binding Protein Alpha. Biology of Blood & Marrow Transplantation 22 (6): 1125-1132.
13. Kurosawa S, Yamaguchi T, Miyawaki S, Uchida N, Kanamori H et al. (2011) A Markov decision analysis of allogeneic hematopoietic cell transplantation versus chemotherapy in patients with acute myeloid leukemia in first remission. Blood 117 (7): 2113-2120.
14. Kurosawa S, Yamaguchi T, Mori T, Kanamori H, Onishi Y et al. (2015) Patient-reported quality of life after allogeneic hematopoietic cell transplantation or chemotherapy for acute leukemia. Bone Marrow Transplantation 50 (9): 1241-1249.
15. Libert Y, Borghgraef C, Beguin Y, Delvaux N, Devos M et al. (2017) Factors associated with self-perceived burden to the primary caregiver in older patients with hematologic malignancies: an exploratory study. Psycho-Oncology 26 (1): 118-124.
16. Lowe JR, Yu Y, Wolf S, Samsa G, LeBlanc TW (2018) A Cohort Study of Patient-Reported Outcomes and Healthcare Utilization in Acute Myeloid Leukemia Patients Receiving Active Cancer Therapy in the Last Six Months of Life. Journal of Palliative Medicine 21 (5): 592-597.
17. Messerer D, Engel J, Hasford J, Schaich M, Ehninger G et al. (2008) Impact of different post-remission strategies on quality of life in patients with acute myeloid leukemia. Haematologica 93 (6): 826-833.
18. Miladinia M, Baraz S, Ramezani M, Malehi AS (2018) The relationship between pain, fatigue, sleep disorders and quality of life in adult patients with acute leukaemia: During the first year after diagnosis. European Journal of Cancer Care 27 (1).
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Excluded due to intervention/comparator (N = 5)

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Excluded SLRs/MA/NMA (N = 12)

1. Berry SM, Broglio KR, Berry DA (2011) Addressing the incremental benefit of histamine dihydrochloride when added to interleukin-2 in treating acute myeloid leukemia: a Bayesian meta-analysis. Cancer Investigation 29 (4): 293-299.
2. Bosshard R, Reilly KO, Ralston S, Chadda S, Cork D (2018) Systematic reviews of economic burden and health-related quality of life in patients with acute myeloid leukemia. Cancer Treatment Reviews 69 224-232.
3. Bryant AL, Drier SW, Lee S, Bennett AV (2018) A systematic review of patient reported outcomes in phase II or III clinical trials of myelodysplastic syndromes and acute myeloid leukemia. Leukemia Research 70 106-116.
4. Bryant AL, Walton AL, Shaw-Kokot J, Mayer DK, Reeve BB (2015) Patient-reported symptoms and quality of life in adults with acute leukemia: a systematic review. Oncology Nursing Forum 42 (2): E91-E101.
5. Buckley SA, Kirtane K, Walter RB, Lee SJ, Lyman GH (2018) Patient-reported outcomes in acute myeloid leukemia: Where are we now? Blood Reviews 32 (1): 81-87.
6. Efficace F, Cottone F, Sommer K, Kieffer J, Aaronson N et al. (2019) Validation of the European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire Core 30 Summary Score in Patients With Hematologic Malignancies. Value in Health 22 (11): 1303-1310.
7. Efficace F, Kemmler G, Vignetti M, Mandelli F, Molica S et al. (2008) Health-related quality of life assessment and reported outcomes in leukaemia randomised controlled trials - a systematic review to evaluate the added value in supporting clinical decision making. European Journal of Cancer 44 (11): 1497-1506.
8. Forsythe A, Brandt PS, Dolph M, Patel S, Rabe APJ et al. (2018) Systematic review of health state utility values for acute myeloid leukemia. Clinicoeconomics & Outcomes Research 10 83-92.
9. Korol EE, Wang S, Johnston K, Ravandi-Kashani F, Levis M et al. (2017) Health-Related Quality of Life of Patients with Acute Myeloid Leukemia: A Systematic Literature Review. Oncology & Therapy 5 (1): 1-16.
10. Park S, Fenaux P, Greenberg P, Mehta B, Callaghan F et al. (2016) Efficacy and safety of darbepoetin alpha in patients with myelodysplastic syndromes: a systematic review and meta-analysis. British Journal of Haematology 174 (5): 730-747.
11. Rashidi A, Walter RB, Tallman MS, Appelbaum FR, DiPersio JF (2016) Maintenance therapy in acute myeloid leukemia: an evidence-based review of randomized trials. Blood 128 (6): 763-773.
12. Stauder R, Lambert J, Desruol-Allardin S, Savre I, Gaugler L et al. (2020) Patient-reported outcome measures in studies of myelodysplastic syndromes and acute myeloid leukemia: literature review and landscape analysis. European Journal of Haematology 27 27.

MA = meta-analysis; NMA = network meta-analysis; SLR = systematic literature review.

Table H-9. Studies excluded at the full-text screening phase (review update)

Excluded due to population (N = 15)
1. Ademi Z, Owen AJ, Zomer E, Parker C, Liew D et al. (2021) Estimating the Productivity Impact of Acute Myeloid Leukemia in Australia Between 2020 and 2029, Using a Novel Work Utility Measure: The Productivity-Adjusted Life Year (PALY). JCO oncology practice OP2000904.
2. Amonoo HL, LeBlanc TW, Kavanaugh AR, Webb JA, Traeger LN et al. (2021) Posttraumatic stress disorder (PTSD) symptoms in patients with acute myeloid leukemia (AML). Cancer
3. Coyle D, Villeneuve PJA (2020) Economic Evaluation of Azacitidine in Elderly Patients with Acute Myeloid Leukemia with High Blast Counts. PharmacoEconomics - Open 4 (2): 297-305.
4. El-Jawahri A, Leblanc TW, Kavanaugh A, Webb JA, Jackson VA et al. (2020) Effectiveness of Integrated Palliative and Oncology Care for Patients with Acute Myeloid Leukemia: a Randomized Clinical Trial. JAMA Oncology
5. Goswami P, Oliva EN, Ionova T, Else R, Kell J et al. (2020) Quality-of-life issues and symptoms reported by patients living with haematological malignancy: a qualitative study. Therapeutic Advances in Hematology 11
6. Goswami P, Salek S, Oliva EN, Ionova T, Else R et al. (2020) Reliability of a Novel Hematological Malignancy Specific Patient-Reported Outcome Measure: HM-PRO. Frontiers in Pharmacology 11 571066.
7. Goswami P, Salek S, Oliva EN, Ionova T, Else R et al. (2020) Hematological Malignancy Specific Patient-Reported Outcome Measure (HM-PRO): Construct Validity Study. Frontiers in Pharmacology 11 1308.
8. Jie Y, Wang Y, Chen J, Wang C, Lin Y et al. (2020) Unmet supportive care needs and its relation to quality of life among adult acute leukaemia patients in China: a cross-sectional study. Health and Quality of Life Outcomes 18 (1): 199.
9. Jimenez-Sahagun D, Buckley SA, Walter RB, Lee SJ, Halpern AB et al. (2020) Development and validation of the AML-QOL: a quality of life instrument for patients with acute myeloid leukemia. Leukemia and Lymphoma 61 (5): 1158-1167.
10. Lennmyr EB, Hoglund M, Hallbook H, Karlsson K, Lubking A et al. (2020) Introducing patient-reported outcome in the acute leukemia quality registries in Sweden. European Journal of Haematology 104 (6): 571-580.
11. Mabrey FL, Gardner KM, Shannon Dorcy K, Perdue A, Smith HA et al. (2020) Outpatient intensive induction chemotherapy for acute myeloid leukemia and high-risk myelodysplastic syndrome. Blood advances 4 (4): 611-616.
12. Oswald LB, Venditti A, Cella D, Cottone F, Fazi P et al. (2021) Fatigue in newly diagnosed acute myeloid leukaemia: general population comparison and predictive factors. BMJ supportive & palliative care
13. Senf B, Grabowski K, Spielmann N, Fettel J (2020) Quality of life and distress assessed with self and external assessment screening tools in patients with hematologic malignancies attending treatment in an acute hospital. Quality of Life Research 29 (12): 3375-3385.
14. Yu H, Zeng X, Sui M, Liu R, Huang W et al. (2021) A head-to-head comparison of measurement properties of the EQ-5D-3L and EQ-5D-5L in acute myeloid leukemia patients. Quality of Life Research 30 (3): 855-866.
15. Zeng X, Sui M, Liu R, Yang J, Huang W et al. (2021) Assessment of the health utility of patients with leukemia in China. Health and Quality of Life Outcomes 19 (1): 65.
Excluded due to study design (N = 16)
16. (2021) Benefits of AML Maintenance Therapy Extend to Quality of Life and Hospitalization. Oncologist 26 (S1): S11-S12.
17. Calzado Gomez G, Gavira Moreno R, Alegre Del Rey EJ, Fenlx Caballero S (2020) Gemtuzumab ozogamicin for the treatment of untreated acute myeloid leukemia. European Journal of Clinical Pharmacy 22 (2): 100-105.
18. Cortes JE, Lin T, Uy GL, Ryan RJ, Faderl S et al. (2020) Quality-adjusted time without symptoms of disease and toxicity(q-twist) analysis of CPX-351 versus 7+3 in older adults with newly diagnosed high-risk/secondary acute myeloid leukemia(AML). Blood 136 (SUPPL 1): 55.
19. El-Jawahri A, Leblanc TW, Kavanaugh AR, Webb JA, Jackson V et al. (2020) Multi-site randomized trial of integrated palliative and oncologycare for patients with acute myeloid leukemia (AML). Blood 136 (SUPPL 1): 26.
20. Leblanc TW, Morris S, Hooks M, Locke SC, El-Jawahri A (2020) Patient experiences with liposomal daunorubicin and cytarabine(CPX-351) versus conventional induction regimens: an analysis of patient-reported outcomes data from a prospective trial. Blood 136 (SUPPL 1): 29.
21. Lockwood B, El-Jawahri A, Walker AR, Russell D, Gustin J et al. (2020) Psychological distress in young adults with acute myeloid leukemia undergoing induction chemotherapy. Blood 136 (SUPPL 1): 17.
22. Morton S, Sekhar M, Smethurst H, Mora A, Hodge R et al. (2020) Results for the REAL pilot randomised trial of red cell transfusion in acute myeloid leukaemia: is there sufficient evidence of equipoise to support a definitive study? British Journal of Haematology 189 36.
23. Nelson A, Kavanaugh A, Webb J, Jackson V, O'Connor N et al. (2021) Palliative care and coping in patients with acute myeloid leukemia (AML): mediation analysis of data from a randomized clinical trial. Psycho-oncology 30 (SUPPL 1): 11.
24. Paquete AT, Ines M, Borges M, Silva Miguel L (2020) PCN264 Cost-Effectiveness Analysis of Gemtuzumab Ozogamicin in Combination with Daunorubicin and Cytarabine for the Treatment of Acute Myeloid Leukaemia in Portugal. Value in Health 23 (Supplement 2): S469-S470.

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25. Roboz G, Dohner H, Pocock C, Dombret H, Ravandi F et al. (2020) Health-related quality of life with CC-486 in patients with acute myeloid leukemia (AML) in first remission following induction chemotherapy (IC): results from the phase iii Quazar AML-001 trial. HemaSphere 4 128.
26. Sanyal A, Heun JM, Sweeney J, Janssen C (2020) Mobile-health tool to improve care of patients with hematological malignancies. Blood 136 (SUPPL 1): 35-36.
27. Sierra J, Mareque M, Oyaguez I, Montesinos P, Guinea JM et al. (2020) Cost-effectiveness of gemtuzumab ozogamicin in combination with standard of care chemotherapy for first-line treatment of patients with CD33-positive acute myeloid leukemia in Spain. HemaSphere 4 (Supplement 1): 795-796.
28. Sorror M, Storer B, Fathi A, Brunner A, Gerds A et al. (2020) AML-145: multicenter 11-Year Experience of Outcomes After Intensive Versus Less-Intensive Therapy for Patients with Acute Myeloid Leukemia: focus on Older and Medically Infirm Patients. Clinical lymphoma, myeloma & leukemia 20 S185.
29. Tervonen T, Cutts K, Seo J, Nehme SA, Torre IL et al. (2020) Patient preferences for maintenance treatment of acute myeloid leukemia: results of a discrete choice experiment. Blood 136 (SUPPL 1): 38.
30. Ying C, Li Y, Yan L, Zhan H, Chen Y et al. (2020) PCN26 Disease Burden of ACUTE Myelogenous Leukemia UNDER the Current Treatment Pattern in China. Value in Health Regional Issues 22 (Supplement): S9.
31. Zeidner JF, Mazerolle F, Bell JA, Cain LE, Faller DV et al. (2020) Randomized phase 2 trial of pevonedistat plus azacitidine versus azacitidine in higher-risk myelodysplastic syndromes/chronic myelomonocytic leukemia or low-blast acute myeloid leukemia: exploratory analysis of patient-reported outcomes. Blood 136 (SUPPL 1): 39.
Excluded due to outcomes (N = 3)
32. Baron F, Efficace F, Cannella L, Vignetti M, Fazi P et al. (2020) Long-term follow-up of a trial comparing post-remission treatment with autologous or allogeneic bone marrow transplantation or intensive chemotherapy in younger acute myeloid leukemia patients. Haematologica 105 (1): E13-E16.
33. Ou Z, Liang Y, He W, Li Y, Zhang M et al. (2020) Analysis of the Global Burden of Disease study highlights the trends in death and disability-adjusted life years of leukemia from 1990 to 2017. Cancer Communications 40 (11): 598-610.
34. Sorror ML, Leisenring WM, Lee SJ, Sandmaier BM, Appelbaum F et al. (2021) Multi-Site 11-Year Experience of Less-Intensive versus Intensive Therapies in Acute Myeloid Leukemia. Blood.
Excluded SLRs/MA/NMA (N = 3)
35. Chakraborty R, Cannella L, Cottone F, Efficace F (2020) Quality of patient-reported outcome reporting in randomised controlled trials of haematological malignancies according to international quality standards: a systematic review. The Lancet Haematology 7 (12): e892-e901.
36. Chang Y, Guyatt GH, Brignardello-Petersen R, Teich T, Dawdy JL et al. (2021) Intensive versus less-intensive antileukemic therapy in older adults with acute myeloid leukemia: A systematic review. PLoS ONE 16 (3 March): e0249087.
37. Golicki D, Jaskowiak K, Wojcik A, Mlynczak K, Dobrowolska I et al. (2020) EQ-5D-Derived Health State Utility Values in Hematologic Malignancies: A Catalog of 796 Utilities Based on a Systematic Review. Value in Health 23 (7): 953-968.
Excluded due to incomplete/insufficient/partial data (N = 3)
38. (2020) A trial comparing the effectiveness and safety of venetoclax to standard chemotherapy in acute myeloid leukaemia patients. Venetoclax or Intensive Chemotherapy for Treatment Of favourable Risk acute myeloid leukaemia: a molecularly guided phase 2 study.
39. (2020) Venetoclax or Intensive Chemotherapy for Treatment Of Favourable Risk Acute Myeloid Leukaemia: a Molecularly Guided Phase 2 Study. Venetoclax or Intensive Chemotherapy for Treatment Of Favourable Risk Acute Myeloid Leukaemia: a Molecularly Guided Phase 2 Study – VICTOR.
40. (2020) A study assessing the impact of frailty on therapy in older people with blood cancers. Geriatric assessment of frailty in patients with Haematological Malignancies - A study determining the impact of frailty in older people with haematological malignancies.
Duplicates excluded (N = 2)
41. Breunis H, Timilshina N, Alibhai SMH, Matelski J, Kundra A et al. (2020) Age-related cytokine effects on cancer-related fatigue and quality of life in acute myeloid leukemia. Journal of Geriatric Oncology 11 (3): 402-409.
42. Tremblay G, Dolph M, Forsythe A, Cariou C, Blanc A-S et al. (2020) Cost-effectiveness of midostaurin in the treatment of newly diagnosed FLT3-mutated acute myeloid leukemia in France. European Journal of Health Economics 21 (4): 543-555.

MA = meta-analysis; N = number; NMA = network meta-analysis; SLR = systematic literature review.

Table H-10 and Table H-11 present the included utility weight studies following screening of the titles and abstracts and full-text publications for the original and updated review, respectively.

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Table H-10. Included utility weight studies (original review)

Author, publication date	Country	Description of population	Treatment arms	N study	Source of data	Utility/HRQoL instruments
Utility elicitation studies						
Castejon et al. (2018)[73]	UK	General population from the UK ≥ 18 years of age	NR	125	TTO	Utility values reported by health states
Joshi et al. (2019)[74]	UK	General population from the UK ≥ 18 years of age	NR	212	TTO	Utility values reported by health states
Matza et al. (2019)[75]	UK	General population from the UK ≥ 18 years of age	NR	232	TTO	Utility values reported by health states
Stein et al. (2018)[76]	US	General population from the US ≥ 18 years of age	NR	300	DCE	Utility values reported by health states
Economic evaluations						
Arenaza et al. (2019)[77a]	Spain	De novo AML patients with mutated FLT3 ages 18-59 years of age	Midostaurin vs. SOC	NA	Literature	Utility values reported by health states
Stein et al. (2019)[78]	US	Adult patients ≥ 18 years of age with de novo FLT3-mutated AML	Midostaurin vs. SOC	NA	Literature	Utility values reported by health states
Tremblay et al. (2018)[79a]	UK	De novo AML patients with mutated FLT3 ages 18-59 years of age	Midostaurin vs. SOC	NA	Literature	Utility values reported by health states
Tremblay et al. (2020)[80a]	France	De novo AML patients with mutated FLT3 ages 18-59 years of age	Midostaurin vs. SOC	NA	Literature	Utility values reported by health states
Disease-specific HRQoL studies						
Alibhai et al. (2007)[81b]	Canada	Patients ≥ 60 years old newly diagnosed AML	IC vs. non-IC	65	Questionnaire	FACT-F
Alibhai et al. (2007)[82b]	Canada	Patients ≥ 60 years old newly diagnosed AML	IC vs. non-IC	65	Questionnaire	EORTC QLQ-C30
Alibhai et al. (2015)[83c]	Canada	Adult AML patients ≥ 18 years old undergoing IC	Older patients (≥ 60 years) vs. younger patients (18-59 years)	237	Questionnaire	FACT-F, EORTC QLQ-C30
Alibhai et al. (2020)[84]	Canada	Newly diagnosed AML patients undergoing IC	NR	219	Questionnaire	FACT-F, EORTC QLQ-C30

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Author, publication date	Country	Description of population	Treatment arms	N study	Source of data	Utility/HRQoL instruments
Albrecht et al. (2017)[85]	US	Newly diagnosed AML patients undergoing IC	NR	19	Questionnaire	FACT-L, FACT-G
El-Jawahri et al. (2019)[86]	US	Patients ≥ 60 years old newly diagnosed AML	IC vs. non-IC	100	Questionnaire	FACT-F, FACT-L
Iverson, 2008[87]	Russia & Norway	Newly diagnosed AML patients ≥ 18 years old	NR	45	Questionnaire	EORTC QLQ-C30
Kayastha et al. (2018)[88]	US	Adults with AML initiating a new line of inpatient chemotherapy	De novo AML *vs.* Relapsed/ refractory AML	De novo: 19	Questionnaire	FACT-L
Mohamedali et al. (2012)[89c]	Canada	Adult AML patients ≥ 18 years old undergoing IC	NR	103	Questionnaire	FACT-F, EORTC QLQ-C30
Timilshina et al. (2019)[90c]	Canada	Adult AML patients ≥ 18 years old undergoing IC	Older patients (≥ 60 years) vs. younger patients (18-59 years)	237	Questionnaire	FACT-F, EORTC QLQ-C30

AML = acute myeloid leukaemia; DCE = discrete choice experiment; EORTC QLQ-C30 = European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire; FACT-F = Functional Assessment of Cancer Therapy–Fatigue; FACT-G = Functional Assessment of Cancer Therapy General; FACT-L = Functional Assessment of Cancer Therapy-Leukemia; HRQoL = health-related quality of life; IC = intensive chemotherapy; NA = not applicable; NR = not reported; SLR = systematic literature review; SOC = standard of care; TTO = time-trade off; UK = United Kingdom; US = United States of America.

[a] Report utility values from the same SLR (Forsythe et al., 2018).

[b] Report outcomes for the same study.

[c] Report HRQoL scores for the same study at different timepoints.

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Table H-11. Included utility weight studies (review update)

Author, publication date	Country	Description of population	Treatment arms	N study	Source of Data	Utility/HRQoL instruments
Utility elicitation studies						
Castejon et al. (2018)[73]	UK	General population from the UK ≥ 18 years of age	NR	125	TTO	Utility values reported by health states
Joshi et al. (2019)[74]	UK	General population from the UK ≥ 18 years of age	NR	212	TTO	Utility values reported by health states
Matza et al. (2019)[75]	UK	General population from the UK ≥ 18 years of age	NR	232	TTO	Utility values reported by health states
Stein et al. (2018)[76]	US	General population from the US ≥ 18 years of age	NR	300	DCE	Utility values reported by health states
Economic evaluations						
Arenaza et al. (2019)[77a]	Spain	*de novo* AML patients with mutated FLT3 ages 18-59 years of age	Midostaurin + SoC vs. SoC	NA	Literature	Utility values reported by health states
Stein et al. (2019)[78]	US	Adult patients ≥ 18 years of age with *de novo* FLT3-mutated AML	Midostaurin + SoC vs. SoC	NA	Literature	Utility values reported by health states
Tremblay et al. (2018)[79a]	UK	*de novo* AML patients with mutated FLT3 ages 18-59 years of age	Midostaurin + SoC vs. SoC	NA	Literature	Utility values reported by health states
Tremblay et al. (2020)[80a]	France	*de novo* AML patients with mutated FLT3 ages 18-59 years of age	Midostaurin + SoC vs. SoC	NA	Literature	Utility values reported by health states
Mareque, 2021[91]	Spain	Adults with previously untreated CD33-positive *de novo* AML	GO + SOC vs. SOC	NA	Literature	Utility values reported by health states
Disease-specific HRQoL studies						
Alibhai et al. (2007)[81b]	Canada	Patients ≥ 60 years old newly diagnosed AML	IC *vs.* non-IC	65	Questionnaire	FACT-F
Alibhai et al. (2007)[82b]	Canada	Patients ≥ 60 years old newly diagnosed AML	IC *vs.* non-IC	65	Questionnaire	EORTC QLQ-C30
Alibhai et al. (2015)[83c]	Canada	Adult AML patients ≥ 18 years old undergoing IC	Older patients (≥ 60 years) *vs.* younger patients (18-59 years)	237	Questionnaire	FACT-F, EORTC QLQ-C30

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Author, publication date	Country	Description of population	Treatment arms	N study	Source of Data	Utility/HRQoL instruments
Alibhai et al. (2020)[84]	Canada	Newly diagnosed AML patients undergoing IC	NR	219	Questionnaire	FACT-F, EORTC QLQ-C30
Albrecht et al. (2017)[85]	US	Newly diagnosed AML patients undergoing IC	NR	19	Questionnaire	FACT-L, FACT-G
El-Jawahri et al. (2019)[86]	US	Patients ≥ 60 years old newly diagnosed AML	IC *vs.* non-IC	100	Questionnaire	FACT-F, FACT-L
Iverson, 2008[87]	Russia & Norway	Newly diagnosed AML patients ≥ 18 years old	NR	45	Questionnaire	EORTC QLQ-C30
Kayastha et al. (2018)[88]	US	Adults with AML initiating a new line of inpatient chemotherapy	De novo AML *vs.* Relapsed/ refractory AML	De novo: 19	Questionnaire	FACT-L
Mohamedali et al. (2012)[89c]	Canada	Adult AML patients ≥ 18 years old undergoing IC	NR	103	Questionnaire	FACT-F, EORTC QLQ-C30
Timilshina et al. (2019)[90c]	Canada	Adult AML patients ≥ 18 years old undergoing IC	Older patients (≥ 60 years) *vs.* younger patients (18-59 years)	237	Questionnaire	FACT-F, EORTC QLQ-C30
Randomized controlled trial						
Wei, 2020;[34] Celgene data on file (2020)[16]	Multi-site	Adult AML patients (≥ 55 years) in CR/CRi following IC, with or without consolidation chemotherapy	Oral AZA vs. placebo	444	Questionnaire	FACIT-Fatigue; EQ-5D-3L

AML = acute myeloid leukaemia; AZA = azacytidine; CR = complete remission; CRi = complete remission with incomplete blood count recovery; DCE = discrete choice experiment; EORTC QLQ-C30 = European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire; FACT-F = Functional Assessment of Cancer Therapy–Fatigue; FACT-G = Functional Assessment of Cancer Therapy General; FACT-L = Functional Assessment of Cancer Therapy-Leukemia; GO = gemtuzumab ozogamicin; HRQoL = health-related quality of life; IC = intensive chemotherapy; NA = not applicable; NR = not reported; SOC = standard of care; TTO = time-trade off; UK = United Kingdom; US = United States of America.

[a] Report utility values from the same SLR (Forsythe et al., 2018).

[b] Report outcomes for the same study.

[c] Report HRQoL scores for the same study at different timepoints.

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Appendix H.4 Selection of Studies for Consideration in the Economic Model

20 utility studies were identified in the SLR, but only 3 considered for the model in the main dossier.

The SLR of health utility evidence (2021) identified 20 studies, of which, only nine reported utilities by health state. These health utility sources (n=9) were evaluated for use in the model using the following criteria:

- The reported utility values correspond to the various health states of the model (ie, RFS on/off treatment and relapse)
- Utility values align with those used in previous HTA assessments
- The values for CR align with the EQ-5D utilities from QUAZAR for RFS derived with Nordic utility weights (RFS: Onureg = 0.889; RFS: Placebo = 0.899; RFS: Pooled data = 0.893)

A table listing the reasons that 6 of the 9 identified studies reporting utility data were excluded from consideration for the economic model is shown below.

Table H-12. Utility Sources Excluded from the Model

Study	Platform	Relevant period for the search
Castejon, 2018	CR: 0.620 Relapse: 0.120	Relapse utility value does not align with values used in previous HTA assessments (TA523, TA399, and TA545).
Matza, 2019	CR: 0.660	Only a utility value for CR was reported. Also, this value does not align with those used in previous HTA assessments (TA523 and TA399) and with EQ-5D utilities from QUAZAR for RFS (Nordic utility weights).
Stein, 2018	CR: 0.875 Relapse: 0.355	The relapse utility value does not align with values used in previous HTA assessments (TA523, TA399, and TA545).
Arenaza, 2019	Maintenance: 0.810 CR: 0.830 Relapse: 0.780	The relapse utility value does not align with values used in previous HTA assessments (TA399 and TA545). However, the relapse utility value of 0.780 aligns with that recommended by the Evidence Review Group in the HTA assessment of Rydapt (TA523).
Tremblay, 2020	Maintenance: 0.810 Relapse: 0.530	A utility value for CR was not reported.
Mareque, 2021	CR: 0.740 Relapse: 0.568	The utility value for CR does not align with values used in previous HTA assessments (TA523 and TA399) and with EQ-5D utilities from QUAZAR for RFS (Nordic utility weights).

CR = complete remission; HTA = health technology assessment; RFS = relapse-free survival; TA = technology appraisal

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Appendix H.5 Quality assessment and generalisability of estimates

The quality of the included utility weight studies was assessed using the quality assessment and relevance criteria presented in the NICE DSU Technical Support Document 9: the identification, review and synthesis of health state utility values from the literature.[92,93] The quality assessments of the 4 utility elicitation studies of most relevance and the QUAZAR AML-001 RCT are presented in Table H-12. Overall, in the review update, 12 of the 20 studies reported health utilities or HRQoL for populations comparable to the population of interest – adults with AML undergoing intensive first-line treatment. Four[77,79,80,91] of the 5 economic evaluations obtained utility values from literature sources that did not fit the PICOS criteria. Overall, the studies were of good quality and were relevant to the review.

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Table H-13. Quality assessment of included utility elicitation studies

Reference	Sample size	Population description	Inclusion/ exclusion criteria	Population comparable to that being modelled?	Response rate	Loss to follow-up	Missing data	Any other problems with the study?	Instrument used to describe health state	Which population evaluated health states?	Valuation population	Technique used to value health state
Stein et al. (2018)[76]	300	General US population	≥ 18 years old, at least 6 years of formal education	No	NR	NR	NR	No	NR	Clinicians (physicians and clinical experts)	General population	DCE
Matza et al. (2019)[75]	232	General UK population	≥ 18 year old UK resident.; able to understand the utility assessment; written informed consent	No	205	27	5	No	NR	Clinicians (physicians and nurses)	General population	TTO
Joshi et al. (2019)[74]	212	General UK population	NR	No	210/212	0	0	No	NR	Clinicians (physicians and nurses)	General population	cTTO
Castejon et al. (2018)[73]	125	General UK population	≥ 18 years old, resided in the UK, and provided written informed consent	No	NR	NR	NR	No	NR	Clinicians (physicians)	General population	TTO
Wei, 2020;[34] Celgene data on file (2020)[16]	445	Global	Adults aged ≥ 55 years with AML in first complete remission	Yes	NR	NR	NR	No	FACIT-Fatigue; EQ-5D-3L	Directly from the patients	US general population aged 65 to 74 years	TTO

AML = acute myeloid leukaemia; cTTO = composite time-trade off; DCE = discrete choice experiment; NR = not reported; TTO = time-trade off; UK = United Kingdom; US = United States

Appendix H.5.1 Unpublished data

The majority of evidence in this submission dossier is published.

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Appendix I. Mapping of HRQoL data

Appendix I.1 Mapped EQ-5D-5L health utilities from EQ-5D-3L using a parametric mapping algorithm and applying Denmark tariffs for the QUAZAR AML-001 trial

Appendix I.1.1 Objective

The purpose of this analysis was to derive EQ-5D-5L health utilities from EQ-5D-3L using a parametric mapping algorithm developed by van Hout and Shaw and applying Danish tariffs.

Appendix I.1.2 Methods

The EQ-5D-3L was mapped onto EQ-5D-5L health utilities using a parametric mapping algorithm developed by van Hout and Shaw (2021)[94] based on an ordinal logistic regression accounting for unobserved heterogeneity using a latent factor and without age and gender as covariates. The R program developed by the authors was adapted in this study by applying the Danish EQ-5D-5L value set based on the heteroscedastic censored hybrid model.[95]

Appendix I.1.3 Results

For the EQ-5D-5L using Danish tariffs, the values ranged from −0.48 to 0.98. Table I-1 summarises prerelapse EQ-5D-5L utilities across visits by treatment arm and overall patients.

Table I-1. Prerelapse EQ-5D-5L utilities

	Mean (SD)
Prerelapse utility: Onureg	0.889 (0.147)
Prerelapse utility: placebo	0.899 (0.139)
Prerelapse utility: combined arms	0.893 (0.144)

EQ-5D-5L = 5-level EQ-5D; SD = standard deviation.

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Appendix J. Probabilistic sensitivity analyses

Probability distributions are parameters are shown in Table J-1. Further information can be found in the model on the 'PSA Inputs' worksheet.

Table J-1. Probability distributions and parameters

	Expected value	Standard error	Probability distribution	Alpha	Beta	Refers to cell (in the Excel model)
Body surface area	1.85	0.37	Normal	NA	NA	='PSA Inputs'!L112
Cost to treat AEs - No Active Therapy	667.70	133.54	Gamma	-17335.29824	17309.33568	='PSA Inputs'!L13
Cost to treat AEs - Onureg	867.48	173.50	Gamma	25	34.69905621	='PSA Inputs'!L17
Cost of end of life care (one-time cost)	132,088.93	26,417.79	Gamma	25	5283.557238	='PSA Inputs'!L18
Disease management costs - Relapse - No Active Therapy	12,951.80	2,590.36	Gamma	25	518.0720015	='PSA Inputs'!L19
Disease management costs - Relapse - Onureg	11,784.41	2,356.88	Gamma	25	471.3764774	='PSA Inputs'!L23
Subsequent therapy costs - No Active Therapy	20,655.77	4,131.15	Gamma	25	826.2307043	='PSA Inputs'!L29
Subsequent therapy costs - Onureg	14,959.58	2,991.92	Gamma	25	598.3830515	='PSA Inputs'!L33
Disease management costs - RFS off treatment - No Active Therapy	1,137.92	227.58	Gamma	25	45.5168213	='PSA Inputs'!L34
Disease management costs - RFS off treatment - Onureg	685.97	137.19	Gamma	25	27.4388213	='PSA Inputs'!L38
Disease management costs - RFS on treatment - No Active Therapy	0.00	0.00	Gamma	NA	NA	='PSA Inputs'!L44
Disease management costs - RFS on treatment - Onureg	833.90	166.78	Gamma	25	33.35609015	='PSA Inputs'!L48
Cost of stem cell transplant (SCT) procedure	659,974	131,995	Gamma	25	26398.96	='PSA Inputs'!L54
Per cycle treatment administration cost - No Active Therapy	0.00	0.00	Gamma	NA	NA	='PSA Inputs'!L55
Per cycle treatment administration cost - Onureg	397.00	79.40	Gamma	25	15.88	='PSA Inputs'!L59

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% of Patients Receiving SCT - No Active Therapy	0.137	0.03	Beta	21.438	135.0437518	='PSA Inputs'!L60
% of Patients Receiving SCT - Onureg	0.063	0.01	Beta	23.362	347.4633968	='PSA Inputs'!L64
AE disutility - No Active Therapy	0.08	0.02	Normal	NA	NA	='PSA Inputs'!L185
AE disutility - Onureg	0.11	0.02	Normal	NA	NA	='PSA Inputs'!L189
Health state utility - Relapse	0.51	0.46	Beta	0.092310964	0.088690926	='PSA Inputs'!L190
Health state utility - RFS off treatment	0.89	0.14	Beta	3.221922984	0.386053482	='PSA Inputs'!L191
Health state utility - RFS on treatment	0.89	0.14	Beta	3.221922984	0.386053482	='PSA Inputs'!L192
Total disutility per transplant procedure	0.02	0.00	Normal	NA	NA	='PSA Inputs'!L193
Weight	74.41	14.88	Normal	NA	NA	='PSA Inputs'!L194
% of patients receiving only one dose reduction of Onureg	0%	0	Beta	NA	NA	='PSA Inputs'!L195
% of patients receiving two dose reductions of Onureg	0%	0	Beta	NA	NA	='PSA Inputs'!L196
Onureg compliance (%)	95%	0.18946	Beta	0.3702	0.020594891	='PSA Inputs'!L197
Spline Model Parameters	NA	NA	Cholesky Decomposition	NA	NA	='PSA Inputs'!L198
Spline 1 Parameter 1	-4.86	NA	Cholesky Decomposition	NA	NA	='PSA Inputs'!L199
Spline 1 Parameter 2	2.22	NA	Cholesky Decomposition	NA	NA	='PSA Inputs'!L200
Spline 1 Parameter 3	0.11	NA	Cholesky Decomposition	NA	NA	='PSA Inputs'!L201
Spline 1 Parameter 4	-1.86	NA	Cholesky Decomposition	NA	NA	='PSA Inputs'!L202
Spline 1 Parameter 5	0.62	NA	Cholesky Decomposition	NA	NA	='PSA Inputs'!L203
Spline 1 Parameter 6	0.02	NA	Cholesky Decomposition	NA	NA	='PSA Inputs'!L204
Spline 2 Parameter 1	-2.69	NA	Cholesky Decomposition	NA	NA	='PSA Inputs'!L205
Spline 2 Parameter 2	1.19	NA	Cholesky Decomposition	NA	NA	='PSA Inputs'!L206
Spline 2 Parameter 3	0.04	NA	Cholesky Decomposition	NA	NA	='PSA Inputs'!L207
Spline 2 Parameter 4	-0.42	NA	Cholesky Decomposition	NA	NA	='PSA Inputs'!L208
Spline 2 Parameter 5	-0.11	NA	Cholesky Decomposition	NA	NA	='PSA Inputs'!L209
Spline 2 Parameter 6	-0.02	NA	Cholesky Decomposition	NA	NA	='PSA Inputs'!L210

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Spline 3 Parameter 1	-4.94	NA	Cholesky Decomposition	NA	NA	='PSA Inputs'!L211
Spline 3 Parameter 2	2.27	NA	Cholesky Decomposition	NA	NA	='PSA Inputs'!L212
Spline 3 Parameter 3	0.09	NA	Cholesky Decomposition	NA	NA	='PSA Inputs'!L213
Spline 3 Parameter 4	-1.62	NA	Cholesky Decomposition	NA	NA	='PSA Inputs'!L214
Spline 3 Parameter 5	0.38	NA	Cholesky Decomposition	NA	NA	='PSA Inputs'!L215
Spline 3 Parameter 6	0.01	NA	Cholesky Decomposition	NA	NA	='PSA Inputs'!L216
Spline 4 Parameter 1	-4.87	NA	Cholesky Decomposition	NA	NA	='PSA Inputs'!L217
Spline 4 Parameter 2	2.24	NA	Cholesky Decomposition	NA	NA	='PSA Inputs'!L218
Spline 4 Parameter 3	0.05	NA	Cholesky Decomposition	NA	NA	='PSA Inputs'!L219
Spline 4 Parameter 4	0.06	NA	Cholesky Decomposition	NA	NA	='PSA Inputs'!L220
Spline 4 Parameter 5	-1.13	NA	Cholesky Decomposition	NA	NA	='PSA Inputs'!L221
Spline 4 Parameter 6	-0.04	NA	Cholesky Decomposition	NA	NA	='PSA Inputs'!L222
Spline 4 Parameter 7	-0.18	NA	Cholesky Decomposition	NA	NA	='PSA Inputs'!L223
Spline 4 Parameter 8	0.21	NA	Cholesky Decomposition	NA	NA	='PSA Inputs'!L224
Spline 5 Parameter 1	-2.55	NA	Cholesky Decomposition	NA	NA	='PSA Inputs'!L225
Spline 5 Parameter 2	1.00	NA	Cholesky Decomposition	NA	NA	='PSA Inputs'!L226
Spline 5 Parameter 3	-0.09	NA	Cholesky Decomposition	NA	NA	='PSA Inputs'!L227
Spline 5 Parameter 4	0.14	NA	Cholesky Decomposition	NA	NA	='PSA Inputs'!L228
Spline 5 Parameter 5	-0.17	NA	Cholesky Decomposition	NA	NA	='PSA Inputs'!L229
Spline 5 Parameter 6	-0.41	NA	Cholesky Decomposition	NA	NA	='PSA Inputs'!L230
Spline 5 Parameter 7	-0.14	NA	Cholesky Decomposition	NA	NA	='PSA Inputs'!L231
Spline 5 Parameter 8	0.14	NA	Cholesky Decomposition	NA	NA	='PSA Inputs'!L232
Spline 6 Parameter 1	-4.85	NA	Cholesky Decomposition	NA	NA	='PSA Inputs'!L233
Spline 6 Parameter 2	2.18	NA	Cholesky Decomposition	NA	NA	='PSA Inputs'!L234
Spline 6 Parameter 3	-0.01	NA	Cholesky Decomposition	NA	NA	='PSA Inputs'!L235
Spline 6 Parameter 4	0.11	NA	Cholesky Decomposition	NA	NA	='PSA Inputs'!L236
Spline 6 Parameter 5	-1.06	NA	Cholesky Decomposition	NA	NA	='PSA Inputs'!L237

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Spline 6 Parameter 6	-0.14	NA	Cholesky Decomposition	NA	NA	='PSA Inputs'!L238
Spline 6 Parameter 7	-0.16	NA	Cholesky Decomposition	NA	NA	='PSA Inputs'!L239
Spline 6 Parameter 8	0.17	NA	Cholesky Decomposition	NA	NA	='PSA Inputs'!L240

AE = adverse event; NA = not applicable; PSA = probabilistic sensitivity analysis; RFS = relapse-free survival; SCT = stem cell transplant

Note: Parameters varied in the base case probabilistic sensitivity analysis are included here. Information on other parameters available in the model are shown in full on the PSA Inputs worksheet

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Appendix K. Company-specific appendices

None

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ASSESSMENT OF ORAL AZACITIDINE (ONUREG®) AS MAINTENANCE THERAPY FOR PATIENTS WITH ACUTE MYELOID LEUKAEMIA

DMC REQUEST OF SUPPLEMENTAL ANALYSES ON 14 DECEMBER 2021

In connection with the examination of the material for the evaluation of oral azacitidine for AML, a request has arisen from the specialist committee for supplementary data in the form of analyses of 3 subgroups.

Such a request would normally trigger a clockstop, but since there is not yet day 0 at this time we would ask that all questions from the validation and the further requested analyses from the specialist committee to be clarified and submitted simultaneously.

In general, the follow-up time for the desired subgroup analyses:

The Danish Medicines Council generally wants data with the longest possible follow-up time and therefore prefers OS data from the latest datacut-off. Since, according to the applicant, measurement of RFS varies according to first data cut, RFS data from the early data cut is preferred.

This is consistent with the applicant's analyses for the ITT population.

1. Subgroup analysis based on number of previous chemotherapy cycles

According to Wei et al., 85% of patients have received more than 1 cycle chemotherapy treatment (pages 2529-2530). The specialist committee wants subgroup analyses of the OS and RFS for both the approximately 15% patients who have received only 1 single cycle of chemotherapy treatment and of the remaining 85% who have received 2 or more chemotherapy cycles. The specialist committee wants KM curves, calculation of median and hazard ratios and estimate of 1 year, 2 year and 3 year survivals/RFS for the subgroups- similar to that indicated for the ITT population.

The specialist committee wants to make sure that the effect is not significantly borne by patients who have not received adequate treatment with chemotherapy before treatment with oral azacitidine.

The QUAZAR AML-001 is a multicenter phase 3 study conducted at 148 sites in 23 countries. The QUAZAR AML-001 enrolled patients with acute myeloid leukaemia (AML) not

eligible for transplantation in complete remission/complete remission with incomplete count recovery (CR/CRi) after induction with intensive chemotherapy (IC) with or without consolidation and was not contingent on the number of cycles of intensive or consolidation chemotherapy received. Indeed, in the absence of a global standard practice for consolidation therapy in patients with advanced age, often associated with frailty and comorbidities, induction and consolidation regimens were administered at the discretion of the treating physician before study screening (Almeida et al., 2016). Therefore, Wei et al. (2020a) undertook an analysis to assess outcomes according to the number of courses of consolidation therapy received prior to study entry. This analysis is only available for the July 2019 database lock.

Figure 1 summarises the treatments received by patients prior to study entry and following randomisation.

AZA = azacitidine, CR = complete remission, CRi = CR with incomplete blood count recovery.

[a] Four patients were enrolled beyond the 4-month (± 7 days) inclusion window (protocol violations).

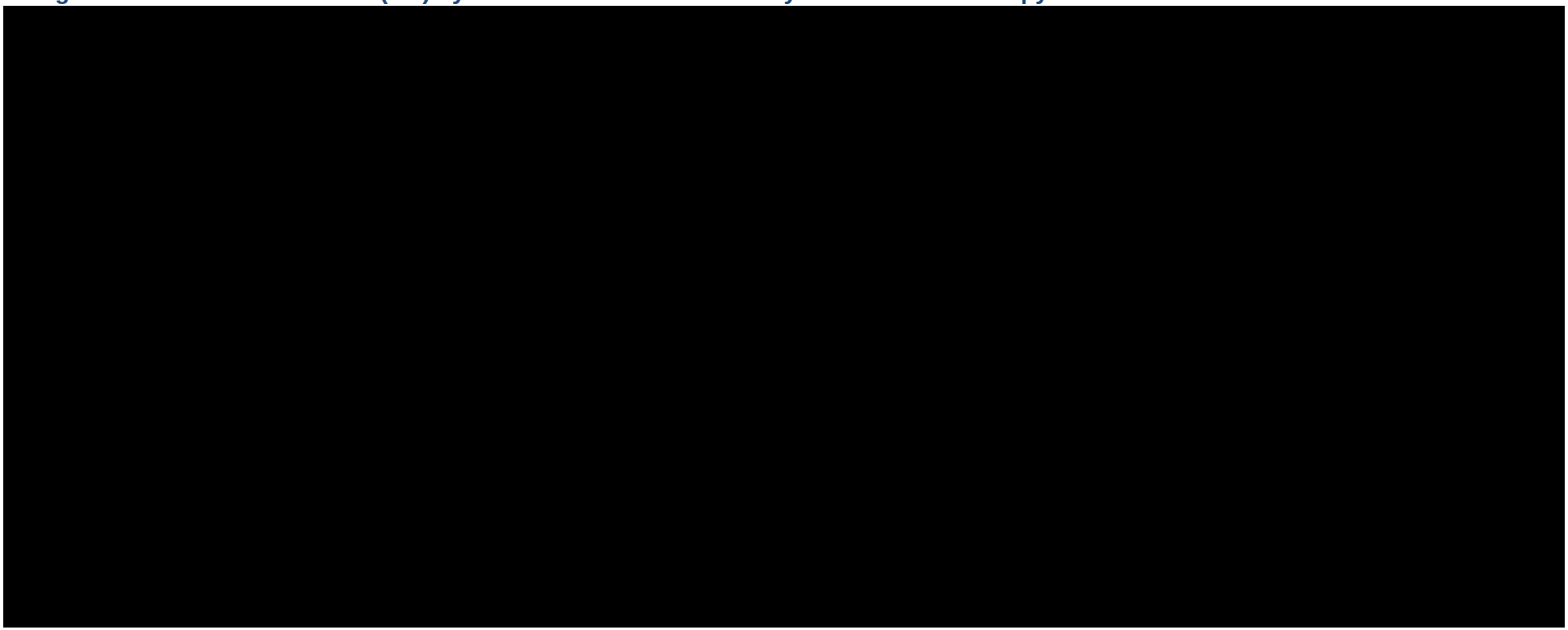
[b] The ≥ 2 Consolidations cohort included 19 patients (ONureg = 6, placebo = 13) who received 3 consolidation cycles.

Source: Wei et al. (2020a).

Relapse-free survival (RFS) was improved with Onureg compared with placebo, regardless of the number of consolidation cycles of chemotherapy received prior to randomisation with hazard ratios (HRs) ranging from 0.55 to 0.72 (Figure 2). Median RFS ranged from 8.4 to 13.0 months in the Onureg arm and 3.9 to 6.1 months in the placebo arm. Similarly, OS was prolonged with Onureg in all consolidation cohorts, with HRs ranging from 0.55 to 0.75 (Figure 3). Median OS ranged from 21.0 to 28.6 months in the Oral-AZA arm and from 10.9 to 17.6 months in the placebo arm.

Figure 2. Relapse-Free Survival (RFS) by Number of Consolidation Cycles of Chemotherapy

Figure 3. Overall Survival (OS) by Number of Consolidation Cycles of Chemotherapy



A further analysis was conducted assessing the numbers of both induction and consolidation cycles prior to randomisation, median OS and RFS were both prolonged with Onureg in all subgroups compared with placebo (Table 1).

Table 1. Survival by Number of Induction and Consolidation Courses of Chemotherapy

	Onureg N = 238		Placebo N = 234		Onureg vs. placebo HR [95% CI]
	n (%)	Median [95% CI]	n (%)	Median [95% CI]	
Relapse-free survival (RFS), months					
1 induction, no consolidation	38 (16%)	10.4 [7.7, 25.1]	35 (15%)	3.9 [1.9, 4.9]	0.47 [0.27, 0.82]
1 induction, 1 consolidation	84 (35%)	9.8 [7.0 11.1]	81 (35%)	5.0 [4.0, 7.6]	0.82 [0.58, 1.17]
1 induction, ≥ 2 consolidations	59 (25%)	13.0 [7.7, 21.1]	78 (33%)	6.1 [4.6, 7.7]	0.56 [0.37, 0.85]
≥ 2 inductions, no consolidation	14 (6%)	4.2 [1.9, 8.4]	7 (3%)	2.7 [0.4, 9.2]	0.66 [0.24, 1.81]
≥ 2 inductions, ≥ 1 consolidation	43 (18%)	12.9 [6.1, 46.1]	33 (14%)	4.4 [2.0, 7.5]	0.58 [0.33, 1.01]
Overall survival (OS), months					
1 induction, no consolidation	38 (16%)	29.3 [13.4, 45.3]	35 (15%)	10.8 [6.2, 15.7]	0.48 [0.28, 0.82]
1 induction, 1 consolidation	84 (35%)	19.4 [14.3, 24.8]	81 (35%)	15.0 [12.2, 24.3]	0.91 [0.64, 1.29]
1 induction, ≥ 2 consolidations	59 (25%)	28.6 [17.6, 36.6]	78 (33%)	16.6 [11.6, 27.0]	0.76 [0.49, 1.17]
≥ 2 inductions, no consolidation	14 (6%)	16.2 [8.9, 37.2]	7 (3%)	11.6 [3.1, NR]	0.90 [0.31, 2.61]
≥ 2 inductions, ≥ 1 consolidation	43 (18%)	36.0 [17.9, 47.2]	33 (14%)	14.2 [8.5, 22.3]	0.49 [0.28, 0.86]

95% CI = 95% confidence interval; HR = hazard ratio; OS = overall survival; RFS = relapse-free survival.

OS and RFS estimates were derived using Kaplan-Meier methods and compared for Onureg vs. placebo using a log-rank test. Hazard ratios and 95% CIs were generated using a stratified Cox proportional hazards model.

Source: Wei et al. (2020a).

It is important to note that the trial was not powered to detect significant differences between these subgroups and patient numbers are low. Nonetheless, the analyses suggest that patients obtain a benefit from Onureg regardless of the previous number of cycles of chemotherapy received (as induction or consolidation) and the efficacy seen is not driven by a large benefit in patients who had received 1 cycle of induction chemotherapy and no consolidation prior to commencing Onureg. Patients who had received at least 2 cycles of induction and 1 cycle of consolidation chemotherapy experienced a very similar level of benefit to those who had only received 1 prior cycle of induction therapy and no consolidation (HR, 0.49 and 0.48, respectively). Consolidation therapy is part of the standard AML treatment algorithm for younger patients who achieve remission after intensive chemotherapy. Reasons for not receiving consolidation therapy were not collected in the QUAZAR AML-001 study. In other studies, the rationale provided for not receiving consolidation included, for example, complications arising from intensive chemotherapy, the

patients were too ill, and patient refusal (Stone et al., 2001; Gardin et al., 2007). Of note, the percentage of patients not receiving consolidation increased with age in the QUAZAR AML-001: [redacted] of patients aged 55 to < 65 years, [redacted] of patients aged 65 to < 75 years, and [redacted] of patients aged ≥ 75 years (BMS Data on file [DOF], 2021a).

In conclusion, the analyses indicate that patients obtain a benefit from Onureg regardless of the number of cycles of chemotherapy received prior to study entry (as induction or consolidation). We do not anticipate that similar analyses from the later data cutoff would substantially alter these findings.

2. Additional subgroup analysis based on MRD status

The specialist committee wants more analyses for the subgroups of patients with positive and negative MRD status, respectively. The specialist committee wants subgroup analyses of the OS and RFS for both subgroups (MRD positive and negative). KM curves, calculation of median and hazard ratios and estimate of 1 year, 2 year and 3 year survivals/RFS for the subgroups - similar to that reported for the ITT population.

The specialist committee wants to investigate whether survival has improved equally for both subgroups, with the specialist committee expressing concern about treating patients who might have been "healthy" (in complete remission) regardless of whether they were given oral azacitidine for maintenance or not.

Data on 2 years of survival (first data cut) are available in the applicant's application. There are also HR calculations in Wei et al. based on the first data cut. These analyses must be complemented by the KM curves, 1 year and 3 years of data and all analyses should be carried out with the longest possible follow-up for the OS.

Roboz et al. (2020) presented subgroup analyses of the QUAZAR AML-001 trial based on baseline measurable residual disease (MRD) status at a median follow-up of 41.2 months (~ 3 years and 5 months, July 2019 data cutoff) (Roboz et al., 2020). In the QUAZAR AML-001 trial, MRD status was an exploratory endpoint, and multiparameter flow cytometry (MFC) assessments were performed centrally using bone marrow aspirates collected at screening (i.e., after CR/CRi and any consolidation), at cycles 3, 6, 9, 12, 15, 18, 21, 24, 30, and 36 (and as clinically indicated), until time of relapse. Samples were analysed with a panel of 22 cell surface markers using a low sensitivity MRD+ cutoff of ≥ 0.1% (Roboz et al., 2020).

The MRD evaluable cohort comprised 463 out of 472 randomised patients (98.1%; Onureg, n = 236; placebo, n = 227) with available baseline and ≥ 1 postbaseline visit data. At baseline, 44% (n = 103) and 51% (n = 116) were MRD+ in the Onureg and placebo arm,

respectively. Baseline characteristics were similar between patients who were MRD+ and MRD-, and between Onureg and placebo within the MRD subgroups (Roboz et al., 2020).

Overall, treatment with Onureg prolonged median OS and RFS compared with placebo regardless of MRD status at baseline. In patients who were MRD+, median OS was 14.6 months for patients treated with Onureg versus 10.4 months for placebo (HR, 0.69 [95% CI, 0.51-0.93]); in patients who were MRD-, median OS was 30.1 months versus 24.3 months (HR, 0.81 [95% CI, 0.59-1.12]), respectively (Figure 4) (Roboz et al., 2020).

AZA, azacitidine; CI = confidence interval; HR = hazard ratio; mo = months; MRD = measurable residual disease; No. = number.

Source: Roboz et al. (2020).

At a median follow-up of 51.7 months (Sept 2020 data cutoff),

Figure 5. Kaplan-Meier Estimated Overall Survival (OS) by Baseline MRD Status and Treatment Arm (Sept 2020 data cutoff)

Median RFS with Onureg was 7.1 months versus 2.7 months for placebo (HR, 0.58 [95% CI, 0.43-0.78]) in patients who were MRD+; and 13.4 months versus 7.8 months (HR, 0.71 [95% CI, 0.52-0.98]) in patients who were MRD-, respectively (Figure 6) (Roboz et al., 2020).

Figure 6. Kaplan-Meier Estimated Relapse-Free survival (RFS) by Baseline MRD Status and Treatment Arm (July 2019 data cutoff)

AZA, azacitidine; CI = confidence interval; HR = hazard ratio; mo = months; MRD = measurable residual disease; No = number.

Source: Roboz et al. (2020).

In a multivariate analysis, Onureg showed a significant treatment benefit versus placebo in both OS (HR = 0.74; *P* = 0.0067) and RFS (HR = 0.63; *P* < 0.0001) independent of baseline MRD status (Roboz et al., 2020). Presence of MRD at study entry was significantly associated with shorter OS and RFS (both *P* < 0.0001) after controlling for each randomised treatment arm (Roboz et al., 2020).

Further, mutations such as NPM1 have been shown to characterise AML risk categories. NPM1 mutation occurs in 25% to 30% of patients with AML and is generally associated with favourable outcomes in the absence of co-occurring *FLT3*-ITD, or when *FLT3*-ITD is present at a low allelic ratio (< 0.5) (Döhner et al., 2017; Döhner et al., 2020a). Döhner et al. (2021) presented analysis at ASH 2021 of the QUAZAR AML-001 trial for patients with NPM1 mutation ($NPM1^{mut}$) at diagnosis by MRD status post-intensive chemotherapy (Sept 2020 data cutoff) (Döhner et al., 2021). NPM1 mutation was assessed locally at AML diagnosis. Of the 469 patients with biomarker analysis available, 137 (29.2%) had an NPM1 mutation (Onureg n = 66, placebo n = 71); out of those, 107 patients were NPM1 mutated (22.8%) without FLT3-ITD mutation. A similar and small number of patients with MRD status post-intensive chemotherapy were available for assessment in both arms: Onureg, MRD- n = 39 and MRD+ n = 27; placebo, MRD- n = 43 and MRD+ n = 24.

In patients with NPM1 mutation at diagnosis, Onureg prolonged median OS compared with placebo regardless of post-intensive chemotherapy MRD status (MRD-, 48.6 months vs. 31.4 months, *P* = 0.182; MRD+, 46.1 months vs. 10.0 months, *P* = 0.033 for Onureg and placebo, respectively) (Figure 7). Relapse-free survival was significantly longer in the Onureg arm compared with the placebo arm irrespective of post-intensive chemotherapy MRD status (MRD- 25.7 months vs. 9.9 months, *P* = 0.019; MRD+, 15.6 months vs. 4.9 months, *P* = 0.037). OS in patients with $NPM1^{mut}$ does not seem to be influenced by co-occurring *FLT3*-ITD mutation in the Onureg arm, although the number of patients was small (Döhner et al., 2021).

Figure 7. Kaplan-Meier Estimated Overall Survival (OS) and Relapse-Free Survival (RFS) in Patients with NPM1 Mutation by Post-Intensive Chemotherapy MRD Status and Treatment Arm (September 2020 data cutoff)

AZA = azacitidine; MRD = measurable residual disease; OS = overall survival; post-IC = post-intensive chemotherapy; RFS = relapse-free survival.

Source: Döhner et al. (2021).

These analyses show that although MRD-negativity after intensive chemotherapy and NPM1 mutations at AML diagnosis are both prognostic of improved survival, treatment with Onureg prolonged median OS and RFS compared with placebo in patients with NPM1 mutation at diagnosis regardless of MRD status. Therefore, the various analyses by MRD status suggest that Onureg is beneficial regardless of MRD status, even in the NPM1 mutated subgroup, typically associated with a relatively favourable prognosis.

3. Subgroup analysis based on dose escalation

According to applicant's application, dose escalation from 14 days of treatment to 20 days of treatment is not included in the health economic analysis. However, patients who received dose escalation in the study covers up to ~20% of the total population. The committee agrees with the applicant that in Danish clinical practice it will have a harder time identifying patients who could get an escalated dose based on blast percentage between5-15 percent, because these studies of blast percentage are not done routinely but only on suspicion of relapse. However, dose escalation in the study may have a positive impact on survival estimates, which will therefore not be possible to recover in practice. The specialist committee therefore wants subgroup analyses of patients who were not dose-

escalated and patients who were dose-escalated. The specialist committee wants subgroup analyses of the OS for both subgroups. The Committee expects RFS data not to be affected, as scaling up occurred after progression (5% blasts). KM curves, calculation of median and hazard ratios and estimate of 1 year, 2 year and 3 years of survival for the subgroups - similar to that reported for the ITT population.

Döhner et al. (2020b) presented analyses of the QUAZAR AML-001 trial for patients who received escalated dosing at ASH 2020. As noted above, patients initially received 300 mg once daily Onureg or placebo for 14 days per 28-day treatment cycle, but patients identified as having early AML relapse with 5% to 15% blasts in peripheral blood or bone marrow could receive an escalated 21-day dosing schedule per 28-day treatment cycle. Therefore, Döhner et al. (2020b) evaluated outcomes for the patients who received escalated doses of Onureg or placebo during the trial, based on the July 2019 database lock.

Overall, 91 of 472 patients (19.3%) (Onureg, n = 51 [21%]; placebo, n = 40 [17%]) received an escalated 21-day dosing schedule. Median time to dose escalation was 9.2 months (range 1.0-52.7) in the Onureg arm and 6.0 months (0.5-19.3) in the placebo arm. Patients received a limited number of escalated dosing cycles (median of 2 cycles) in both the Onureg (range 1-45) and placebo (1-16) arms, but proportionally more patients in the Onureg arm received > 3 cycles of escalated dosing (Onureg, 43%; placebo, 18%) (Döhner et al., 2020b).

Among patients who received an escalated dosing schedule, median OS from time of randomisation was 22.8 months versus 14.6 months with Onureg and placebo, respectively (unstratified HR, 0.66 [95% CI, 0.42, 1.04]; *P* = 0.0729), and 1-year survival rates were 80.4% versus 59.5% (+20.9% [2.1, 39.7]) (Figure 8) (Döhner et al., 2020b). These results, and the Kaplan-Meier plots are very similar to those seen in the intention to treat (ITT) population, as presented in Figure 7 of the submission and repeated in Figure 9 below. In the ITT population, the median OS was 24.7 months for the Onureg arm compared with 14.8 months for the placebo arm; 1 year OS was 72.8% for Onureg and 55.8% for placebo (Wei et al., 2020b).

Figure 8. Kaplan-Meier Estimated Overall Survival (OS) From Time of Randomisation Among Patients Who Received Escalated Dosing Schedules (July 2019 data cutoff)

CC-486 = Onureg.

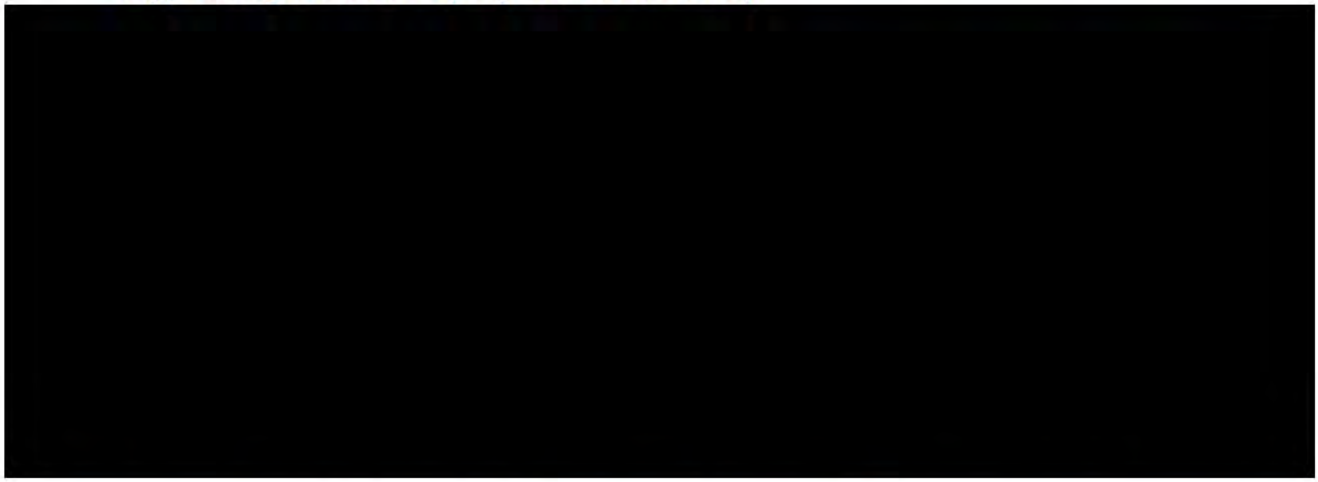
Source: Döhner et al. (2020b).

Figure 9. Kaplan-Meier Estimated Overall Survival (OS) From Time of Randomisation in the ITT population (July 2019 data cutoff)

CC-486 = Onureg; ITT = intention to treat; mo = months.

Source: Wei et al. (2020b).

Figure 10. Randomisation and Disposition of Patients Who Received Extended (21-day) Dosing Schedules (July 2019 data cutoff)



Data are not available from the September 2020 data cutoff; however, most patients were off treatment at the time of the first analysis (Figure 10) and therefore the overall conclusions in terms of the impact of dose escalation are unlikely to be different based on the later data cutoff.

Dose escalation is unlikely to be standard practice in Denmark. These data show that the median OS in QUAZAR AML-001 was lower in the dose-escalated population compared with the ITT population. Further, a small number of patients escalated to the 21-day dosing schedule and the number of escalated dosing cycles received was low (median of 2 cycles), probably because of relapse with bone marrow blasts > 15%, leading to treatment discontinuation.

Overall, this suggests that the OS benefit seen in the trial is not driven by an increased benefit in patients experiencing relapse and thus, receiving the 21-day escalated dosing schedule and that comparable benefit would be expected in a setting without dose escalation.

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