Medicinrådet

Bilag til Medicinrådets anbefaling vedr. sotorasib til andenlinjebehandling af uhelbredelig ikke-småcellet lungekræft med KRAS G12C-mutation

Vers. 1.0

Bilagsoversigt

1. Ansøgers notat til Rådet vedr. sotorasib
2. Forhandlingsnotat fra Amgros vedr. sotorasib
3. Ansøgers endelige ansøgning vedr. sotorasib

Til Medicinrådet

Ballerup d. 26. august 2022

Hermed Amgens tilbagemelding på udkast til vurderingsrapport for Sotorasib (Lumykras) andenlinjebehandling af KRASG12C muteret ikke-småcellet lungekræft.

Vi ønsker at fremhæve den betydelige innovation Sotorasib bringer til patienter med uhelbredelig ikke-småcellet lungekræft med relaps efter forudgående behandling. En innovation der anerkendes af EMA, der tilkendte Sotorasib en konditionel marketingsautorisation grundet det betydelige *unmet need* som Sotorasib adresserer. Vi er derfor overordnet tilfredse med at medicinrådet vurderer, at de anvendte studier afspejler dansk klinisk praksis, samt at de anvendte metoder muliggør en sundhedsøkonomisk evaluering.

Der er dog forhold i denne vurderingsrapport, som Amgen ønsker at benytte muligheden for at kommentere på:

1. Ingen inklusion af uønskede bivirkninger i gennemgangen

Det er uklart hvorfor medicinrådssekretariatet ikke har inkluderet en gennemgang af uønskede bivirkninger i forbindelse med vurderingen af Sotorasib. Dette på trods af, at sammenlignende tabeller over disse var udarbejdet og vedlagt ansøgningsmaterialet, samt at det er muligt at inkludere disse i den sundhedsøkonomiske model. I denne konkrete sag er det vanskeligt at vurdere om uønskede hændelser forårsages af Sotorasib i Codebreak 100, eller om de forårsages af tidligere behandlingslinjer, hvilket også kommenteres i rapporten. Det kunne have været yderligere belyst, hvis der også var taget stilling til uønskede bivirkninger.

Sotorasib forårsager færre uønskede bivirkninger af grad 3+ i Codebreak 100 (20,6%) sammenlignet med Docetaxel i SELECT-1 (30%) på trods af, at patienter i Codebreak 100 var på aktiv behandling i mere end dobbelt så lang tid som i SELECT-1, havde modtaget flere tidligere behandlingslinjer, og patienter i SELECT-1 har bedre performance score end patienterne i Codebreak 100. Vi er opmærksomme på, at en sammenligning af uønskede bivirkninger kan introducere en vis bias, da dette er investigatorbedømt, men i denne konkrete sag vil det nuancere vurderingen yderligere.

2. Medicinrådssekretariatet påkræves ikke den samme grad og konsistens i argumentationen for tilvalg, fravalg og ændringer i hovedanalysen, som der påkræves ansøgende virksomhed.

Under valideringen af virksomheders indsendte ansøgninger rejses der krav om dokumentation og/eller, som minimum, fuldstændig entydig argumentation for alle valg og antagelser foretaget i forbindelse med indholdet af ansøgningen. Dette er en praksis vi selvfølgelig bifalder og til fulde anerkender nødvendigheden af.

Der forekommer dog ikke at være anlagt samme praksis i sekretariatets vurdering, hvilket vi gerne vil illustrere ved følgende eksempler:

Eksempel 1, ændring i ekstrapolation af overlevelse.

Herunder findes citater fra medicinrådet i denne konkrete sag, hvor vi vurderer at argumentationen ikke er konsistent i rapporten.

"Medicinrådet vurderer, baseret på klinisk erfaring, at ansøgers valgte ekstrapolering for docetaxel er for optimistisk, da det er usandsynligt, at ca. 4 % af patienterne forsat er i live ved docetaxelbehandling efter 5 år. Derfor ændrer Medicinrådet ekstrapoleringen af OS for docetaxel til eksponentiel fordeling, se den orange kurve i Figur 4. Dette skyldes, at den eksponentielle fordeling har det bedste statistiske fit (jf. AIC/BIC) af de tre fordelinger (Weibull, Gompertz og eksponentiel), der vurderes at være klinisk plausible. Medicinrådet ekstrapolerer ligeledes OS for sotorasib med eksponentiel fordeling, da der ikke er kliniske argumenter for, at den parametriske fordeling bør variere mellem de to behandlingsarme."

1: https://www.lungecancer.dk/wp-content/uploads/2022/06/Lungecancer_-aarsrapport-2021offentlig.pdf

Tidligere i ansøgningen har medicinrådet fremført følgende argument baseret på det danske lungecancer register:

"*Femårsoverlevelsen for den samlede patientgruppe med uhelbredelig NSCLC er 2-3 % (patienter diagnosticeret i 2015*)"

Siden 2015 er IO behandling rykket i første linje for hele patientpopulationen, hvilket med rimelighed kan antages at forbedre femårsoverlevelsen fremover. Medicinrådssekretariatet vælger altså at reducere overlevelsen for begge behandlingsarme betragteligt på baggrund af en usikkerhed vedrørende 1% i komparatorarmen. Dette underbygges i nogen grad af årsrapporten fra DLCG 2021, hvor der ses en markant øgning af 5 årsoverlevelsen for patienter fra 2016 sammenlignet med 2015[1] (fra 3.7-5.3), dette indikere en betydelige forbedring i overlevelse på området.

Eksempel 2, ændring af omkostningsestimater.

"*Medicinrådet accepterer ansøgers antagelser vedrørende administrations- og testomkostninger for sotorasib. Derimod anvender ansøger en DRG-takst for intravenøs administration af docetaxel, som inkluderer lægemiddelprisen på docetaxel, hvilket betyder, at ansøger tæller lægemiddelomkostningerne for docetaxel dobbelt (enhedsomkostning på 17.556). Medicinrådet ændrer derfor administrationsomkostningerne for docetaxel til et administrationsbesøg. Hertil anvendes enhedsomkostningen på 2.180 DKK, svarende til 2022 DRG-taksten (04MA98) MDC04 1-dagsgruppe, pat. mindst 7 år), jf. Interaktiv DRG med diagnosekode: 'Kræft i lunge og procedurekode: Medicingivning med intravenøs injektion'*.

Uden at forholde sig til om den nævnte takst over- eller underestimerer ressourceforbruget ifbm. behandling med docetaxel, kan det da retfærdiggøres at reducere en takst med +15.000 kr på baggrund af at taksten skulle inkludere et lægemiddel der koster 150 kr per dosis?

Hvis medicinrådet er usikre på risikoen for dobbelttælling, som det beskrives her, så burde løsningen, på baggrund af denne argumentation, være at reducere lægemiddelomkostningen for docetaxel til 0 istedet.

Set i lyset af at Amgen her har dokumenteret valget af denne takst, ved at konsultere to kliniske eksperter på forskellige hospitaler, der har adspurgt relevant personale på deres respektive afdelinger om hvilke takster der anvendes ifbm. administration af docetaxel - og at disse klinikeres kontaktoplysninger er delt med medicinrådet - så finder vi ikke ovenstående argumentation fyldestgørende.

3. Medicinrådet præsenterer ikke resultaterne fra ansøgers hovedanalyse.

Amgen ønsker, som andre tidligere ansøgere, at stille sig undrende overfor medicinrådetssekretariatet praksis med ikke at præsentere resultaterne af ansøgeres sundhedsøkonomiske analyser. Beslutningstagere bør tage begge parters analyser i betragtning, da det sande estimat må antages at være et sted imellem resultaterne fra de to hovedanalyser.

I denne konkrete sag giver Amgens analyse en QALY-gevinst på 0,63 imod Medicinrådets 0,52 og en ICER på ca. 550.000 DKK/QALY imod Medicinrådets ICER på ca. 839.000 DKK/QALY.

Vi ser frem til at sagen kan få en afgørelse d. 28. september, så vi sammen kan sikre, at G12C-muteret NSCLC-patienter har adgang til en effektiv standardbehandling i anden linje.

Med venlig hilsen

Tore von Würden
Country Director
Amgen, Danmark

1: https://www.lungecancer.dk/wp-content/uploads/2022/06/Lungecancer_-aarsrapport-2021offentlig.pdf

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02.09.22

DBS, SNI

Forhandlingsnotat

Dato for behandling i Medicinrådet	28.09.2022
Leverandør	Amgen
Lægemiddel	Lumykras (sotorasib)
Ansøgt indikation	Andenlinjebehandling af uhelbredelig ikke-småcellet lungekræft med KRAS G12C-mutation

Forhandlingsresultat

Amgros har opnået følgende betinget pris på Lumykras (sotorasib):

Tabel 1: Forhandlingsresultat

Lægemiddel	Styrke	Pakningsstørrelse	AIP	Nuværende SAIP	Forhandlet SAIP	Rabatprocent ift. AIP
Lumykras (sotorasib)	120 mg/stk	240 stk.	57.464,13	57.464,13	[redacted]	[redacted]

Amgros har indgået en aftale på Lumykras (sotorasib). Aftalen er **betinget** af medicinrådets anbefaling. Aftalen vil løbe i 4 år og kan starte d. 29. september 2022. Anbefaler Medicinrådet ikke Lumykras (sotorasib) indkøbes lægemidlet til AIP.

Informationer fra forhandlingen

[redacted]

[redacted]

Konkurrencesituationen

Der er ingen andre lægemidler godkendt til denne indikation med KRAS mutation.

Tabel 2: Sammenligning af lægemiddelpriser

Lægemiddel	Styrke/dosis	Pakningsstørrelse	Pakningspris SAIP	Antal pakninger/år	Årlig lægemiddelpris SAIP pr. år
Lumykras (sotorasib)	120 mg/stk *960 mg én gang dagligt (8 stk)*	240 stk.	[redacted]	12,18	[redacted]
Docetaxel (Kabi)	80 mg/4 ml *75 mg/m^2 dag ét i cykler på 21 dage*	4 ml	[redacted]	29,51	[redacted]

*Ved gennemsnitligt BSA på 1,81 m^2

Status fra andre lande

Norge: Dokumentation indsendt men metodevurdering er ikke påbegyndt[1]
Sverige: Vurderes ikke til brug på hospitaler[2]
England: Godkendt til brug gennem Cancer Drug Fund (managed entry agreement) hvor yderligere dataopsamling foretages[3]

Konklusion

Det er Amgros' vurdering, at der er opnået den størst mulige rabat, som leverandøren kan give på nuværende tidspunkt.

[1] https://nyemetoder.no/metoder/sotorasib-lumykras
[2] https://janusinfo.se/nationelltinforandeavlakemedel/beslutomsamverkansniva/lakemedelsominteomfattasavnationellsamverkan.4.11b119de1639e38ca5f33bb.html
[3] https://www.nice.org.uk/guidance/ta781/chapter/1-Recommendations

Application for the assessment of sotorasib for previously treated KRAS G12C-mutated, advanced or metastatic non-small cell lung cancer (NSCLC)

Version 9.0

DK-510-1221-00003

[redacted]

Table of contents

1. Basic information

Contact information	
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Overview of the pharmaceutical	
Proprietary name	LUMYKRAS
Generic name	Sotorasib
Marketing authorization holder in Denmark	Amgen Denmark
ATC code	L01XX73
Pharmacotherapeutic group	KRAS *G12C* inhibitor
Active substance(s)	Sotorasib
Pharmaceutical form(s)	Tablets for oral use
Mechanism of action	Sotorasib is an inhibitor of KRAS G12C, a tumor-restricted, mutant-oncogenic form of the RAS GTPase, KRAS. Sotorasib forms an irreversible, covalent bond with the unique cysteine of KRAS G12C, locking the protein in an inactive state that prevents downstream oncogenic signaling and inhibits cell growth.
Dosage regimen	Sotorasib is administered orally at a dose of 960mg (8 x 120mg tablets) once daily until disease progression or unacceptable toxicity.
Therapeutic indication relevant for assessment (as defined by the European Medicines Agency, EMA)	LUMYKRAS (sotorasib) as monotherapy is indicated for the treatment of adults with advanced non-small cell lung cancer (NSCLC) with KRAS G12C mutation and who have progressed after at least one prior line of systemic therapy.
Other approved therapeutic indications	None

Overview of the pharmaceutical	
Will dispensing be restricted to hospitals?	Yes
Combination therapy and/or co-medication	No
Packaging – types, sizes/number of units, and concentrations	Pack of 240 tabs of 120mg.
Orphan drug designation	No

2. Abbreviations

Abbreviation term	Definition
1L	First-line
2L	Second-line
2L+	Second-line and beyond
3L	Third-line
4L	Fourth-line
AE	Adverse event
AIC	Akaike information criterion
AJCC	American Joint Committee on Cancer
ALK	Anaplastic lymphoma kinase
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
ATT	Average treatment effect of the treated
BIC	Bayesian information criterion
BRAF	B-Raf proto-oncogene
CI	Confidence interval
Consort	Consolidated Standards of Reporting Trials
CR	Complete response
CRD	Centre for Reviews and Dissemination
CT	Computed tomography
CTCAE	Common Terminology Criteria for Adverse Events
DLCR	Danish Lung Cancer Registry
DLCG	Danish Lung Cancer Group
DMC	Danish Medicines Council
DOR	Duration of response
DRG	Diagnosis related groups
DSU	Decision support unit

ECOG	Eastern Cooperative Oncology Group
EGFR	Epidermal growth factor receptor
EMA	European Medicines Agency
EORTC	European Organisation for Research and Treatment of Cancer
EPAR	European Public Assessment Report
EQ-5D	EuroQol - 5 Dimension
EQ-5D-5L	EuroQol - 5 Dimension – 5 Level
ESS	Effective sample size
FAS	Full analysis set
FDA	Food and Drug Administration
GTPases	Guanosine triphosphatases
HR	Hazard ratio
HRQoL	Health-related quality of life
HSUV	Health state utility values
ICER	Incremental cost-effectiveness ratio
ICI	Immune checkpoint inhibitor
ILD	Interstitial lung disease
IQR	Interquartile range
ITT	Intention to treat
IV	Intravenous
KM	Kaplan-Meier
KRAS	Kirsten rat sarcoma viral oncogene homolog
LOT	Line of therapy
LUAD	Lung adenocarcinoma
MAIC	Matching-adjusted indirect comparison
MCID	Minimal clinically important difference
MET	Mesenchymal epithelial transition gene
MMRM	Mixed model with repeated measures

NCCN	National Comprehensive Cancer Network®
NE	Not evaluable
NICE	National Institute for Health and Care Excellence (UK)
NSCLC	Non-small cell lung cancer
NTRK1	Neurotrophic receptor tyrosine kinase 1 gene
ORR	Objective response rate
OS	Overall survival
PD-1	Programmed death cell protein-1
PD-L1	Programmed death-ligand 1
PET-CT	Positron emission tomography- computed tomography
PFS	Progression-free survival
PR	Partial response
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
PS	Performance status
PSA	Probabilistic sensitivity analysis
QALY	Quality-adjusted life-year
RCT	Randomized controlled trial
RECIST	Response Evaluation Criteria in Solid Tumors
RET	Rearranged during transfection
ROS1	C-ros oncogene 1
SD	Stable disease
SEER	Surveillance, Epidemiology, and End Results
SLR	Systematic literature review
SmPC	Summary of Product Characteristics
TNM	Tumor-Node-Metastasis
TRAE	Treatment-related adverse events
TTD	Time to treatment discontinuation
TTNT	Time to next treatment

TTP	Time to progression
UK	United Kingdom
WT	Wild-type

3. Tables and figures

3.1 Tables of tables

3.2 Table of figures

4. Summary

This single technology assessment investigates the clinical value of sotorasib (Lumykras™) compared to the relevant current treatment used in Denmark for adult patients with advanced non-small cell lung cancer (NSCLC) with KRAS G12C mutation who have progressed after at least one prior line of systemic therapy.

There are several approved treatments targeting specific driver mutations in NSCLC that have improved patient survival significantly compared with non-targeted treatments for patients with an actionable mutation(1). However, currently, no approved treatment is available that specifically targets the KRAS G12C driver mutation in NSCLC.

Standard of care treatment for KRAS G12C mutated NSCLC is currently the same as for patients with non-targetable mutations. This includes PD-(L)1 inhibitors (with or without platinum chemotherapy) for first-line (1L) treatment of advanced NSCLC. Nearly all patients progress on these treatments and receive limited benefit from SOC cytotoxic chemotherapy treatments in subsequent lines of therapy. Most patients experience a decline in performance status during 1L therapy that limits their tolerance for and the effect of second line and beyond (2L+) chemotherapy. Therefore, this patient group (KRAS G12C NSCLC) has a particularly high unmet need for effective and tolerable therapies, that can improve survival outcomes without compromising health-related quality of life (HRQoL) including toxicity.

Population

The population of interest for this application is advanced NSCLC patients with *KRAS G12C* mutation who have received prior systemic therapy, in line with the EMA label of sotorasib. In Denmark, all patients diagnosed with NSCLC benefit from next-generation sequencing (NGS) diagnostics, which include genetic identification of the KRAS G12C mutation. The NSCLC population of interest will therefore already be identified in Denmark with the current SOC testing in all five regions of Denmark.

Based on registry data and clinical expert validation, approximately 110-140 NSCLC patients with KRAS G12C mutation are expected to be eligible for 2L treatment with sotorasib every year(2-5).

Intervention

Sotorasib is a novel, first-in-class, highly selective small-molecule inhibitor that covalently binds to KRAS proteins harboring a G12C mutation. The Committee for Medicinal Products for Human Use (CHMP) has adopted a positive opinion, recommending the granting of a marketing authorization for sotorasib as for treatment of adult patients with advanced non-small cell lung cancer (NSCLC) with KRAS G12C mutation who have progressed after at least one prior line of systemic therapy.

Sotorasib is administrated orally and the recommended dose for adult patients is 960 mg (8x 120 mg tablets) once daily, at the same time each day. At the prescriber's discretion, treatment with sotorasib should be administered until disease progression or unacceptable toxicity.

Comparator

Other than sotorasib, no therapies exist specifically have received positive opinion by the CHMP for the treatment of KRAS G12C-mutated NSCLC. Doxetaxel is currently the standard 2L treatment for the majority of patients with advanced NSCLC in the current clinical treatment guideline from Danish Lung Cancer Group (DLCG)(6). Hence, docetaxel is the relevant comparator for NSCLC patients considered in this submission (2L+ KRAS G12C). The recommended dose of docetaxel is 75 mg/m2, administered as a one-hour infusion every three weeks. Treatment continuation is based on an individual assessment of clinical tolerability and efficacy in consideration of adverse events, which may prompt either dose reduction or complete treatment discontinuation.

Clinical comparison

The CodeBreak 100 phase 2, single-arm trial provides the relevant efficacy and safety data for sotorasib in patients with KRAS G12C-mutated NSCLC. Evidence from CodeBreak 100 indicates that sotorasib is highly effective when used in line with its indication as a second- or subsequent-line therapy. Median progression-free survival (PFS) was 6.8 months, and median overall survival (OS) was 12.5 months in the trial.

There is a lack of head-to-head trial data specifically considering KRAS G12C-mutated NSCLC. However, indirect treatment comparisons using robust data sources and methods provide plausible early evidence of clinically meaningful improvements in survival outcomes for patients treated with sotorasib compared with the current standard of care, non-targeted therapy. For Docetaxel, the SELECT-1 trial was identified as the data basis in KRAS G12C-mutated NSCLC 2L patients. Median PFS [redacted] and median OS was [redacted] OS in SELECT-1 for docetaxel monotherapy.

The clinical value of sotorasib compared to docetaxel is best demonstrated by the critical outcome measures PFS and OS. The results from the matching-adjusted indirect comparison (MAIC) for PFS, demonstrate that sotorasib provides [redacted] gain in median PFS compared with docetaxel monotherapy ([redacted] This exceeds the minimal clinically important difference of 3 months in median PFS(7) set by the Danish Medicines Council (DMC). For OS, the MAIC indicates that sotorasib provides a [redacted] gain in median OS compared with the primary comparator docetaxel monotherapy ([redacted]. This exceeds the minimal clinically important difference of 3 months in median OS(7) set by DMC.

Safety outcomes were compared narratively and were limited by the fact that exposure times in the available evidence were not comparable between the sotorasib and docetaxel. The median duration of treatment was 5.5 months for sotorasib and 2.4 months for docetaxel. Sotorasib presented a lower occurrence of grade 3 or worse treatment-related adverse events (TRAE) (20% vs 30%) and a lower numerical rate of treatment discontinuations due to AEs (9% vs 14.5%). Patients with NSCLC generally report high symptomatic burden and impaired physical function and quality of life(8, 9). Health-related quality of life was investigated in CodeBreak 100 using the EORTC QLQ-C30 measure. Patients treated with sotorasib generally sustained or improved compared with baseline. Sotorasib is expected to be safer and more tolerable compared to docetaxel, aligning with the clinical expectation of safety of a targeted therapy compared to chemotherapies.

In conclusion, sotorasib can address the significant unmet need for a targeted, more effective, tolerable, and convenient treatment that improves clinical outcomes for patients with *KRAS G12C*-mutated NSCLC compared to the current standard chemotherapy option.

Health economic model

A cohort-based partitioned survival model was developed in Microsoft Excel® to evaluate the cost-effectiveness of sotorasib vs. docetaxel from a Danish restrictive societal perspective over a lifetime horizon (20 years).

Clinical efficacy and safety data for sotorasib were taken from the CodeBreak 100 study. Relative efficacy of sotorasib vs. docetaxel was estimated using a MAIC which used data from the SELECT-1 study.

Health outcomes are expressed in terms of life-years and quality-adjusted life years (QALYs). Health state utility values were calculated from EQ-5D-5L data collected in CodeBreak 100 and valued using Danish EQ-5D-5L tariffs.

Cost estimates are presented as aggregated total costs, direct costs included drug costs (acquisition, administration and management of adverse events, subsequent therapy), disease management and gene-mutation testing costs. Costs and outcomes were discounted at 3.5% per annum. Both deterministic and probabilistic analyses were performed.

In the model, the monthly drug cost of sotorasib is estimated to be [redacted] per month, and the monthly drug cost of docetaxel is estimated to be 333 DKK per month.

Outcome of health economic evaluation

In the base-case where docetaxel is considered the comparator, the discounted incremental total life year gain of sotorasib versus docetaxel was [redacted] years. The discounted incremental costs of [redacted] and incremental QALYs of [redacted] resulted in an incremental cost-effectiveness ratio (ICER) of [redacted] versus docetaxel. This would be cost-effective at a willingness-to-pay threshold of DKK 750,000 per QALY.

The deterministic sensitivity analysis demonstrated that the five parameters which had the largest influence on the ICER were: (i) the hazard ratio (HR) to derive sotorasib time to treatment discontinuation; (ii) the administration cost of docetaxel; (iii) the relative dose intensity of sotorasib; (iv) the health state utility of progression-free; and (v) the hazard ratio to derive docetaxel time to treatment discontinuation.

Results of the probabilistic sensitivity analysis (PSA) are consistent with the base-case results. The PSA modelled a [redacted] probability that sotorasib is cost-effective vs. docetaxel at the given threshold of DKK 750,000 per QALY.

The estimated budget impact of recommending sotorasib as standard treatment in Denmark is calculated to be DKK [redacted] in year 1 and DKK [redacted] in year 5, when assumed 125 new patients eligible for treatment with sotorasib each year.

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

5.1 The medical condition and patient population

5.1.1 Disease information

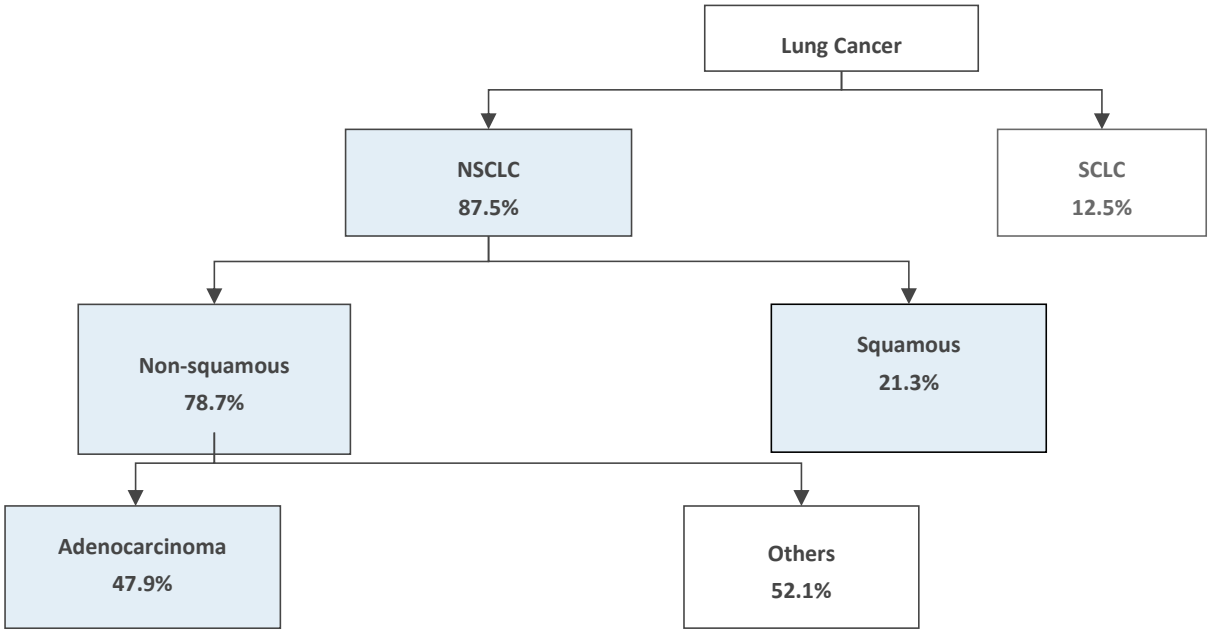
Lung cancer is a histopathologically and molecularly heterogeneous group of tumors that arise from abnormal and uncontrolled cell growth in the respiratory epithelium (bronchi, bronchioles, and alveoli). Lung tumors differ widely in terms of growth rates and response to treatment (10-12). However, metastatic lung cancer is almost uniformly and rapidly fatal (10). Therefore, early diagnosis and treatment are essential to improve the prognosis of patients with lung cancer.

While the survival of lung cancer patients has been steadily increasing the last half decade, likely due to introduction of immunotherapy and targeted therapies for managing advanced NSCLC in Denmark(4), lung cancer still remains the leading cause of cancer mortality in Denmark, representing 21.9% of cancer related death for males and 23.5% for females between 2015 and 2019(13). Data from the Danish Lung Cancer registry showed that the observed 2-year survival for patients on palliative treatment was 23.2%, an increase of 10% from 2014 (12.7%). While the observed 5-year survival for patients on palliative treatment was 4% for the latest cohort.

In 2020, 4876 patients were diagnosed with lung cancer in Denmark(4). NSCLC accounts for approximately 87.5% of lung cancer cases in Denmark(4) and comprises several histological subtypes, which can be categorized into squamous and non-squamous. Approximately 79% of NSCLC is non-squamous, adenocarcinomas (~ 48%) (4), represents the most common subtype of NSCLC in Denmark.

Adenocarcinomas develop from the mucus-producing cells of smaller airways along the periphery (outer edges) of the lung (14, 15). Although adenocarcinomas mostly occur in current or former smokers, they are also the most common type of lung cancer in people who have never smoked (15). The remainder of the non-squamous NSCLC tumors are rare subtypes and non-small cell carcinoma and other specified carcinomas (52.1%)(4). Brain metastases are found in approximately 10% of patients with newly diagnosed NSCLC and 26% of patients with stage IV disease (16). Other common sites of metastases include the liver, adrenal glands, and bones. The distribution of types of lung cancer by histology in Denmark is shown in Figure 1.

Figure 1. Distribution of Types of Lung Cancer by Histology in Denmark (Classified by Shape and Size of Cancer Cells) (4)



5.1.2 Molecular alterations

NSCLC tumors are characterized by a high degree of molecular heterogeneity (17, 18), of which adenocarcinoma is considered to be the most genetically heterogeneous and aggressive subtype (19). Lung adenocarcinomas also have a very high tumor mutation burden (~ 8.9 somatic mutations per megabase) (20-22), and more than 50% of lung adenocarcinomas have at least 1 genetic mutation, rearrangement, fusion, and/or amplification that is known to initiate and drive tumor growth (23).

The introduction of genomic testing and drug therapies targeting specific driver mutations represent major breakthroughs in the treatment of NSCLC (24). Currently, targeted therapies are approved by EMA for NSCLC tumors with alterations in anaplastic lymphoma kinase (*ALK*), B-Raf proto-oncogene (*BRAF*), epidermal growth factor receptor (*EGFR*), mesenchymal-epithelial transition gene (*MET*), rearranged during transfection (*RET*), c-ros oncogene 1 (*ROS1*), and neurotrophic receptor tyrosine kinase 1 (*NTRK1*) genes (25). Comprehensive molecular testing at NSCLC diagnosis is recommended to optimize the use of tissue for testing and to inform treatment selection for metastatic disease in Denmark(2, 3). The timely identification of patients who are candidates for targeted therapies and administration of appropriate therapy has been shown to improve clinical outcomes in NSCLC (1, 26-28). However, oncogenic driver mutations still remain for which no targeted therapy has been successfully developed. These include KRAS mutations, of which the most frequently occurring in NSCLC is the KRAS G12C mutation (29).

5.1.2.1 KRAS G12C mutation in NSCLC

KRAS genes encode proteins located in the cellular membrane which are important for intercellular signal transduction, and are found in active/inactive states depending on their binding with guanosine tri/diphosphate (GTP/GDP) (30). Mutations in *KRAS* genes can disrupt the processes involved in the proliferation and survival of tumor cells. Of the *KRAS* mutations, an estimated 80% occur at codon 12. The *KRAS* gene with a mutation resulting in a G12C amino acid substitution (*KRAS G12C* mutation) in codon 12 is a single guanine to thymine substitution that results in a glycine to cysteine substitution at amino acid position 12. This structural change in the protein results in a defect in the association of GTPase-activating proteins (GAPs), which reduces the normal hydrolysis of GTP by GTPases, and resulting in the accumulation of KRAS proteins in the 'active' state. The resulting accumulation of active, GTP-bound KRAS proteins disrupts the process of apoptosis and promotes tumor proliferation and survival (31). The *KRAS G12C* mutation is therefore an oncogenic driver and *KRAS*

mutations are generally acknowledged as negative prognostic factors for both treatment response and survival outcomes in patients with NSCLC, as well as other solid tumors (32, 33).

5.1.3 Diagnosis and staging

Lung cancer is diagnosed based on physical examination, presenting symptoms, medical history, and imaging (e.g., chest radiograph, computed tomography [CT]/positron emission tomography [PET]-CT scan). If lung cancer is suspected, a tissue biopsy is obtained to make the pathological diagnosis, identify the histological subtype, and confirm the stage of the disease (34). The stage at diagnosis helps inform treatment decisions, predicts prognosis, and determines eligibility for inclusion in clinical trials (35). In Denmark, all patients diagnosed with NSCLC undergo NGS-testing as part of the diagnostic trail to identify relevant targetable mutations including (EGFR, ERBB2, BRAF, ROS1/ALK, RET, KRAS). As part of this NGS panel, KRAS G12C can be identified in the SOC diagnostic trail. (2, 3, 36).

In this dossier, the term “advanced NSCLC” is used to describe the locally advanced and unresectable or metastatic disease.

5.1.4 Clinical presentation

NSCLC is often asymptomatic until the disease is advanced, making early diagnosis challenging (37). A diagnosis is generally not made until the tumor begins to obstruct the airway, resulting in dyspnea (shortness of breath), atelectasis (partial/complete lung collapse), pneumonia, bleeding from the airway mucosa, or pain due to pleural effusion (build-up of fluid and cancer cells between the chest wall and lungs) (38). Approximately two-thirds of patients with NSCLC have advanced disease at diagnosis (39), when curative treatment is not possible. Advanced NSCLC is highly symptomatic, with most patients experiencing symptoms related to the location and size of the tumor, such as shortness of breath, cough, and pain, as well as constitutional symptoms, such as fatigue (40, 41). These symptoms significantly impair quality of life by interfering with daily activities, relationships, life plans, treatment adherence, and mood (41-48).

5.1.4.1 Prognosis of KRAS G12C-mutated NSCLC

At present, no targeted therapy is available for patients with *KRAS G12C*-mutated NSCLC. Treatment options are limited for 2L+, and outcomes are suboptimal following progression with 1L treatment including an immune checkpoint inhibitor (ICI) with or without platinum-based chemotherapy (24, 49).

5.1.4.1.1 Prognosis of KRAS G12C-mutated NSCLC in Denmark

Real-world Data from Danish national registries indicate that patients with advanced *KRAS G12C*-mutated NSCLC have generally similar clinical characteristics in terms of age, smoking history, and similar poor survival outcomes as other NSCLC patients (5).

In this retrospective data analysis of incident advanced NSCLC patients captured through the Danish national registries, including the Danish Lung Cancer Registry (DLCR), was conducted to describe incidence, molecular biomarkers, and treatment patterns with survival outcomes in patients diagnosed with advanced NSCLC(5). Data on patients were collected between 1 January 2018 and 31 December 2020 and analyzed according to the predefined statistical analysis plan and protocol (50, 51). This period of times was chosen as NGS testing including KRASG12C was first initiated systematically around the beginning of 2018. Baseline characteristics of patients with the KRAS G12C mutation are reported in Table 1. The analysis found that survival outcomes with existing treatments were poor for all advanced NSCLC patients including KRAS G12C mutated NSCLC.

Median OS outcomes for the full population of advanced NSCLC ([redacted]) were observed to be [redacted] months from the start of a first-line treatment, while median OS outcomes for patient population with the KRAS G12C mutation ([redacted]) appeared to be slightly longer, at [redacted] months from the start of the first-line treatment. For the overall advanced NSCLC population, survival outcomes appear to decrease with each line of treatment. Outcomes of this analysis

indicate that survival outcomes with KRAS G12C-mutated NSCLC are poor, consistent with those of the overall population of advanced NSCLC (52-57).

Table 1. Baseline characteristics at start 1L of therapy (unless otherwise stated) of patients with the KRAS G12C mutation (Danish registry analysis)

Baseline characteristics	Danish KRAS G12C patients
Age at start of 1L, 2L, 3L systemic treatment (mean)	[redacted]
Brain metastases (%)	[redacted]
ECOG PS0, PS1, PS<2	[redacted]
Gender (% female)	[redacted]
Metastatic disease stage at baseline (% IIIB [vs IV])	[redacted]
Smoking history (% yes)	[redacted]

Key: ECOG, Eastern cooperative oncology group; PS, performance status. Note:
Note: [1], age at start of 1L systemic treatment; [2], age at start of 2L systemic treatment; [3], age at start of 3L systemic treatment; *Data is missing for <5 patients; [x], data missing for 11%.

Table 2. Overall survival by line of therapy in patients with a*dvanced NSCLC* (Danish registry analysis)

Analysis Set	N	N with event	Median OS, Months (95% CI)	6-month OS, % (95% CI)	12-month OS, % (95% CI)
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Key: 1L, first-line; 2L second-line; 3L, third-line; 4L, fourth-line; NSCLC, non-small cell lung cancer; OS, overall survival.
Source: Data on file (5)

Table 3. Overall survival by line of therapy in patients with *KRAS G12C mutation* (Danish registry analysis)

Analysis Set	N	N with event	Median OS, Months (95% CI)	6-month OS, % (95% CI)	12-month OS, % (95% CI)
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]			
[redacted]	[redacted]	[redacted]			

Key: 1L, first-line; 2L second-line; 3L, third-line; 4L, fourth-line; NE, not evaluable; NSCLC, non-small cell lung cancer; OS, overall survival
Source: Data on file (5)

5.1.5 Epidemiology

In Denmark, according to the annual report from the Danish Lung Cancer Registry (DLCR) from 2020, the incidence of advanced-stage non-squamous NSCLC patients eligible for 1L treatment was 1623 patients(4). Based on a register study in the capital region, the *KRAS G12C* mutation occurred in [redacted] of non-squamous NSCLC patients (Data on file(5)). This equates to 292 *KRAS G12C-mutated* NSCLC cases in Denmark in 2020. The estimated incidence of the *KRAS G12C* mutation is similar to the incidence suggested by two Danish clinical experts within NSCLC(2, 3). The two clinical experts suggested an annual incidence of 250-300 KRAS G12C mutations eligible for 1L treatment. Based on clinical validation, approximately 50% of the patients reach 2L treatment each year. This equates to approximately 140 potential incident patients per year in Denmark.

Furthermore, it was reported in the DLCR report that up to 26% of patients that started 1L treatment in 2020 was treated with curatively intended treatment this reduces the estimate to approximately 110 patients per year in Denmark (4). To accommodate annual variation and uncertainty around the estimate, a range of 110-140 eligible patients is assumed for 2L treatment with sotorasib in Denmark every year (see Table 4).

Table 4. Estimated number of patients eligible for target population

Year	2022	2023	2024	2025	2026
Number of incident patients in Denmark who are expected to use the pharmaceutical in the coming years	110-140	110-140	110-140	110-140	110-140

5.1.6 Patient populations relevant for this application

Sotorasib (LUMYKRAS^{TM}) is the first KRAS G12C inhibitor to be submitted for marketing authorization. It is a once-daily oral therapy that is licensed by the European Medicines Agency (EMA) "*as monotherapy is indicated for the treatment of adults with advanced non-small cell lung cancer (NSCLC) with KRAS G12C mutation and who have progressed after at least one prior line of systemic therapy*." Sotorasib will provide treatment for NSCLC patients who have received prior systemic therapy including platinum-based chemotherapy and/or immunotherapy. NSCLC patients' progression following either chemotherapy or immunotherapy leaves limited options for subsequent treatment.

The population of interest for this submission is advanced NSCLC patients with *KRAS G12C* mutation who have received prior systemic therapy, in line with the EMA label of sotorasib.

5.2 Current treatment options and choice of comparator(s)

5.2.1 Current treatment options

Tumor-targeted therapy is the cornerstone of treatment for patients with advanced NSCLC with molecular alterations in *EGFR*, *ALK*, *BRAF*, *ROS*, and *RET proteins*. However, the *KRAS G12C* mutation rarely occurs at the same time as these other actionable mutations, meaning that existing tumor-targeted therapies are not an option for patients with KRAS G12C mutation (58-61). Patients with *KRAS G12C*-mutated NSCLC are therefore managed in the same way as those without an actionable mutation.

In line with the current treatment guidelines from the DLCG (6), clinical experts (2, 3) confirmed that an increasing majority of patients in Denmark with NSCLC without currently actionable mutations now receive anti-PD-1/PD-L1 immunotherapy in combination with platinum-based chemotherapy or as monotherapy in the first-line of therapy.

Clinical experts confirmed that sotorasib would be used as an alternative to docetaxel monotherapy following recurring disease after frontline therapy with immunotherapy and/or platinum-based chemotherapy(2, 3). The proposed positioning of sotorasib, in line with its licensed indication, is therefore as a second or subsequent line therapy following prior treatment with platinum-based chemotherapy and/or anti-PD-1/PD-L1 immunotherapy.

This positioning is aligned with the pivotal clinical trial data supporting the conditional EU regulatory approval (CodeBreak 100) and confirms that the relevant comparator for sotorasib is docetaxel monotherapy. Further, as docetaxel monotherapy is recognized in the DOLG guideline as the second- and subsequent-line option in NSCLC, docetaxel is deemed the appropriate comparator for this appraisal (6).

Docetaxel has not been approved as standard treatment for NSCLC by the DMC and according to the DMC guidelines if this is the case companies should develop CUA that estimates the cost-effectiveness of the chosen comparator against either placebo or BSC. This has not been developed as there are no clinical data enabling a CUA between docetaxel and placebo/BSC for the relevant patient population. Furthermore, we consider docetaxel to be the most relevant and cost-effective comparator. In current clinical practice, the majority of patients in 2nd line who are candidates for treatment will be offered treatment with docetaxel.

We find it very unlikely that patients will be offered an inferior treatment, such as placebo or BSC, in that docetaxel is both a cheap treatment regimen with demonstrated efficacy and is an established treatment in current Danish and international clinical practice. This is also supported by the fact that in the recent assessment of selpercatinib for non-small cell lung cancer, the Medicine Council concluded that active treatment, including docetaxel, was the appropriate comparator to address the decision issue.

We find it very likely that docetaxel will be a cost-effective alternative in a comparison with either placebo or BSC. As mentioned above, recent changes in frontline treatment means platinum-based chemotherapy is now a relevant treatment alternative for patients with PD-L1>50% in 2L that has been given checkpoint inhibitor monotherapy in 1L.

Amgen is not aware of specific clinical trials investigating the efficacy of platinum chemotherapy as a 2.L treatment for the relevant patient population after first-line immunotherapy, and therefore it has not been possible to include platinum-based chemotherapy as a comparator arm in an appropriate manner in the application.

As there is no relevant data for platinum-based chemotherapy to address the decision question, we have consulted a clinical expert and validated that Docetaxel is also a relevant comparator across PD-L1>50% levels for NSCLC as a chemoalternative. Docetaxel is also referred to in the DMCG clinical guidelines for the treatment of 2L NSCLC.

We expect that the cost-effectiveness of sotorasib versus platinum-based chemotherapy will be equal to the cost-effectiveness versus docetaxel, since these are low-cost treatment regimens, both of which have a very limited clinical efficacy. The expected incremental costs as well as effects for sotorasib versus platinum-based chemotherapy as well as docetaxel are therefore assumed to be comparable. The best alternative to assessing cost-effectiveness versus platinum-based chemotherapy is to use data from the Flatiron database (Appendix L - Flatiron). These data are based on a basket of chemotherapy regimens, including platinum-based chemotherapy which is the most common regime in the basket (Table 60).

This analysis was performed as a confirmatory analysis to validate the primary MAIC analysis of sotorasib versus docetaxel monotherapy using a basket of chemotherapies as a source to represent docetaxel. However, given that the most common chemoregimen in the basket of chemotherapy regimens in the Flatiron dataset was platinum-based chemotherapy the analysis also represent a pragmatic approach to show that the result of sotorasib versus platinum-based chemo does not differ significantly from the comparison of sotorasib vs docetaxel.

The analysis using the Flatiron chemobasket as a comparator was included as a scenario analysis. The dataset for the comparator arm can be changed in the CE model.

5.2.2 Choice of comparator(s)

As described in section 5.2.1, docetaxel have been deemed the appropriate comparator for this appraisal based on clinical guidelines by DLCG(6) and validation by two Danish clinical experts(2, 3).

5.2.3 Description of the comparator (docetaxel)

The recommended dose of docetaxel for adult patients is an initial dose of 75 mg/m2 as a one-hour intravenous infusion every three weeks. Treatment is continued based on an individual assessment of clinical tolerability and efficacy in consideration of several adverse events, which may prompt either dose reduction or complete treatment discontinuation.

Table 5. Description of docetaxel monotherapy

Subject	Description
Generic name (ATC-code)	Docetaxel (L01CD02)
Mode of action	Antineoplastic agent which acts by promoting the assembly of tubulin into stable microtubules and inhibits their disassembly which leads to a marked decrease of free tubulin. As microtubules do not disassemble in the presence of docetaxel, they accumulate inside the cell and cause the initiation of apoptosis.
Pharmaceutical form	Concentrate and solvent for solution for infusion.
Posology	Docetaxel is administered as a one-hour infusion every three weeks. Docetaxel is given at 75 mg/m2 in monotherapy.
Method of administration	Docetaxel is given as an I.V infusion.
Should the pharmaceutical be administered with other medicines	Premedication consisting of an oral corticosteroid, such as dexamethasone 16 mg per day (e.g., 8 mg BID) for 3 days starting 1 day prior to docetaxel administration, unless contraindicated, can be used. Prophylactic G-CSF may be used to mitigate the risk of hematological toxicities as per SmPC.
Treatment duration / Criteria for end of treatment:	Treat until disease progression or unacceptable toxicity.
Necessary monitoring, both during administration and during the treatment period	Hematological assessment of e.g. leukocytes, thrombocytes, and liver function throughout treatment. In patients who experienced either febrile neutropenia, grade 3 or 4 stomatitis, neutrophil count < 500 cells/mm^3 for more than one week, severe or cumulative cutaneous reactions or severe peripheral neuropathy during docetaxel therapy, the dose of docetaxel should be reduced from 75 to 60 mg/m^2 for all subsequent cycles. If the patient continues to experience these reactions at 60 mg/m^2, the treatment should be discontinued.
Need for diagnostic or other tests	No diagnostic tests are required. Regular monitoring of blood chemistry abnormalities.

5.3 The intervention

Sotorasib (LUMYKRAS™) is the first KRAS G12C inhibitor submitted for marketing authorization. It is a once-daily oral therapy that is licensed by the EMA "*as monotherapy is indicated for the treatment of adults with advanced non-small cell lung cancer (NSCLC) with KRAS G12C mutation and who have progressed after at least one prior line of systemic therapy.*"

Current 2L treatment options are very limited. Patients who are eligible for further treatment in 2L or subsequent-line therapy receive docetaxel as also described in the clinical guideline by the DLCG (6). Sotorasib, is therefore expected to displace docetaxel in 2L treatment.

Sotorasib is an inhibitor of the KRAS G12C-mutated protein. It forms an irreversible covalent bond highly-specifically with the unique cysteine of KRAS G12C, locking the protein in an inactive state that inhibits downstream signaling, inhibits cell growth, and promotes apoptosis in *KRAS G12C* tumor cell lines (62). No other wild-type or mutant protein or receptor has been identified to which sotorasib binds, nor has any effect been observed in cells without the *KRAS G12C* mutation. As the *KRAS G12C* mutation only has been found in tumor tissues, and not in normal tissue (63, 64), sotorasib has the potential to be highly tolerable compared with standard of care chemotherapy.

As an inhibitor of KRAS G12C, the presence of a KRAS G12C mutation must be confirmed using a validated test prior to initiation of therapy with sotorasib. In Denmark, KRAS testing is part of regional standards for NGS panels used as part of the diagnosis of NSCLC patients. Therefore, no additional tests beyond the routine diagnostic workup and management of patients with NSCLC are required alongside the introduction of sotorasib. This has been confirmed by two Danish clinical experts(2, 3).

With clinical evidence indicating meaningful improvements in PFS and OS, sotorasib is highly innovative and provides a step-change in therapy for patients with *KRAS G12C*-mutated NSCLC who currently have no targeted therapy options available. A summary of sotorasib is provided in Table 6 and further details can be found in **Appendix C - Baseline characteristics of patients in studies used for the comparative analysis of efficacy and safety**.

Table 6. Description of sotorasib (LUMYKRAS™)

Subject	Description
Generic name (ATC-code)	Sotorasib (L01XX73)
Mode of action	Selective KRAS G12C inhibitor, which covalently and irreversibly binds to the unique cysteine of KRAS G12C. Inactivation of KRAS G12C by sotorasib blocks tumor cell signaling and survival, inhibits cell growth, and promotes apoptosis selectively in tumors harboring KRAS G12C, an oncogenic driver of tumorigenesis across multiple cancer types.
Pharmaceutical form	Immediate release, film-coated tablet.
Posology	Sotorasib is administered orally at a dose of 960mg (8 x 120mg tablets) once daily until disease progression or unacceptable toxicity.
Method of administration	Oral tablets
Should the pharmaceutical be administered with other medicines	No
Treatment duration / Criteria for end of treatment:	Treat until disease progression or unacceptable toxicity. Dose reductions as per SmPC.

Necessary monitoring, both during administration and during the treatment period	Monitor liver function tests (ALT, AST, and total bilirubin) prior to the start every 3 weeks for the first 3 months of treatment, then once a month or as clinically indicated. Monitor patients for new or worsening pulmonary symptoms indicative of Interstitial Lung Disease /pneumonitis
Need for diagnostic or other tests	The presence of a *KRAS* G12C mutation must be confirmed using a validated test prior to initiation of sotorasib therapy.

6. Literature search and identification of efficacy and safety studies

6.1 Identification and selection of relevant studies

A detailed description of the literature search is provided in **Appendix A - Literature search for efficacy and safety of intervention and comparator(s).** In summary, a global systemic literature review (SLR) was used as the evidence base for this submission, and was locally adapted to fit the scope of the assessment in Denmark. This approach is deemed feasible as the global SLR was broader and will therefore have included all studies relevant for the scope of this application.

The local adaptation was conducted to restrict the literature included in the global SLR to studies with either sotorasib or docetaxel in adult patients with KRAS G12C-mutated advanced or metastatic NSCLC treated in 2L+. The local adaptation only included comparator studies with sufficient sample size and reporting to allow for a MAIC, which was necessary as the primary evidence for sotorasib was a single-arm trial. These selection criteria were applied to the studies as they reflect the EMA-indication and proposed scope of the application for sotorasib for KRAS G12C-mutated NSCLC in Denmark.

In brief, an SLR was commissioned to identify RCTs that report clinical effectiveness and safety of 2L therapies licensed in the United States and the EU. As mentioned above, the initial scope of the global SLR was broader and included more interventions than relevant for the single technology assessment of sotorasib in Denmark. Randomized controlled trials (phase II-IV) of adults (≥18 years) with locally advanced and unresectable or metastatic (stage IIIB-IV) NSCLC who had received at least one prior systemic therapy were eligible for inclusion. Outcomes of interest include OS, PFS, event-free survival (65), time to progression (TTP), time to next treatment (TTNT), response rates, disease control rate, treatment duration, and adverse events. Studies were identified by searching electronic databases, reference lists of relevant articles, conference proceedings, and other supplementary sources.

The SLR conformed to published guidelines issued by the Cochrane Collaboration (1) and the Centre for Reviews & Dissemination (CRD; York, UK) and followed the methodological requirements of the National Institute for Health and Care Excellence (NICE), UK. Reporting was in line with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) (66), and the Consolidated Standards of Reporting Trials (CONSORT) and statements (66-70). The SLR search was initially conducted in June 2020, and an updated search was conducted on 26 January 2021.

Details of the search strategies used are presented in **Appendix A - Literature search for efficacy and safety of intervention and comparator(s)**. Searches were conducted in Embase, Medline, and The Cochrane Central Register of Controlled Trials (CENTRAL), for the original and updated searches.

A total of 61 references were included in the global SLR for safety and efficacy (both RCT and single-arm studies).

Based on the references included at the full-text level for the global SLR, Amgen made a local adaptation to the Danish context using the detailed PICOS-criteria described in **Appendix A - Literature search for efficacy and safety of intervention and comparator(s),** which included a total of two references from two studies. Studies in

the full-text screening from the global SLR with docetaxel as the comparator were excluded, which either 1) had too small a study population, 2) did not include the correct population, or 3) held insufficient information to conduct a MAIC analysis. Only the SELECT-1 study was deemed feasible to conduct a MAIC and is consequently the only study used to derive comparative efficacy estimates.

Additional sources of evidence have been added to support the application, as some results were not reported in the primary publications of the studies(71).

A full PRISMA diagram outlining the selection process in the global SLR and local adaption is given in **Appendix A - Literature search for efficacy and safety of intervention and comparator(s)**.

6.2 List of relevant studies

For full detailed information on study characteristics of the included studies, please consult **Appendix B - Main characteristics of included studies**.

Table 7. Relevant studies included in the assessment

Reference (title, author, journal, year)	Trial name	NCT number	Dates of study (start and expected completion date)
Sotorasib for Lung Cancers with KRAS p.G12C Mutation. F. Skoulidis, et Al. N Engl J Med. 2021. 384(25):2371-81.	CodeBreak 100	NCT03600883	27.08.2018 – 28.12.2025
Selumetinib Plus Docetaxel Compared with Docetaxel Alone and Progression-Free Survival in Patients With KRAS-Mutant Advanced Non–Small Cell Lung Cancer - The SELECT-1 Randomized Clinical Trial. Pasi A. Jänne, et al. JAMA. 2017;317(18):1844-1853.	SELECT-1	NCT01933932	25.09.2013 – 31.12.2021

7. Efficacy and safety

The clinical trial (CodeBreak 100) conducted for sotorasib is a single-arm study whereas SELECT-1 for docetaxel includes two study arms: placebo plus docetaxel, and selumetinib plus docetaxel.

In the absence of head-to-head studies, the two studies CodeBreak 100 and SELECT-1 examining the efficacy and safety of sotorasib, and docetaxel are presented in section 7.1.2**.**

In section 7.2, an indirect treatment comparison of the relative efficacy is performed of sotorasib and docetaxel using an unanchored MAIC. Safety outcomes were compared narratively in section 7.2.2, as exposure times were not comparable between sotorasib and docetaxel.

7.1 Efficacy and safety of sotorasib versus docetaxel in previously treated adults (2L or subsequent-line) with KRAS G12C-mutated NSCLC

7.1.1 Relevant studies

Two relevant clinical studies (72, 73) were identified for the assessment which reflect the expected clinical practice in Denmark where sotorasib is expected to be used in 2L or as subsequent-line in adult patients with KRAS G12C-mutated NSCLC, who previously failed 1L therapy.

CodeBreak 100 (73) is an open-label, multi-national, single-arm, phase II study evaluating the clinical efficacy, safety, and tolerability in adult subjects with locally advanced or metastatic KRAS G12C-mutated NSCLC who are

candidates to 2L or a subsequent-line of therapy. All patients were required to have experienced disease progression after the receipt of anti–PD-1 or anti–PD-L1 immunotherapy or platinum-based combination chemotherapy or after the receipt of both immunotherapy and platinum-based combination chemotherapy. Study design and baseline characteristics of the study population are respectively presented in Table 11 and Table 12.

SELECT-1 (72) was identified as the appropriate study to be used as the comparator study, where patients receive docetaxel. SELECT-1 is a multi-national, randomized, phase III study evaluating the clinical efficacy of selumetinib in combination with docetaxel as second-line therapy for advanced *KRAS*-mutant NSCLC. SELECT-1 included placebo plus docetaxel as a comparator arm, this comparator arm will form the data basis for the clinical evidence of docetaxel in this appraisal. All patients were required to have radiological documentation of disease progression following 1L or subsequent anti-cancer therapy. Study design and baseline characteristics of the study population are respectively presented in Table 11 and Table 12.

The study designs might affect the comparison of outcomes as CodeBreak 100 is an open-label single-arm study and SELECT-1 is a randomized placebo-controlled study. Further, CodeBreak 100 include patients with prior anti-PD-1 treatment, whereas there were no patients with prior PD-1 treatment included in SELECT-1. Although CodeBreak 100 included patients with 1-3 prior therapies, restricting matches to only patients with 1 prior therapy, as were included in SELECT-1, would reduce the available CodeBreak 100 trial population by 57%, which would have significant implications for the precision of any relative treatment effect estimates. The inability to robustly match for number of prior lines of therapy or prior use of immunotherapy is a potential limitation that arises due to limited comparator trial data specifically in KRAS-mutant NSCLC. However, PFS and OS outcomes are likely to be worse for patients with each successive line of therapy. Given that CodeBreak 100 included 57% of patients with 2 or more prior lines of therapy, a comparison of PFS and OS data from the whole of the CodeBreak 100 NSCLC population against PFS and OS data from patients in SELECT-1, who had received only one prior line of therapy, is likely to be conservative. This assumption is further validated as subgroup analysis from CodeBreak 100 showed median OS in patients that received only 1 prior line of therapy was 17.7 months (7.9, NE) (Amgen data on file)

Table 8 patient subgroups by prior lines of therapy (Amgen data on file)

Patient subgroups	N (OS)	mOS months (95% CI)
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]

For further assessment of comparability between the studies please consult the MAIC feasibility in **Appendix K - MAIC**.

7.1.2 Efficacy and safety – results per study

7.1.2.1 CodeBreak 100 study

In Table 9, relevant study outcomes are presented based on the data from March 2021 data cut for all outcomes except for the outcome EORTC QLQ-C30, which were based on the September 2020 data cut. The detailed results for both study arms in CodeBreak 100 are presented in **Appendix D - Efficacy and safety results per study**.

Table 9. CodeBreak 100 results

Outcome	Study arm	N	Result	Reference

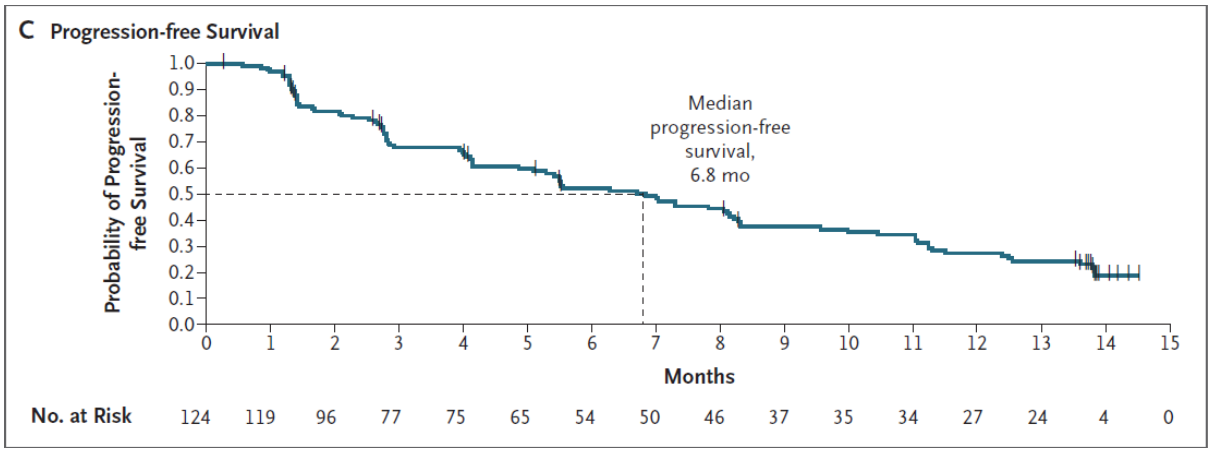
Median PFS (CI)	Sotorasib	126	6.8 months (5.1-8.2 months)	(73)
Median OS (CI)	Sotorasib	126	12.5 months (10.0-NE months)	(73)
Treatment discontinuations due to TRAEs - n (%)	Sotorasib	126	9 (7.1%)	(73)
TRAEs grade 3+ - n (%)	Sotorasib	126	26 (20.6%)	(73)
Treatment discontinuations due to AEs - n (%)	Sotorasib	126	11(8.7%)	(73)
AEs grade 3+ n (%)	Sotorasib	126	77 (61%)	(73)
EORTC QLQ-C30 – mean change from baseline (SD)	Sotorasib	[redacted]	[redacted]	(71)

Key: PFS, progression-free survival; OS, overall survival; EORTC QLQ-C30, European Organization for Research and Treatment of Cancer Quality of Life Questionnaire, TRAE, treatment-related adverse event. Study outcomes are presented based on the data from March 2021 data cut for all outcomes except for the outcome EORTC QLQ-C30, which was based on the September 2020 data cut.

Median progression-free survival (PFS)

Median PFS was assessed according to RECIST, version 1.1 both by independent central review and by an investigator. Below graphs are plotted from analysis of data from independent central review. As of the data cut-off date, the median PFS was 6.8 (95% CI 5.1-8.2) months (Figure 2). The Kaplan-Meier estimate of survival was 52.2% (95% CI 42.6-60.9) at 6 months and 16.3% (95% CI 7.4-28.2) at 12 months. Seventy patients (56.5%) had experienced disease progression and 13 (10.5%) death events. A total of 41 patients (33.1%) were censored, and of those, 25 (20.2%) were on study without disease progression 7 (5.6%) started new anticancer therapy, 5 (4.0%) missed more than 1 consecutive assessment, and 3 (2.4%) withdrew consent (71).

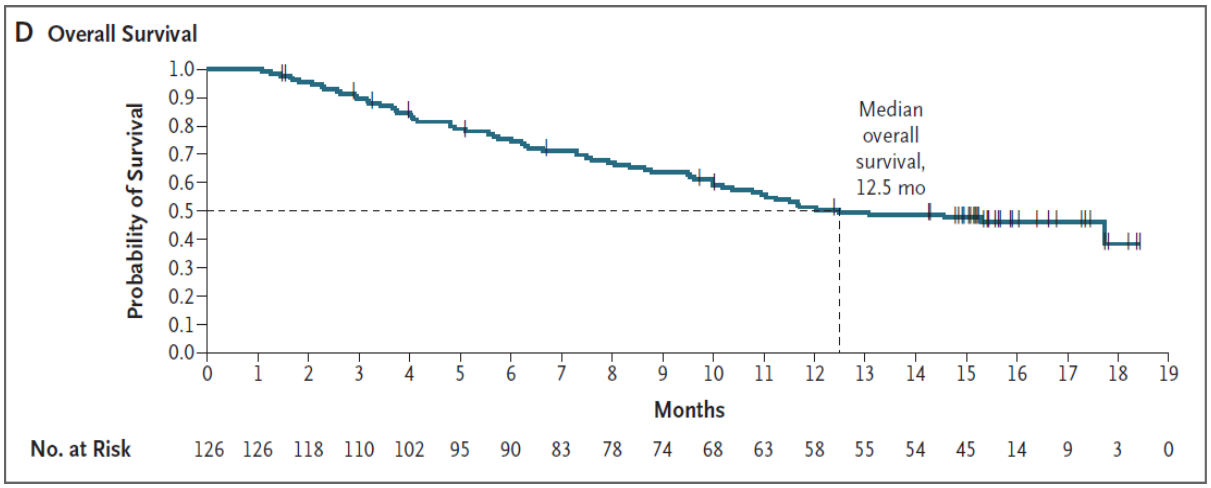
Figure 2. Median PFS for patients receiving sotorasib.



Median overall survival (OS)

OS is defined as the time from the date of randomization until death due to any cause. Median OS was 12.5 (95% CI 10.0-NE) months (Figure 3). The Kaplan Meier estimate of survival was 75.5% (95% CI 66.8-82.2) at 6 months and 51.4% (95% CI 41.9-60.1) at 12 months. As of the data cut-off date, 59 (46.8%) patients had died. A total of 67 patients (53.2%) were censored, and of those, 56 (44.4%) were alive at the last follow-up and 9 (7.1%) withdrew consent (71).

Figure 3. Median OS for patients receiving sotorasib.



Description of the safety profile

Treatment-related adverse events (TREAs) were reported for a total of 88 patients (69.8%). TRAEs of grade 3 was observed in 25 patients (19.8%) and of grade 4 observed in 1 patient (0.8%; pneumonitis and dyspnea), and no TRAEs of grade 5 were reported (73). The most frequent TRAEs were diarrhea in 40 patients (31.7%), nausea in 24 (19.0%), increase in the alanine aminotransferase level in 19 (15.1%), increase in the aspartate aminotransferase level in 19 (15.1%), and fatigue in 14 (11.1%) patients. TRAEs led to dose modification (dose interruption, reduction, or both) in 28 patients (22.2%) and discontinuation of sotorasib in 9 (7.1%) patients.

Health-related quality of life (HRQoL)

HRQoL was assessed using the EORTC QLQ-C30 measure in the CodeBreak 100 study. At baseline, subjects had a high symptomatic burden for EORTC QLQ-C30. Over time, mean global health status/QoL scores were generally sustained or improved compared with baseline, with mean change (for cycles 2 to 13 where there were > 5 patients) ranging from 1.9 (cycle 3) to -5.3 (cycle 11) (see **Error! Reference source not found.**). Results were similar for the other domain scores, e.g., physical functioning, role functioning, emotional functioning, and cognitive functioning. Changes from baseline were slightly greater for the domain of social functioning with a mean change from baseline ranging from 4.9 (cycle 2) to 11.1 (cycle 7).

The mean change from baseline to the end of the treatment phase was increased for all domains; -11.20 for global health status/QoL, -8.75 for physical functioning, -13.54 for role functioning, -5.21 for emotional functioning, -8.85 for cognitive functioning and -9.90 for social functioning.

See **Error! Reference source not found.** for a Summary table of QLQ-C30 Functional scales and Global health status/QOL change over time

[redacted]

[redacted]There are currently no known estimates of what constitutes a meaningful within-subject change in EORTC QLQ-C30 scores within a population of subjects with KRAS p.G12C-mutated NSCLC. However, a study exploring within-group change in physical function and global health status among patients with NSCLC, exist (Maringwa JT, Quinten C, King M, et al; EORTC PROBE project and the Lung Cancer Group. Minimal important differences for interpreting health-related quality of life scores from the EORTC QLQ-C30 in lung cancer patients participating in randomized controlled trials. Support Care Cancer. 2011;19(11):1753-1760.)

Based on this study, approximate thresholds for meaningful improvement and worsening on key scales are as follows:

- Physical functioning: improvement 5 (range 5 to 9), worsening 4 (range 4 to 6) (Maringwa et al, 2011)

- Global health status/QoL: improvement 4 (range 4 to 9), worsening 4 (range 4 to 6) (Maringwa et al, 2011)

Normative values for the EORTC QLQ-C30 scores are available, representing scores assessed among the general population (Nolte et al, 2019) and in a sample of patients with NSCLC (Scott et al, 2008). These can be used as a frame of reference to determine the extent of symptomatic burden experienced by subjects at baseline in this study, and is especially useful in single-arm studies. Reference mean scores for a general population (based on 11 countries from the European Union weighted by national age/sex distributions) on key scales are:

- Physical functioning (85.1),
- Global health status/QoL (66.1).

Reference mean scores for a NSCLC population (N 1 262, primarily Stage III-IV) on key scales are:

- Physical functioning (78.4)
- Global health status/QoL (58.8).

7.1.2.2 SELECT-1 study

In Table 10, relevant study outcomes are presented, based on the data cut-off in June 2016 (72). Only results for placebo plus docetaxel study arm are presented in the table, as the other study arm is not of interest for this assessment and the indirect comparison, which uses an unanchored MAIC due to the single-arm design of CodeBreak 100. The detailed results for both study arms in SELECT-1 are presented in **Appendix D - Efficacy and safety results per study**.

Table 10. SELECT-1 results

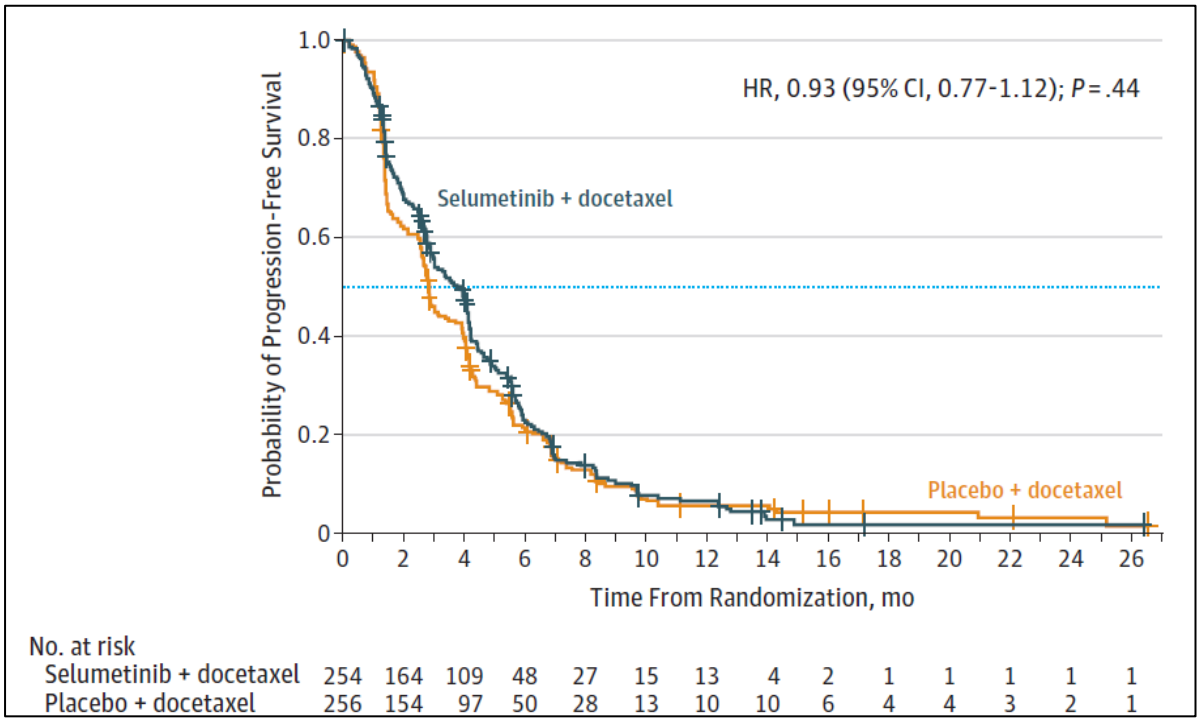
Outcome	Study arm	N	Result (IQR)	References
Median PFS	Placebo + Docetaxel	256	2.8 (1.4-5.5) months	(72)
Median OS	Placebo + Docetaxel	256	7.9 (3.8-20.1) months	(72)
Treatment discontinuations due to AEs (%)	Placebo + Docetaxel	256	37 (14.5%)	(72)
AEs grade 3+ (%)	Placebo + Docetaxel	256	115 (45.0%)	(72)
EORTC QLQ-C30	NA	NA	NA	NA

Key: NA, not available; OS, overall survival; PFS, progression-free survival; TRAE, treatment-related adverse event. Data cut-off in June 2016 for all outcomes.

Median progression-free survival (PFS)

Median PFS was assessed according to RECIST, version 1.1. As of the data cut-off date (June 7, 2016), the median PFS for patients receiving placebo plus docetaxel was 2.8 (IQR, 1.4-5.5) months (Figure 4) (72).

Figure 4. Median PFS for patients receiving placebo plus docetaxel (patients of interest for treatment comparison) and selumetinib plus docetaxel.

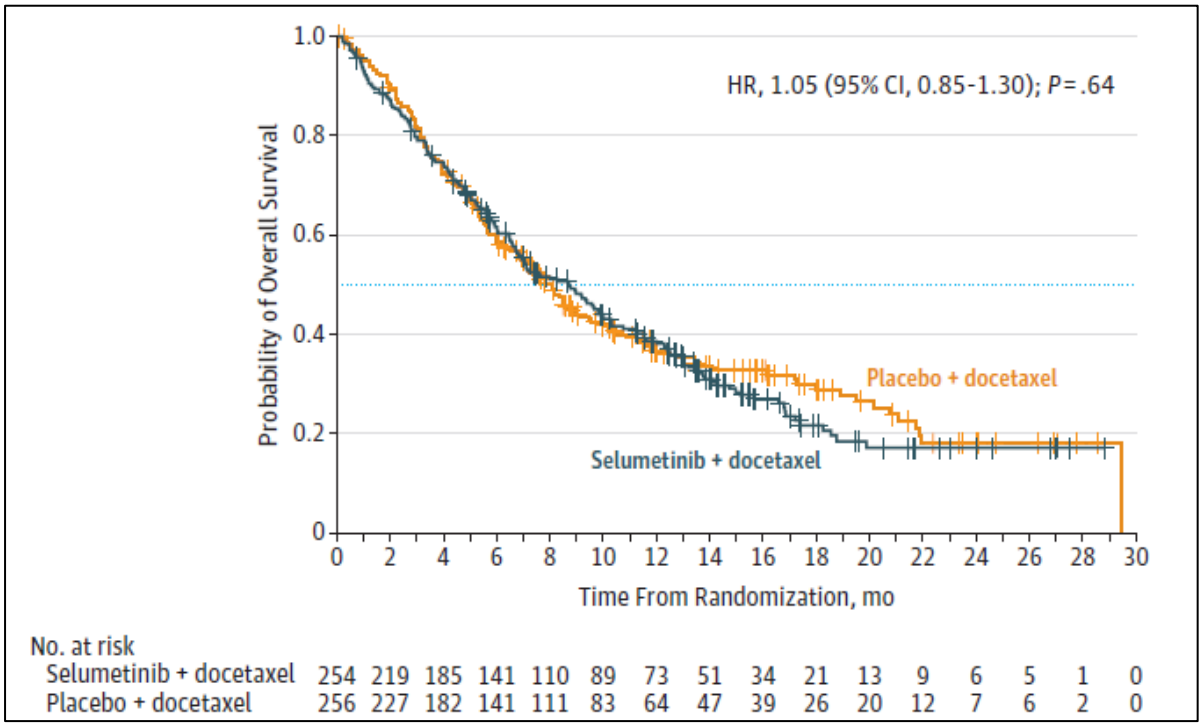


Key: HR, Hazard ratio; The dotted line indicates median survival.

Median overall survival (OS)

As of the data cut-off date (June 7, 2016), the median OS was 7.9 months (Interquartile range, 3.8-20.1) for patients receiving placebo plus docetaxel, corresponding to 170 events (Figure 5).

Figure 5. Median OS for patients receiving placebo + docetaxel (patients of interest for treatment comparison) and selumetinib plus docetaxel.



Key: HR, Hazard ratio; IQR, Interquartile range. The dotted line indicates median survival.

Description of the safety profile

Most patients experienced at least 1 adverse event. For patients receiving placebo plus docetaxel, the most frequent AEs, affecting 10% or more patients were diarrhea (89 events, 35%), fatigue (79 events, 31%), alopecia (64 events, 25%), and nausea (62 events, 24%). The most frequent adverse events reported as CTCAE grade 3 or higher were anemia (11 events, 4%), fatigue (10 events, 4%), neutropenia (10 events, 4%), and (7 events, 3%). 76 patients (30%) had adverse events leading to hospitalization (72). A total of 115 events (45%) grade 3 or higher adverse events were reported for patients receiving docetaxel as monotherapy.

Of the patients treated with docetaxel, 32% had serious AEs (grade ≥3) causally related to the randomized treatment. In total, 76 patients (30%) had adverse events leading to hospitalization (72).

Dose reductions of docetaxel were required in 25 patients (10%) and docetaxel dose delays were required in 55 patients (22%). Discontinuation of docetaxel due to adverse events was observed in 37 patients (15%) (72).

Health-related quality of life (HRQoL)

EORTC QLQ-C30 HRQoL outcomes were not investigated in SELECT-1 and therefore, no results are reported for HRQoL of patients treated with placebo plus docetaxel. No other instruments were used to measure HRQoL in SELECT-1 comparable to the patient's HRQoL in CodeBreak 100.

7.2 Comparative analyses of efficacy and safety

As CodeBreak 100 is a single-arm clinical trial, no direct head-to-head evidence was available to compare the clinical efficacy of sotorasib and docetaxel. Instead, the relative efficacy of two treatments can often be estimated using indirect treatment comparisons for OS and PFS. In this analysis, the relative efficacy was assessed using an unanchored MAIC, a method that allows assessment of efficacy benefit between treatments when a common comparator is missing by adjusting for population-level differences present in different data sources (74).

The MAIC used data from two clinical studies: the CodeBreak 100 trial for sotorasib and the SELECT-1 trial for docetaxel. Comparability of the data sources, and hence the feasibility and appropriateness of performing a MAIC, was assessed through a review of the design and population profiles of the studies involved in the analyses. The MAIC for OS and PFS is presented in section 7.2.1. Details of the comparison of studies, populations, and methods used in the studies are presented in **Appendix K - MAIC**.

As for the safety outcomes of interest, no MAIC analysis has been conducted, and data is therefore presented narratively in section 7.2.2. A comparison of HRQoL was not feasible as the relevant data was not available and SELECT-1 used a different patient reported outcomes-tool for the docetaxel arm. However, HRQoL results have been reported for sotorasib from CodeBreak 100 in section 7.1.2.1.

7.2.1 MAIC for OS and PFS

7.2.1.1 MAIC overview

Data for sotorasib are derived from CodeBreak 100 study (75). CodeBreak 100 is an open-label Phase II study which evaluated the safety, tolerability, and clinical efficacy of sotorasib in (n = 126) subjects with NSCLC with *KRAS G12C* mutation.

Docetaxel is a current standard of care for this patient group in Denmark and was therefore chosen as the comparator. A comparison of the CodeBreak 100 and SELECT-1 studies is presented in Table 11. A feasibility analysis is presented in **Appendix K - MAIC**.

Both CodeBreak 100 and SELECT-1 were multicenter studies and had similar inclusion and exclusion criteria, which included subjects with confirmed locally advanced or metastatic NSCLC (stage IIIB – IV) who had failed one prior line of therapy (LOT). The enrolled population in the CodeBreak 100 study is slightly wider than that of SELECT-1, as patients who have failed two (35%) or three (21%) prior LOTs were also included

Patient-level baseline characteristics and outcomes data for NSCLC patients treated with sotorasib were taken from the CodeBreaK 100 trial (March 2021 data cut). Data on docetaxel-treated patients was taken from the SELECT-1 Phase 3 RCT of patients randomized to selumetinib plus docetaxel or docetaxel plus placebo (Janne et al, 2017). As patient-level data was not available for docetaxel, baseline patient characteristics and Kaplan–Meier PFS and OS curves were digitized and pseudo-patient-level data were created using the algorithm of Guyot et al. (Guyot P. et al, 2012).

CodeBreak 100 and SELECT-1 reported PFS and OS as primary or secondary endpoints. In SELECT-1, PFS was measured by RECIST 1.1 every 6 weeks by the investigator. In CodeBreak 100, PFS was also measured by RECIST 1.1 every 6 weeks for the first 8 assessments, and every 12 weeks subsequently. PFS was assessed by both independent central review and by an investigator. The latter (investigator-based PFS) was used in the base-case of the MAIC analyses, as it is aligned with the progression assessment reported in the SELECT-1 trial.

CodeBreak 100 is a single-arm Phase II study, whereas SELECT-1 is a randomized placebo-controlled phase III study. These differences in the trial design may confound the outcomes; this potential issue is not adjusted for in the MAIC.

Table 11. Overview of CodeBreak 100 and SELECT-1 study designs

Element	Sotorasib (CodeBreak 100)	Docetaxel (SELECT-1)
Blinding	Open label	Double-blinded
Inclusion criteria	Male or female patients (> 18 years) Histologically confirmed locally advanced or metastatic NSCLC	Male or female patients (> 18 years) Histologically confirmed locally advanced or metastatic NSCLC WHO Performance Status 0 – 1

	Confirmed KRASG12C mutation as assessed by central testing of tumor biopsies	Confirmed KRAS mutant tumor as assessed by central testing
Exclusion criteria	Active brain metastases from non-brain tumors Anti-tumor therapy including chemotherapy, antibody therapy, molecular targeted therapy, retinoid therapy within 28 days of study day 1	Symptomatic brain metastases or spinal cord compression. Patients with asymptomatic brain metastasis, or treated and stable off steroids and anticonvulsants for at least 1 month prior to entry into the study are eligible Mixed small cell and NSCLC histology Received >1 prior anti-cancer drug regimen for advanced or metastatic NSCLC Patients who develop disease progression while on switch maintenance therapy (Maintenance using an agent, not in the first-line regimen) will not be eligible Prior treatment with a MEK inhibitor or any docetaxel-containing regimen (prior treatment with paclitaxel is acceptable)

Key: MEK, mitogen activated protein kinase; NSCLC, non-small cell lung cancer; WHO, World Health Organization.

The analysis was conducted to achieve a scientifically accurate MAIC while balancing precision against the absence of bias. Adjusting for all available variables would have resulted in a small bias, but also in a very low precision, with stochastic uncertainty causing results to be imprecise and inaccurate. Therefore, the number of variables adjustment for was restricted, keeping the variables that are most likely to remove bias. Variables that were considered less important in terms of bias, but would still increase stochastic uncertainty, were considered for removal. Variables identified as relevant prognostic variables were included for the base-case analysis. These are the variables that were identified as very important or somewhat important from the elicitation process.

7.2.1.2 Population characteristics

The comparison of baseline characteristics in the CodeBreak 100 and SELECT-1 studies is presented in Table 12. The distribution of patients between the two studies is similar in terms of age, with median ages of 63 and 61 years reported, respectively. Gender distribution is balanced in CodeBreak 100 and is slightly skewed towards males in the SELECT-1 study. Approximately 82% of subjects are white in CodeBreak 100, with comparable estimates higher in SELECT-1 (where 95% of patients are white).

Adjustment for brain metastases was not possible as they were not reported for SELECT-1.

KRAS G12C mutation status could not be used for the adjustment, as all CodeBreak 100 patients were *KRAS G12C* patients, and for the docetaxel arm in SELECT-1, there was no patient-level data available. CodeBreak 100 includes patients with prior anti-PD-(L)1 treatment, whereas SELECT-1 patients did not. This difference is accounted for as anti-PD-(L)1 therapies were not yet approved for treatment when SELECT-1 was conducted. Adjusting for anti PD-(L)1 treatment in prior lines would result in the removal of 91% of CodeBreak 100 patients and was therefore unfeasible.

For prior lines of therapy, 57% of patients included in CodeBreak 100 had 2 or more prior line of therapy, while all patients in SELECT-1 only received one prior line of therapy. Adjusting for prior line of therapy would results in a loss of 43% of patients in CodeBreak 100, a substantial loss in effective sample size, and therefore not feasible. The effect estimates for sotorasib are therefore likely to be conservative as confirmed in subgroup analysis (data on file), as prior lines of therapy would be considered an important indicator of poor prognosis.

Table 12. Comparison of baseline characteristics in CodeBreak 100 and SELECT-1

Baseline characteristics [a]	Sotorasib (CodeBreak 100) N = 126	Docetaxel (SELECT-1) N = 256
Age (mean)	62.9	60.9
Gender (% female)	50%	43%
Brain metastases (%)	21%	NR[b]
ECOG (% PS 1 [vs PS 0])	70%	59%
Race (% white)	82%[c]	95%
% KRAS-G12C	100%	42%[d]
Anti-PD-(L)1 in prior line(s)	91%	0%
Number of prior lines (% with 1/2/3 prior lines)	43%/35%/22%	100%/0%/0%
Metastatic disease stage at baseline (% IIIB [vs IV])	97%	96%
Histology (% Non-squamous)	99%	95%
Smoking status (% ever smoker)	93%[e]	92%
Other targetable mutations (EGFR, ALK, BRAF, ROS-1)	3%	NR[f]
PD-L1 protein expression level (<5% [vs. ≥5%])	48%	58%

Key: ECOG, European Co-operative Oncology Group.
Note:
[a], all reported baseline characteristics in SELECT-1 and other key characteristics.
[b], not reported for SELECT-1. Both studies had exclusion criteria for active brain metastases.
[c], 15 percentage points of the 18% remaining correspond to Asian patients.
[d], the rest of the population has KRAS mutations other than G12C.
[e], 2 percentage points of the remaining 7% are missing data.
[f], probably very low due to KRAS mutant.

7.2.1.3 MAIC approach

A MAIC was applied to compare differences in OS and PFS between patients treated with sotorasib and docetaxel. Outcomes are reported in terms of HRs and corresponding 95% confidence interval (CI) for the different MAIC models. Parameter uncertainty was quantified based on robust standard errors.

The starting list of candidate prognostic covariates was based on literature reviews and informed by discussions with experienced NSCLC physicians in the UK. These discussions involved separate interviews with physicians experienced in treating advanced NSCLC patients who have a robust understanding of the current NSCLC treatment landscape. The literature was also reviewed to better understand what the most important confounding factors are (for prognosis), and to consider their inclusion in the matching algorithm/propensity score analysis. A total of six individual interviews were conducted via teleconferences with two physicians from Canada and one each from the US, Germany, France, and the UK. Pre-read documents (including a questionnaire) were circulated to the physicians; their corresponding responses and individual summary reports were shared with each of them for validation. Further details about the elicitation are provided in a supplementary document (76).

Five covariates were considered very important, and 13 were considered as somewhat important. Three additional prognostic covariates were added to the list based on their inclusion in recently conducted MAICs in treatment interventions in the NSCLC disease area, as noted by the expert clinicians (Amgen data on file 2020). Additional covariates related to race, ethnicity, and histology at baseline were also considered. These covariates had been included in previously reported MAICs conducted in NSCLC (77-79). Details of the identification of these studies are presented in the MAIC protocol (80). The covariates considered in the various MAIC analyses are presented in Table 13.

PD-L1 protein expression at baseline was excluded as it is only a relevant prognostic factor for anti-PD-(L)1 treatment. However, for treatment with sotorasib and docetaxel, based on clinical expert feedback PD-L1 protein expression was not regarded as an important predictor.

Table 13. Starting list of prognostic covariates

Category	Covariate
Very important	**Baseline ECOG (0, 1) ***
	Presence of brain metastases (Y, N)
	Metastatic at baseline (Y, N) *
	PD-L1 protein expression (<5%, >5%)
	Presence of at least one of the following mutations/alterations: EGFR, ALK, BRAF, ROS-1 (Y, N)
Somewhat important	**Age ***
	Smoking status (history of smoking vs. no history of smoking) *
	Body mass index
	Presence of liver metastases (Y, N)
	Presence of bone metastases (Y, N)
	Number of sites of metastasis (0, 1, 2, 3 or more)
	Number of prior lines of therapies (1, 2, 3)
	Type of therapies administered in prior lines
	Time from prior line initiation to the index date (<3 months, 3 - 6 months, >6 months)
	Albumin at baseline
	Serum LDH
	Liver function (ALT, AST) at baseline
	Renal function (EGFR) at baseline
Additional covariates reported in other MAIC	Sex (F; M)
	Race/Ethnicity (White; Others)
	Histology at baseline (non-squamous; squamous)

Key: ALT, alanine transaminase; AST, aspartate aminotransferase; BMI, body mass index; ECOG, Eastern Co-operative Oncology Group; eGFR, estimated glomerular filtration rate; LDH, lactic acid dehydrogenase.
Note: *, Covariates in bold were reported in the SELECT-1 trial and therefore potentially available for adjustment.

Table 14. Covariates used across different MAIC analyses

Covariates	All variables pre-specified as important (Set1)	All available variables (Set2)
ECOG (% PS 1 [vs PS 0])	X	X
Age (mean)	X	X
Metastatic disease stage at baseline (% IIIB [vs IV])	X	X
Smoking status (% ever smoker)	X	X
PD-L1 expression level		X
Gender (% female)		X
Histology (% Non-squamous)		X
Race (% white)		X

Key: ECOG, Eastern Co-operative Oncology Group; PS, performance status.

In the conduct of the MAIC analyses, all categorical data were converted into binary variables. These data adjustments were applied to smoking status, race, and PD-L1 expression level. The methods used to estimate weights in the MAIC are presented in **Appendix K - MAIC**.

7.2.1.4 MAIC Results

Survival data for docetaxel were generated by digitizing the KM plots in the SELECT-1 publication and reproducing pseudo-patient-level data using a published algorithm (Guyot et al, 2012). The reconstructed KM data were compared with the published results in SELECT-1 study for validation purposes—median OS [redacted]

The median values in the reconstructed data were very close to the reported data for PFS and slightly higher for the OS endpoint. Given this approximation for OS, these predicted median values are favorable to docetaxel, which would result in a conservative estimation of the relative efficacy of sotorasib versus docetaxel. Outcomes are reported in terms of HRs, with 95% CIs based on robust standard errors.

A comparison of the pre- and post-matching for covariates included in the base-case MAIC analysis is presented in Table 15. Baseline characteristics post-matching were well balanced, with perfect matching for the four covariates included in the MAIC, and a difference of less than 5 percentage points for all other comparable characteristics.

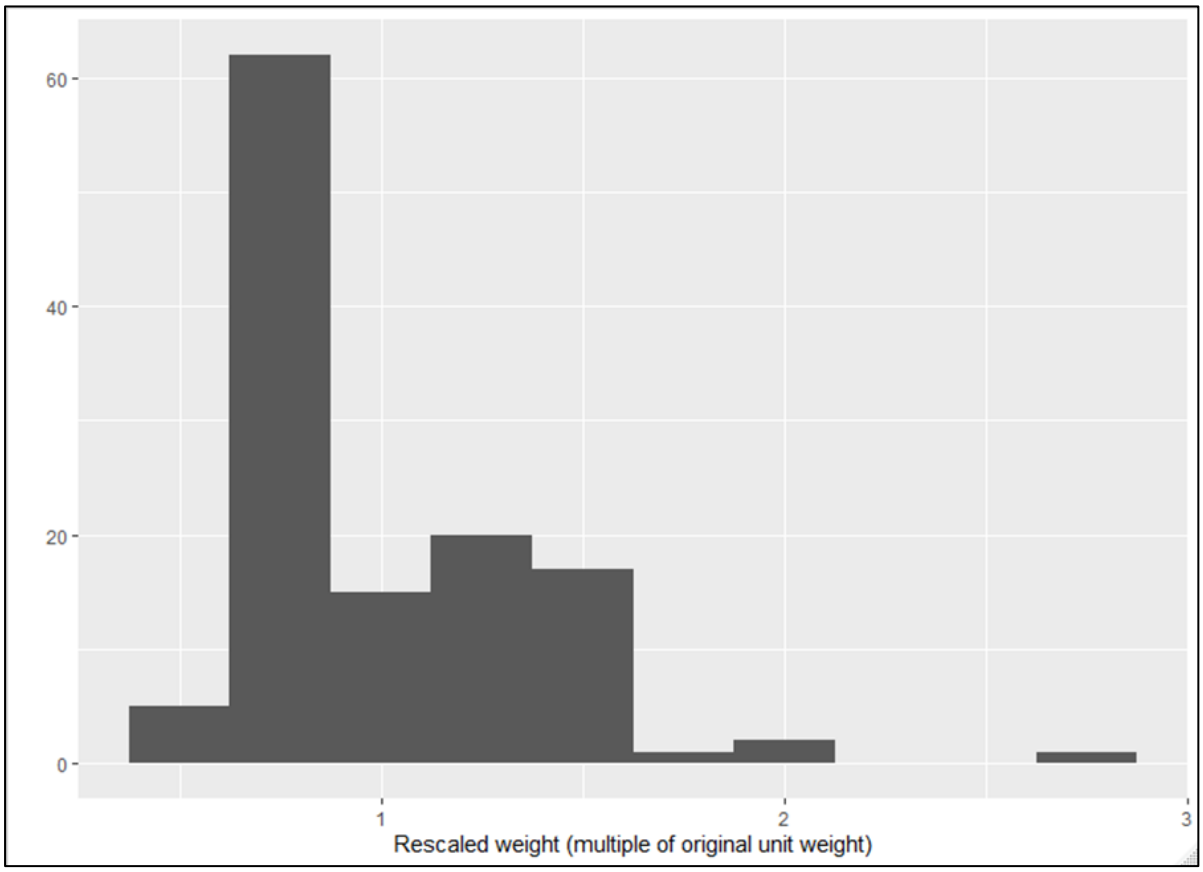
Table 15. Post-matching balanced baseline characteristics

	As reported For docetaxel	Pre-matching For sotorasib	Post-matching (Base-case) [a] For sotorasib
Covariates	**SELECT-1**	**CodeBreak 100**	**CodeBreak 100**
Age (mean)	60.9	62.9	60.9
ECOG (% PS 1 [vs PS 0])	59%	70%	59%
Metastatic disease stage at baseline (% IIIB [vs IV])	96%	96%	96%
Smoking status (% ever smoker)	92%	93% [b]	92%

Key: ECOG, European Co-operative Oncology Group; PD-(L1), programmed death-ligand 1; PS, performance status.
Note:
[a], when adjusting for four covariates
[b], 2 percentage points of the remaining 7% are missing data.

The distribution of statistical weights based on the balancing of four covariates is presented in Table 16. Application of these weights to the dataset caused the effective sample size to drop to 109; retaining more than 86% of the enrolled patients in the CodeBreak 100 study.

Table 16. Distribution of statistical weights of MAIC (adjusting for ECOG, age, metastatic at baseline and smoking status)



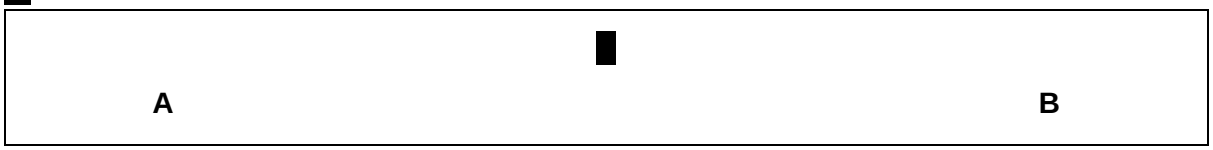
Key: ECOG, European Co-operative Oncology Group; MAIC, matching-adjusted indirect comparison.
Histogram, with the vertical axis representing the frequency.

Unanchored MAICs are associated with uncertainty, and compared to anchored MAICs, a higher risk of bias. However, the similarity of patient populations in the current case, the risk of bias is expected to be low. Furthermore, due to the highly pre-treated population of CodeBreak 100, the potentially remaining bias is expected to favor docetaxel. Therefore, the outcomes of the MAIC are expected to be conservative as previously mentioned. A summary of the strengths and limitations of the analysis is presented in **Appendix K - MAIC**. Two sets of included covariates were defined for MAIC analyses. SET 1 included all those variables pre-specified as important and SET 2 included all covariates available for adjustment. For the base-case MAIC analysis, SET 1 was used. The MAIC results for SET 2, explored in scenario analyses, are presented in **Appendix K - MAIC**.

7.2.1.4.1 OS curve

A plot comparing the MAIC-weighted KM OS curve for sotorasib (in blue) to the unadjusted docetaxel OS curve from SELECT-1 (in yellow) is shown in **Error! Reference source not found.**, panel A. The comparison of the unadjusted KM OS curve for sotorasib from CodeBreak 100 (in blue) to the unadjusted docetaxel OS curve from SELECT-1 (in yellow) is shown in **Error! Reference source not found.**, panel B. The MAIC-adjustment results in a slight improvement in survival of patients treated with sotorasib compared to the unadjusted results.

[redacted]



Key: KM, Kaplan-Meier; MAIC, matching-adjusted indirect comparison; OS, overall survival.
A: adjusted sotorasib curve, B: unadjusted sotorasib curve.
Note: Numbers at risk for adjusted KM is equivalent to sum of weights

7.2.1.4.2 PFS curve

Error! Reference source not found. panel A shows the base-case MAIC-weighted KM PFS curve for sotorasib (in blue) vs. the unadjusted KM PFS curve for docetaxel from SELECT-1 (in yellow). **Error! Reference source not found.** panel B shows the unadjusted KM PFS curve for sotorasib from CodeBreak 100 (in blue) vs. the unadjusted KM PFS curve for docetaxel from SELECT-1 (in yellow). For the PFS adjusted curves, the adjustment does not impact the relative survival, hence curves are similar between panel A and B in **Error! Reference source not found.**.

[redacted]

[redacted]

7.2.1.4.3 PFS and OS results

Two sets of covariates were selected for inclusion. The sets included (i) all covariates pre-specified as important (SET 1) and (ii) all covariates available for adjustment (SET 2).

Patients with missing values for included covariates were not adjusted for in the MAIC analyses; no imputation was performed. Within the different MAIC analyses, three patients with no smoking status and 28 patients with no PD-L1 expression level information were excluded from the analyses.

The results of unadjusted and adjusted HRs derived using the weighted Cox models fitted to the different MAIC-adjusted KM datasets are presented in **Error! Reference source not found.**. The results demonstrate a directional decrease in the HR point estimate for the OS endpoint. However, HR point estimates remained similar for the PFS endpoint. The base-case used SET 1, as the effective sample size of SET 2 was significantly smaller, which would have resulted in more uncertainty and less precision of the estimate.

[redacted]

[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

7.2.1.5 Conclusion on MAIC analysis – sotorasib vs. docetaxel

In a comparison using the most plausible indirect method possible given the data limitations (MAIC), sotorasib was statistically and clinically superior to docetaxel monotherapy for both PFS) and OS ( ). For PFS, matching adjustment indicated that sotorasib provided a -month gain in median PFS compared with the primary comparator docetaxel monotherapy, exceeding the minimal clinically important difference of 3-month median PFS, previously defined by the lung cancer expert committee at DMC(7). For OS, matching adjustment indicated that sotorasib provided a month gain in median OS compared with the primary comparator docetaxel monotherapy, exceeding the minimal clinically important difference of 3 months median OS, previously defined by the lung cancer expert committee at DMC(7). Corresponding Kaplan-Meier plots for OS are presented in **Error! Reference source not found.**, and in **Error! Reference source not found.** for PFS. The estimated hazard ratios for OS and PFS were similar between the unadjusted analysis and base-case MAIC analysis ( ). The primary MAIC analysis focused on available covariates of prognostic importance, and the matching preserved an effective sample size of over 106 patients. This represented a small loss of data compared with the pre-adjusted sample size. Sensitivity analysis, and the fact that the analyses could not be adjusted for the greater negative prognostic factors in the sotorasib trial population, suggest these estimates may be conservative.

Given the phase 2 single-arm trial data currently available in support of sotorasib, and the lack of data for the relevant comparators specifically in KRAS G12C-mutated NSCLC, every effort has been made to derive the most robust possible indirect estimates of relative efficacy for this innovative therapy. These analyses indicate that sotorasib is a highly effective therapy that plausibly provides clinically meaningful improvements in survival outcomes compared with current, non-targeted standard of care therapies (docetaxel). Sotorasib, therefore, provides a much-needed targeted treatment option in patients with KRAS G12C-mutated NSCLC.

7.2.2 Safety

A formal statistical comparison between the two studies on safety outcomes was deemed unfeasible due to differences in follow-up times and the study design, as this is grounds for high uncertainty in a comparison. Treatment discontinuations due to either adverse events or grade 3-5 adverse events more specifically, were not included in the MAIC. The safety comparison of these between sotorasib and docetaxel will therefore be narrative.

Grade 3-4 is not presented in this section, as it was not possible to conduct any narrative comparison to SELECT-1, where only grade 3+ have been reported. Please refer to **Table 43** for reporting of grade 3-4 adverse events for sotorasib from CodeBreak100.

7.2.2.1 Discontinuations due to adverse events

In Table 17, treatment discontinuation due to adverse events is presented for sotorasib and docetaxel. The median duration of treatment was 5.5 months (range: 0.2-17.8) for sotorasib (73), and 2.4 months (range: 0.1-27.4) for docetaxel (72) (approximately 2.4 months). The proportion of patients discontinuing treatment due to adverse events were lower for sotorasib (8.7%) and docetaxel (14.5%), docetaxel showed a higher discontinuation rate. The absolute difference between the median duration of treatment corresponds to approximately 3.1 months, which complicates the comparison of the two treatments. Nevertheless, as fewer patients discontinued treatment with sotorasib and the median duration of treatment was more than double compared to docetaxel, sotorasib reveals a better safety profile compared to docetaxel.

Table 17. Treatment discontinuation due to adverse events

Treatment	N	n (%)	Median duration of treatment	References
Sotorasib	126	11 (8.7%)	5.5 months (range: 0.2-17.8 months)	Skoulidis et al. 2021
Docetaxel	256	37 (14.5%)	2.4 months (range: 0.1-27.4 months)	Jänne et al. 2017.

7.2.2.2 Grade 3-5 treatment related adverse events

In Table 18, TRAEs are presented for sotorasib and docetaxel. All TRAEs are retrieved from the CodeBreak 100 study for sotorasib, and TRAEs were matched for docetaxel from SELECT-1 in Table 18, if possible. The available adverse events (diarrhea, nausea, fatigue, vomiting, dyspnea, and neutropenia) were higher for treatment with docetaxel compared to sotorasib. When comparing grade ≥3 TRAEs in the studies, patients who were treated with sotorasib had fewer TRAEs (20.6%) compared to patients who were treated with docetaxel (30%). As mentioned in section 7.2.2.1, the median duration of treatment was much longer for sotorasib (5.5 months) compared to docetaxel (approximately 2.4 months). Therefore, sotorasib is expected to be safer, as fewer TREAs events were observed, despite the duration of exposure being more than double as long, compared to docetaxel. This aligns with the clinical expectation of targeted therapies compared to chemotherapies.

Table 18. Treatment related adverse events

Adverse events	Sotorasib (CodeBreak-100)* n=126		Docetaxel + placebo (SELECT-1)** n=254	
	Any grade	Grade ≥3	Any Grade	Grade ≥3
Any TRAE	88 (69.8%)	26 (20.6%)	NR	76 (30.0%)
Diarrhea	40 (31.7)	5 (4.0)	64 (25)	6 (2)
Nausea	24 (19.0)	0	29 (11)	0
Alanine aminotransferase increase	19 (15.1)	8 (6.3)	NA	NA
Aspartate aminotransferase increase	19 (15.1)	7 (5.6)	NA	NA
Fatigue	14 (11.1)	0	43 (17)	4 (2)
Vomiting	10 (7.9)	0	17 (7)	1 (1)
Blood alkaline phosphatase increase	9 (7.1)	1 (0.8)	NA	NA
Maculopapular rash	7 (5.6)	0	NA	NA
Hypokalemia	5 (4.0)	1 (0.8)	NA	NA
Drug-induced liver injury	3 (2.4)	2 (1.6)	NA	NA
γ-Glutamyltransferase increase	3 (2.4)	3 (2.4)	NA	NA

Lymphocyte count decrease	3 (2.4)	1 (0.8)	NA	NA
Dyspnea	2 (1.6)	1 (0.8)	4 (2)	0
Pneumonitis	2 (1.6)	2 (1.6)	NA	NA
Abnormal hepatic function	2 (1.6)	1 (0.8)	NA	NA
Lymphopenia	1 (0.8)	1 (0.8)	NA	NA
Neutropenia	1 (0.8)	1 (0.8)	8 (3)	4 (2)
Hepatotoxic event	1 (0.8)	1 (0.8)	NA	NA
Drug hypersensitivity	1 (0.8)	1 (0.8)	NA	NA
Cellulitis	1 (0.8)	1 (0.8)	NA	NA
Lipase increased	1 (0.8)	1 (0.8)	NA	NA
Increase in liver-function level	1 (0.8)	1 (0.8)	NA	NA
Neutrophil count decrease	1 (0.8)	1 (0.8)	NA	NA
Abnormal aminotransferase level	1 (0.8)	1 (0.8)	NA	NA

*Treatment-related adverse events (TRAEs) occurring in ≥ 5% patients, Adverse events were graded with the use of the Common Terminology Criteria for Adverse Events version 5.0, Median duration of treatment: 5.5 months (range: 0.2-17.8 months) (73)
**Adverse events causal to treatment, reported during randomized treatment, Adverse events were graded with the use of the Common Toxicity Criteria for Adverse Events, Median duration of treatment: 2.4 months (range: 0.1-27.4 months) (72)

7.2.3 Conclusion for comparative analyses between sotorasib and docetaxel

The clinical value of sotorasib compared to docetaxel is best demonstrated by the critical outcome measures PFS and OS. The results from the MAIC for PFS, demonstrate that sotorasib provides [redacted] gain in median PFS compared with docetaxel monotherapy ([redacted] exceeding the minimal clinically important difference of 3 months in median PFS(7). For OS, matching adjustment indicates that sotorasib provides a [redacted] gain in median OS compared with the primary comparator docetaxel monotherapy ([redacted]), exceeding the minimal clinically important difference of 3 months in median OS, previously defined by the lung cancer expert committee at DMC(7).

Safety outcomes were compared narratively and limited, as exposure times were not comparable between sotorasib and docetaxel. As the median duration of treatment varied from 5.5 months for sotorasib to 2.4 months for docetaxel. Sotorasib presented a lower occurrence of grade 3 or worse TRAEs (20.6% vs 30%) and a lower numerical rate of treatment discontinuations due to AEs (8.7% vs 14.5%). Sotorasib is expected to be safer and more tolerable compared to docetaxel, aligning with the clinical expectation of safety of a targeted therapy compared to chemotherapies.

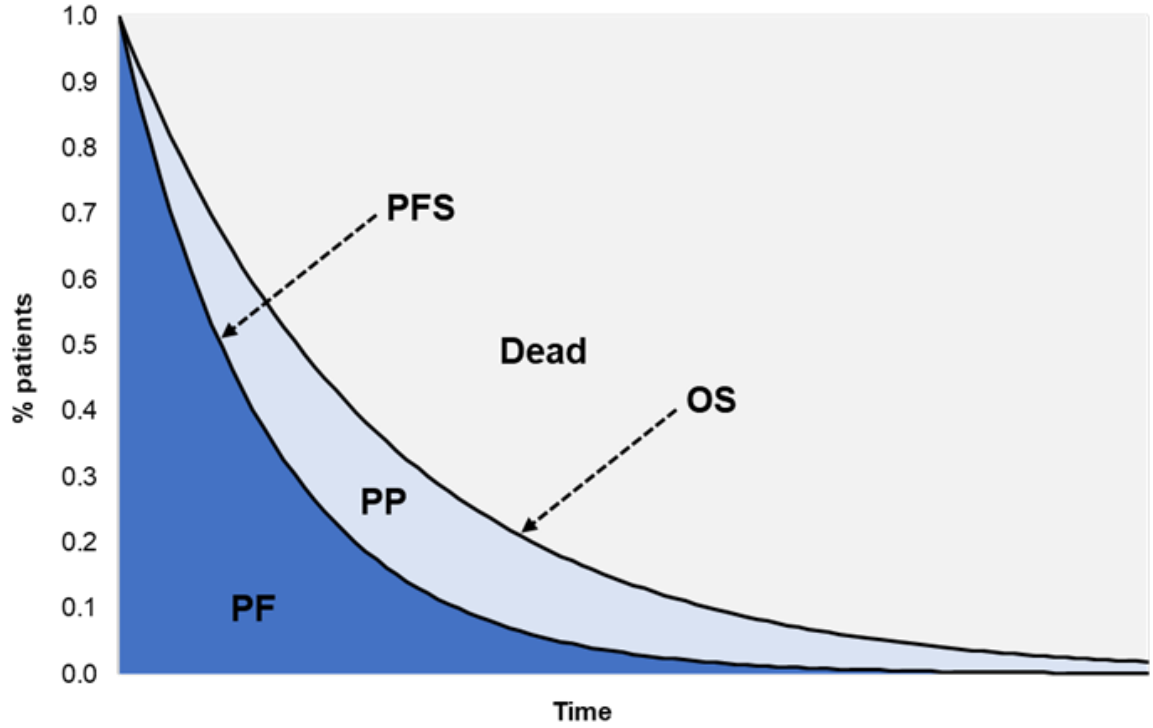
As the presented clinical evidence indicates, sotorasib can address the significant unmet need for a targeted, more effective, tolerable, and convenient treatment that improves clinical outcomes for Danish patients with *KRAS G12C*-mutated NSCLC compared to the current cytotoxic chemotherapy option.

8. Health economic analysis

8.1 Model

The economic evaluation was developed using a cost-effectiveness framework in Microsoft Excel®. A partitioned survival analysis was used based on three distinct health states (Figure 6): progression-free, progressed disease, and dead. All patients entered the model in the progression-free state and were at risk of progression of disease or death. Transitions to the death state occurred from either the progression-free or progressed disease health states. Death was an 'absorbing state', where once entered, patients reside for the remainder of the model time horizon.

Figure 6. Partitioned survival analysis model



OS, Overall survival; PF, progression free; PFS, progression-free survival; PP, post progression

This model structure is fully aligned with the primary objectives of treatment in oncology and NSCLC, namely avoiding disease progression and prolonging life. Furthermore, the structure and health states selected are typical of modelling in oncology and have been used in previous NSCLC technology appraisals.

The model contains the three most relevant disease related health states:

- *Progression-free:* Patient disease is in a stable or responding state and not actively progressing. Patients in this state are assumed to incur costs associated with treatment, administration, medical management of the condition and the management of grade 3/4 adverse events.
- *Progressed:* Patient disease has progressed. This health state is associated with costs of disease management in post-progression.
- *Death:* This is an absorbing state.

The proportions of patients in each health state at the beginning of each model cycle are calculated from the PFS and OS survival functions from relevant clinical trials as follows, where PF(t) is the proportion of patients who are progression-free at time (t), Dead(t) is the proportion of patients who are not alive at time (t) (1 – OS)

and PP(t) is the proportion of patients who are not progression-free and who are still alive at time (t). In the model, all patients start treatment in the progression-free health state:

$$PF(t) = PFS(t)$$

$$Dead(t) = 1 - OS(t)$$

$$PP(t) = OS(t) - PF(t)$$

The estimated time on treatment for each treatment in the analysis was used to inform acquisition costs and related administration costs. Additional costs included in the analysis include disease management costs per health state and subsequent treatment cost. As discussed in Section 8.5.2.3, costs associated with genetic mutation testing are not required to be captured in the model because *KRAS G12C* testing is routinely funded as part of panel testing at diagnosis. It is therefore assumed that all patients entering the model have a *KRAS G12C* mutation-positive status.

The progression-free health state typically reflects a relatively higher HRQoL associated with disease before progression, where patients are receiving benefit from an active treatment, whereas the progressed disease state is designed to capture the relatively poor HRQoL following disease progression. As the use of progression-status based utilities is common practice within oncology modelling, this have been chosen as the base-case in the model. However, as previous studies have shown NSCLC patients to have markedly decreased utilities towards the end of life, the measurements included in the model as a scenario analysis were informed by a time-to-death analysis (81). This approach has been used in previous NICE TAs (82-84).

Time-to-death sub-health states were therefore implemented to capture patients' quality of life as a function of how much lifetime patients had left until they eventually died as predicted in the model. The use of time-to-death sub-health states was implemented considering four health states: less than 1 month before death, 1–3 months before, 3–6 months before, and more than 6 months before death. This time-to-death approach was explored in a scenario analysis.

The analyses were conducted from a restricted societal perspective and are consistent with DMC guidelines(85). The model uses a 7-day cycle length, with a half-cycle correction applied and a time horizon of 20 years. This aligns with the maximum life expectancy of the cohort predicted by parametric survival analysis and was considered appropriate by clinically experts given that it is highly unlikely for patients with NSCLC with the *KRAS G12C* mutation with advanced or metastatic disease to survive beyond this time point. The impact of the selection of the time horizon on results is explored in a sensitivity analysis. A discount rate of 3.5% per annum was applied for costs and outcomes. The perspective chosen, time horizon assessed, and the discount rate used are all in line with the DMC guidelines.

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

8.2.1 Presentation of input data used in the model and how they were obtained

The model is based on efficacy and safety data from the clinical trials, CodeBreak 100 and SELECT-1. A MAIC has been conducted to establish the relative efficacy estimates between sotorasib and docetaxel, as described in the clinical section of the dossier, section 7.2.1. The adverse events rates are directly derived from CodeBreak 100 and SELECT-1, as described in section 8.2.2.5. Health state utilities have been estimated using the Danish tariff set(86) and the EQ-5D-5L data from CodeBreak 100, described in section 8.4.

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 for this economic assessment is NSCLC patients with *KRAS G12C* mutation in 2nd line, in line with the EMA label of sotorasib. Sotorasib provides a treatment for 2nd line NSCLC patients, where no targeted treatment is currently available, and chemotherapy would be the only available treatment for the patients. The efficacy and safety of sotorasib and docetaxel in 2nd line for KRAS G12C mutation NSCLC patients were investigated in CodeBreak 100 and SELECT-1. Therefore, to fit the scope of this assessment, data from CodeBreak 100 trial is included in the model. In Table 19, data on the patient population from the clinical trial is presented, as well as the inputs for the model. Based on consultation with two Danish clinical experts(2, 3) and validation through a the Danish registry study (see Table 1)(5), it is expected that age and gender distribution differ slightly from Danish clinical practice, however, as the prognosis already is poor for this patient population, it is not expected a major impact on the modeled results.

Table 19. Patient population

Patient population Important baseline characteristics	Clinical documentation / indirect comparison etc.	Used in the model	Danish clinical practice (including source)
Age (mean)	62.9	62.9	Danish patients are expected to be slightly older. (2, 3, 5) (see Table 1)
Gender (% female)	50.0%	50.0%	More women are expected in Danish clinical practice. (2, 3, 5) (see Table 1)
Weight (kg)	71.08	71.08	Expected to be similar(2, 3)
Body surface area (m2)	1.81	1.81	Expected to be similar(2, 3)

8.2.2.2 Sotorasib

Sotorasib (LUMYKRAS™) is the first KRAS G12C inhibitor to be submitted for marketing authorization. It is a once-daily oral therapy licensed by the EMA "*as monotherapy is indicated for the treatment of adults with advanced non-small cell lung cancer (NSCLC) with KRAS G12C mutation and who have progressed after at least one prior line of systemic therapy*." Please consult section 5.3 for full details on sotorasib.

Sotorasib is administered orally at a dose of 960mg (given as 8 x 120mg tablets) once daily until disease progression or unacceptable toxicity.

As a targeted therapy, the presence of KRAS G12C mutation should be confirmed using a validated test prior to initiation of sotorasib. KRAS G12C is now included routinely for cancer genomic testing of patients with NSCLC in Denmark via NGS. Therefore, no additional tests beyond those used in the routine diagnostic workup and management.

Table 20. Intervention

Intervention	Clinical documentation (including source)	Used in the model (number/value including source)	Expected Danish clinical practice (including source if known)
Posology	960 mg (8x 120 mg tablets) once-daily orally	Same as clinical documentation	Same as clinical documentation
Treatment duration / Criteria for end of treatment:	Treat until disease progression or unacceptable toxicity • Dose reduction as per SmPC	Treat until disease progression or unacceptable toxicity Dose reduction captured using RDI from CodeBreak 100 in the model.	Same as clinical documentation

8.2.2.3 Comparators

Docetaxel is selected as comparator for the application, please consult section 5.2 for full details on docetaxel.

The recommended dose of docetaxel for adult patients is an initial dose of 75 mg/m2 as a one-hour infusion every three weeks. Treatment is continued based on an individual assesment of clinical tolerability and efficacy in consideration of several adverse events, which may prompt either dose reduction or complete treatment discontinuation. Patients will rarely have more than 6 cycles.

Table 21. Comparator

Comparator	Clinical documentation (including source)	Used in the model (number/value including source)	Expected Danish clinical practice (including source)
Posology	Docetaxel is administered as a one-hour i.v. infusion every three weeks. Docetaxel is given at 75 mg/m2 in monotherapy	Same as clinical documentation	Same as clinical documentation
Treatment duration / Criteria for end of treatment:	Treat until disease progression or unacceptable toxicity	Treat until disease progression or unacceptable toxicity Dose reduction captured using RDI from SELECT-1 in the model	Same as clinical documentation

8.2.2.4 Relative efficacy outcomes

The relative efficacy outcomes have been described in section 8.3. A MAIC analysis has been conducted to establish the relative efficacy between sotorasib and docetaxel. Results of the MAIC analysis have been described in section 8.3.1. Description of overall survival has been provided in section 8.3.2, description of progression-free survival has been provided in section 8.3.3 and description of treatment duration have been provided in section 8.3.5

8.2.2.5 Adverse reaction outcomes

Grade 3 or above TRAEs with an incidence of ≥ 0.5% in any of the comparator arms (sotorasib and docetaxel) are included in the model. Sotorasib adverse events are informed by the CodeBreak 100 Clinical Study Report for the March 2021 data cut (87). Docetaxel adverse events are informed by the SELECT-1(72).

A table of the adverse events and incidence used in the model is shown in Table 22. In the base-case analysis TRAEs are utilized for the sotorasib and docetaxel treatment arms. TRAEs were preferred to minimize bias given the absence of randomized data and the fact that some AEs may be driven by the underlying disease.

Table 22. Adverse reaction outcomes

Adverse reaction outcome	Sotorasib[a]	Docetaxel[b]
Decreased neutrophils	0.8%	0.0%
Diarrhea	4.0%	2.4%
Fatigue	0.0%	1.6%
Increased alanine aminotransferase	6.3%	0.0%
Increased aspartate aminotransferase	5.6%	0.0%
Neutropenia	0.8%	1.6%

Note: [a], CodeBreak 100 phase 2 NSCLC cohort, TRAEs reported. March 1, 2021 data cut-off (87)
[b]Janne 2017 eTable 1 Most Frequently Reported Adverse Events Causally Related to treatment(72)

8.3 Extrapolation of relative efficacy

As described in section 7.2.1,CodeBreak 100 is a single-arm clinical trial, no direct head-to-head evidence to compare the clinical efficacy of sotorasib and docetaxel was available, an unanchored MAIC have therefore been conducted to allow the assessment of relative efficacy between the two comparators.

The MAIC used data from two clinical studies: the CodeBreak 100 trial for sotorasib and the SELECT-1 trial for docetaxel. Comparability of the data sources – and hence the feasibility and appropriateness of performing a MAIC – was assessed through a review of the design and population profiles of the studies involved in the analyses. Details of the comparison of studies, populations and methods used in the studies are presented in **Appendix K - MAIC**. Please consult section 7.2.1 for full details and the results of MAIC.

For extrapolation, parametric curves were fitted to the MAIC-weighted time-to-event data. A variety of options were assessed which considered alternative distribution functions, i.e., consideration of independently versus jointly fitted parametric models. As per the NICE decision support unit (DSU) guidance, extrapolations were assessed using goodness-of-fit statistics, visual match between the parametric fittings and the Kaplan-Meier (KM) data, and the clinical plausibility of long-term outcomes (88).

For the given MAIC-weighted data, the proportional hazards assumption and the presence of accelerated failure time were assessed. This was done based on log cumulative hazard plots, Schoenfeld residuals, and QQ plots. The proportional hazards assumption was found not to be certain for either OS or PFS. Aligned with these findings and based on goodness-of-fit, a restricted and jointly fitted model was selected as the input for the cost-effectiveness model, with details provided for OS in Section 8.3.2 and for PFS in Section 8.3.3.

The extrapolations were assessed for visual match between the parametric fittings and the KM data, goodness-of-fit statistics and the clinical plausibility of long-term outcomes, in line with NICE DSU guidance (TSD 14) (88).

In addition to the MAIC vs. SELECT-1, the Flatiron real-world data were used for sensitivity analysis. Here, a real-world chemotherapy-basket served as a proxy for docetaxel treatment. The rationale for this confirmative

analysis was first, that the SELECT-1 population was anti PD-(L)1 naïve. Second, as CodeBreak 100 is a single-arm trial, this alternative approach was applied to demonstrate the robustness of the results. See **Appendix L - Flatiron** for further information on the Flatiron data set.

8.3.1 MAIC results

Two sets of co-variates were selected for inclusion in the model. The sets included (i) all covariates pre-specified as important (SET 1) and (ii) all covariates available for adjustment (SET 2).

The results of unadjusted and adjusted HRs derived using the weighted Cox models fitted to the different MAIC-adjusted KM datasets are presented in **Error! Reference source not found.**. The results demonstrate a directional decrease in the HR point estimate for the OS endpoint, however, they remained similar for the PFS endpoint. The base-case used SET 1, as the effective sample size of SET 2 was significantly smaller and would have resulted in more uncertainty and less precision of the estimate (**Error! Reference source not found.**).

Key: CI, confidence interval; ESS, effective sample size; HR, hazard ratio; MAIC, matching-adjusted indirect comparison; mth, months; OS, overall survival; PFS, progression-free survival.

8.3.2 Overall survival

A plot comparing the MAIC-weighted KM OS curve for sotorasib (in blue) to the unadjusted docetaxel OS curve from SELECT-1 (in yellow) is shown in **Error! Reference source not found.** panel A. The comparison of the unadjusted KM OS curve for sotorasib from CodeBreak 100 (in blue) to the unadjusted docetaxel OS curve from SELECT-1 (in yellow) is shown in **Error! Reference source not found.** panel B. The MAIC-adjustment results in a slight improvement in survival.

A B

Key: KM, Kaplan-Meier; MAIC, matching-adjusted indirect comparison; OS, overall survival.
A: adjusted, B: unadjusted.

Subsequently, parametric model fitting was carried out to docetaxel and the MAIC-weighted OS data for sotorasib, in line with the methods detailed in NICE DSU TSD 14 (88). Standard parametric distributions were fitted to the unadjusted KM data with an independent fitting and joint fitting (unrestricted and restricted model)

approach using the statistical software R (ver. 4.0.3) using '*flexsurv*' packages. The parametric distributions that were fitted include the exponential, Weibull, Gompertz, generalized gamma, log-normal and log-logistic (Table 23).

The joint fit (unrestricted) model in practice is identical to independent fitting curves (i.e. fitting independent survival functions by arm). The unrestricted model fit statistics were presented so that the fit statistics (AIC/BIC) could be meaningfully compared between independent fitted and joint fitted models (Table 23).

For the unrestricted models, any information relating to treatment arm does not inform the shape of the parametric distribution. In consequence, the curves of both treatment arms do not only differ in terms of a location parameter, but also the parameters that determine the shape are being estimated independently. In contrast, for the restricted model the treatment difference in both parameters depends solely on a location parameter. The shape determining parameters are estimated jointly. For the generalized gamma, log-logistic and log-normal distribution, the restricted model corresponds to an accelerated failure time model. For the Gompertz and the Weibull distribution the implemented restricted time to event corresponds to a proportional hazards model. For the exponential distribution there is no difference between the restricted and the unrestricted model, as by treatment arm there is only one location parameter (i.e. the time-independent eventrate).

Statistical goodness-of-fit

Goodness-of-fit statistics using Akaike information criterion (AIC), and Bayesian information criterion (BIC) are presented for jointly fitted (unrestricted and restricted) and independent models (Table 23). For individually fitted curves, the log-normal distribution was the best statistically fitting curve with the lowest AIC and BIC across both sotorasib and docetaxel and the relative performance of each distribution was similar between arms. As a result, jointly fitted survival models (either restricted or unrestricted) were considered the most appropriate since they can reduce uncertainty due to the estimation of fewer parameters and the use of a larger data set.

For the jointly fitted curves, AIC and BIC indicate that the best fitting curve for both the restricted and unrestricted models was the log-normal followed by the generalized gamma and log-logistic models. There was a notable deterioration in the performance of other distributions based on the statistical AIC and BIC criteria. For the best-fitting distributions, AIC and BIC consistently favored the restricted versus unrestricted joint fits.

Table 23. Goodness-of-fit Statistics for Independent and Jointly Fitted OS Models

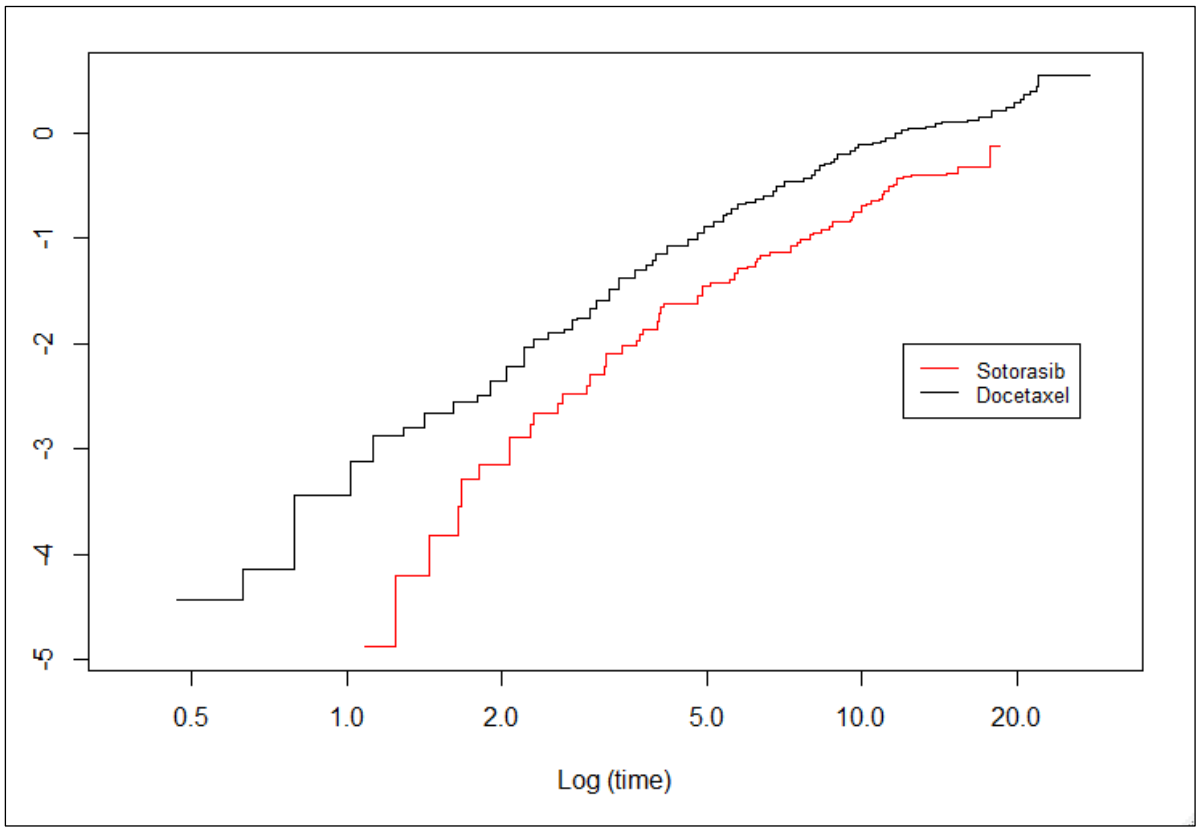
Model	Independent fit – sotorasib		Independent fit - docetaxel		Joint fit (unrestricted)		Joint fit (restricted)	
	AIC	BIC	AIC	BIC	AIC	BIC	AIC	BIC
Exponential	454.3	457.1	1209.7	1213.2	1663.9	1671.8	1663.9	1671.8
Gompertz	456.2	461.9	1211.4	1218.5	1667.7	1683.4	1665.8	1677.6
Weibull	454.1	459.8	1209.6	1216.7	1663.8	1679.5	1662.2	1674.0
Generalized Gamma	446.9	455.3	1194.6	1205.2	1641.5	1665.1	1639.3	1655.0
Log-logistic	450.6	456.2	1196.3	1203.4	1646.9	1662.6	1645.0	1656.8
Log-normal	447.4	453.0	1192.8	1199.9	1640.2	1656.0	1638.2	1650.0

Key: AIC, Akaike information criterion; BIC, Bayesian information criterion.
Note: Underlined values indicate the best statistically fitting parametric distribution.

Diagnostics (Proportional Hazards, Schoenfeld residuals and QQ Plots)

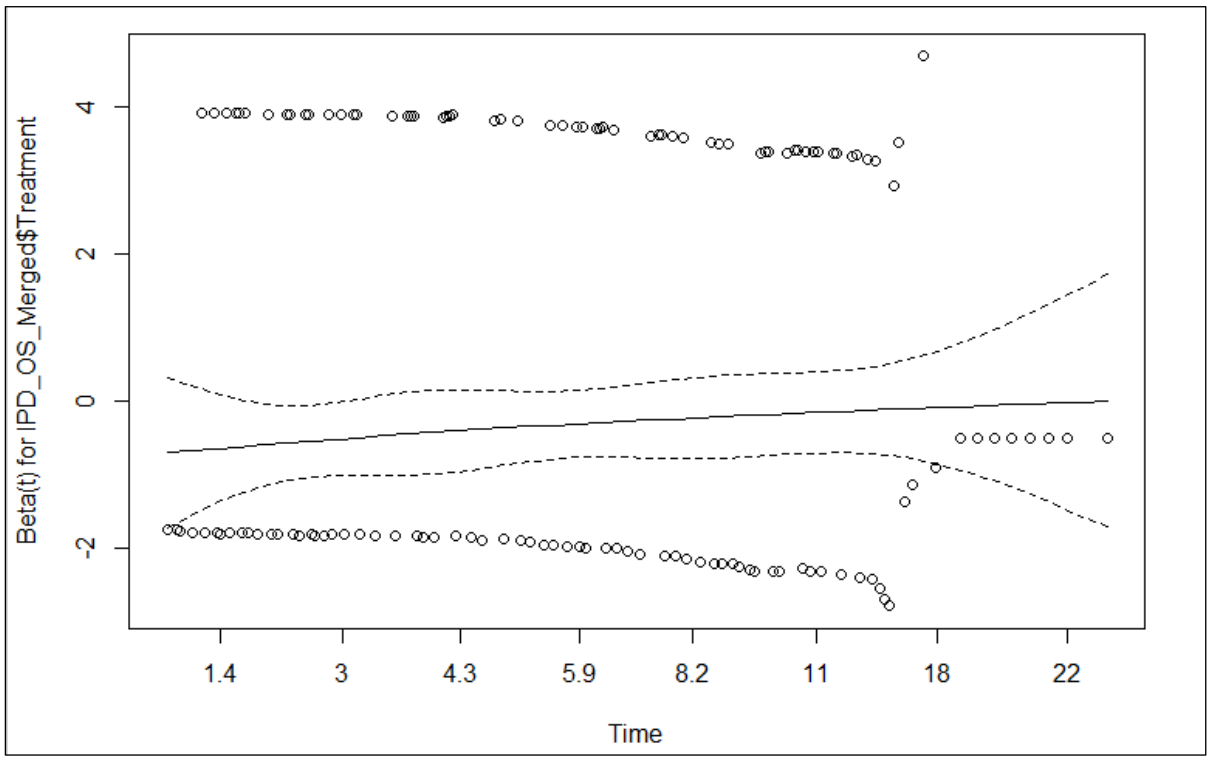
The proportional hazards assumption and the presence of accelerated failure time were assessed for independent fitted extrapolations using log cumulative plots, Schoenfeld residuals, and QQ plots. The assumption of proportional hazards between the two datasets was assessed using the log-cumulative hazards plot (Figure 7) and the Schoenfeld residuals plot (Figure 8). The log-cumulative hazards and the Schoenfeld residuals plot for sotorasib and docetaxel indicated that the proportional hazards assumption may stand true. The log-cumulative hazards plots for the first few months converge and form a kink at the 5 months mark; with a different slope apparent beyond 5 months (Figure 7). Most of the time, the point-wise CIs of the Schoenfeld residuals included zero; however, at around two months, the non-significance was borderline (Figure 8). Considering the slope, and the sample size, the validity of the proportional hazard's assumption was considered uncertain. The QQ plot almost gave a perfectly straight line, indicating the use of accelerated failure time was valid (Figure 9).

Figure 7. Log-cumulative hazards plot for OS using base-case MAIC



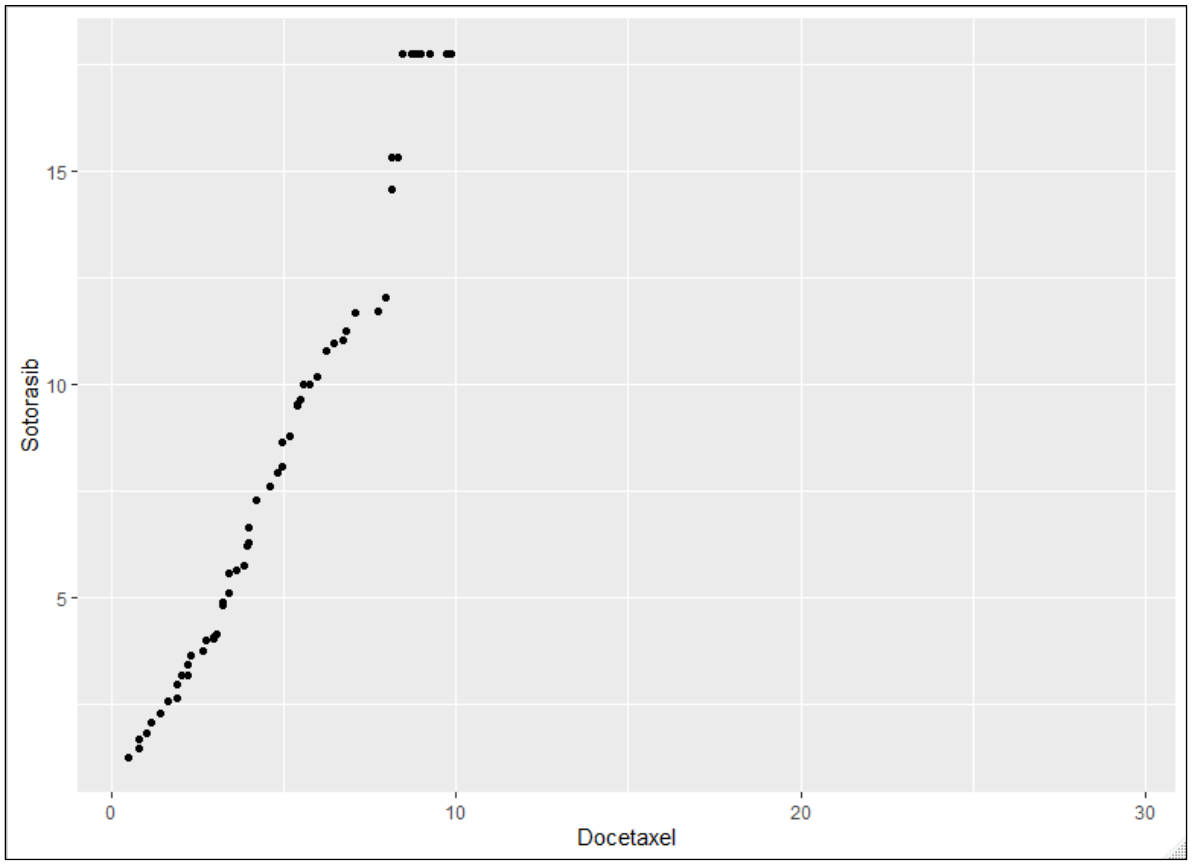
Key: MAIC, matching-adjusted indirect comparison; OS, overall survival.

Figure 8. Schoenfeld residuals plot for OS using base-case MAIC



Key: MAIC, matching-adjusted indirect comparison; OS, overall survival.

Figure 9. QQ plot for OS using base-case MAIC



Key: MAIC, matching-adjusted indirect comparison; OS, overall survival.

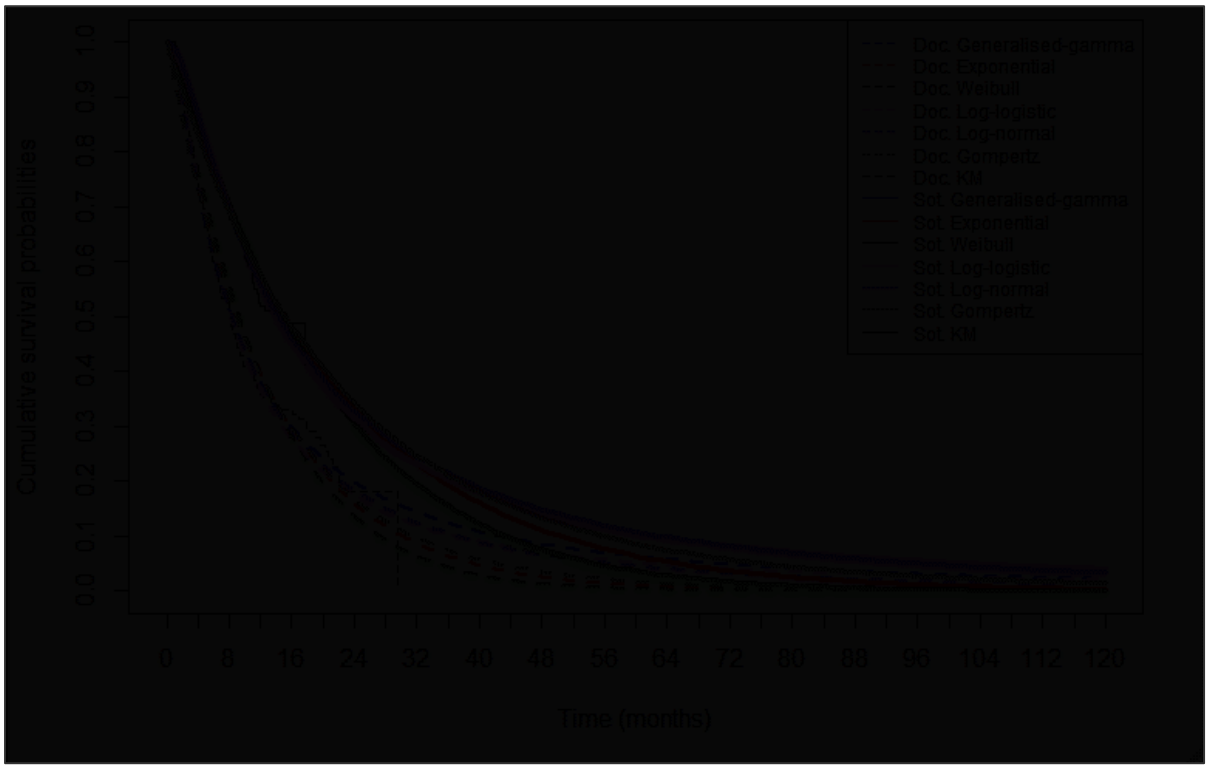
In summary, there was evidence to suggest the proportional hazards assumption did not hold true and, therefore, the application of a proportional hazard approach was not considered appropriate. There was no evidence against the use of an accelerated failure time model being appropriate. The goodness of-fit statistics indicated that the log-normal approach to extrapolation was the best statistically fitting distribution (Table 23). Given the log-normal distribution, the goodness-of-fit statistics pointed to the restricted model, rather than the unrestricted one. Therefore, the approach taken to modeling OS was the jointly fitted restricted log-normal model, considering a treatment effect for sotorasib.

Visual inspection of observed data

A plot of jointly fitted parametric distributions fitted to the MAIC-adjusted KM curves for sotorasib and docetaxel is shown below (**Error! Reference source not found.**). Visual inspection of the plots indicated that extrapolated data matched the KM plots well (**Error! Reference source not found.**). All extrapolations for sotorasib indicate improved OS of sotorasib compared to docetaxel.

Visual inspection of the docetaxel plot confirm that the log-normal distribution is giving the best fit. In terms of other distributional assumptions, the plot indicates that the Weibull and Gompertz distributions overestimated OS in the first 14 months but were very conservative beyond the KM plot (**Error! Reference source not found.**). The sotorasib plot indicated that the Weibull and Gompertz plots underestimated OS in the first 2 months and were the most conservative OS estimates for the long-term projections (**Error! Reference source not found.**).

[redacted]



Key: KM, Kaplan-Meier; MAIC, matching-adjusted indirect comparison; OS, overall survival.

[redacted]

	Exp	Gompertz	Weibull	GG	Log-logistic	Log-normal
Sotorasib						
2 months	91.3%	91.0%	92.9%	95.8%	94.7%	95.5%
6 months	76.0%	75.6%	77.7%	76.9%	78.0%	77.4%
12 months	57.8%	57.7%	57.9%	55.7%	56.0%	56.1%

Docetaxel						
2 months	85.8%	85.5%	88.3%	89.1%	89.2%	89.3%
6 months	63.3%	62.7%	65.5%	60.7%	62.0%	61.6%
12 months	40.0%	39.9%	39.9%	38.2%	37.0%	38.1%

Key: Exp, exponential; GG, Generalized gamma; OS, overall survival.

Base-case parametric survival curve selection

In summary, the goodness-of-fit statistics indicated that the log-normal approach to OS extrapolation was the best statistically fitting distribution, with the Weibull, Exponential and Gompertz performing relatively poorly. There was some evidence to suggest that the proportional hazards assumption did not hold true and, therefore, the application of a HR to estimate a treatment effect was not considered appropriate. However, the QQ diagnostic plot clearly demonstrated that an accelerated failure time model was valid, which was supported by the performance of these restricted models and the visual inspection versus the observed data. Based on these conclusions, the jointly fitted (restricted) log-normal was considered to be the most appropriate approach for the base-case analysis. The 2nd and 3rd best performing distributions (jointly fitted [restricted] generalized gamma and log-logistic, respectively) were considered for sensitivity analyses.

Clinical plausibility of long-term extrapolations

The clinical plausibility of the long-term extrapolations used in the economic analysis was evaluated by considering the predicted OS landmark results at timepoints of 1-year, 5-years, and 10-years, and the shape of the underlying hazard function was assessed. The OS predictions for the joint fitting (restricted) models at landmark time points are presented in **Error! Reference source not found.**.

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[redacted]						

Clinical experts consulted by Amgen considered docetaxel survival predictions at 5-years of approximately 5% to be reasonable in this population and would expect a small proportion of patients to remain alive at the 10-year landmark. Although it was acknowledged that patients in clinical practice could perform slightly worse, the more pessimistic curves presented (exponential, Gompertz and Weibull) were considered to underestimate the long-term survival and did not reflect clinical experience.

The base-case log-normal model was determined to provide clinically valid projections of docetaxel and was well-aligned with clinical expectation at the 5-year ([redacted] and 10-year ([redacted] landmarks. Furthermore, the projections of sotorasib at 5-years ([redacted] and 10-years ([redacted] were considered reasonable given the observed response rate, duration

of response, and survival data available from CodeBreak 100, as well as the ability to receive more effective subsequent therapies.

Finally, the clinical plausibility of the hazard function shape was assessed. The exponential (constant hazard), Weibull (logarithmic increase), and Gompertz (exponential increase) were not considered to reflect the hazard of the population in NSCLC whereas the log-normal, generalized gamma, and log-logistic (increase to peak within 6-9 months) with subsequent decline over time were considered appropriate by clinical experts. This was rationalized based on the relatively high (and increasing) risk reflecting patients with a poor prognosis and non-responders early in the modelled time horizon, followed by decreasing risk for patients who respond to treatment and have an improved relative prognosis as the time horizon progresses.

To further validate long term OS predictions Instantaneous hazard plots for OS has been added in Appendix G - Extrapolation

In conclusion, the base-case selection of the jointly fitted (restricted) log-normal distribution was considered to be clinically valid and reflects the expected survival of the population under consideration.

8.3.3 Progression-free survival

Error! Reference source not found. panel A shows the base-case MAIC-adjusted KM PFS curve for sotorasib (in blue) vs. the unadjusted KM PFS curve for docetaxel from SELECT-1 (in yellow). **Error! Reference source not found.** panel B shows the unadjusted KM PFS curve for sotorasib from CodeBreak 100 (in blue) vs. the unadjusted KM PFS curve for docetaxel from SELECT-1 (in yellow).

For the PFS adjusted curves, the adjustment does not impact the relative survival: The PFS curves look almost the same.

Key: KM, Kaplan-Meier; MAIC, matching-adjusted indirect comparison; PFS, progression-free survival.
A: adjusted curves, B: unadjusted curves.

Subsequently, parametric model fitting was carried out for docetaxel and MAIC-weighted time-to-event data for sotorasib, in line with the methods detailed in NICE DSU TSD 14 (88). Standard parametric distributions were independently and jointly (with unrestricted and restricted models) fitted using the statistical software R (ver. 4.0.3) and the 'flexsurv' package. The parametric distributions modeled included exponential, Weibull, Gompertz, generalized gamma, log-normal and log-logistic distributions (Table 24).

Statistical goodness-of-fit

Goodness-of-fit statistics using AIC and BIC are presented for jointly fitted (unrestricted and restricted) and independent models (Table 24). For individually fitted curves, the AIC and BIC both indicated that the log-normal distribution provided the best statistical fit for sotorasib, whereas the generalized gamma performed the best for docetaxel. However, across both distributions, the AIC and BIC were not meaningfully different with little separating the two. Given this, and consistent with the approach taken for OS, jointly fitted survival models (either restricted or unrestricted) were considered more appropriate to reduce uncertainty through the estimation of fewer parameters and the use of a larger data set.

For the jointly fitted models, the AIC indicates that the generalized gamma distribution is the best performing, whereas the BIC indicates that the log-normal provides the best statistical fit to the observed data, although again differences are minor. In this instance, the BIC statistic was preferred as its use mitigates the risk of overfitting statistical noise in the tails of the observed distributions. Similar to the conclusions from the OS survival analysis, there was a notable deterioration in the performance of the Exponential, Weibull, and Gompertz distributions. For the best-fitting distributions, BIC consistently favored the restricted versus unrestricted joint fits.

Table 24. Goodness-of-fit statistics for independent and jointly fitted PFS models

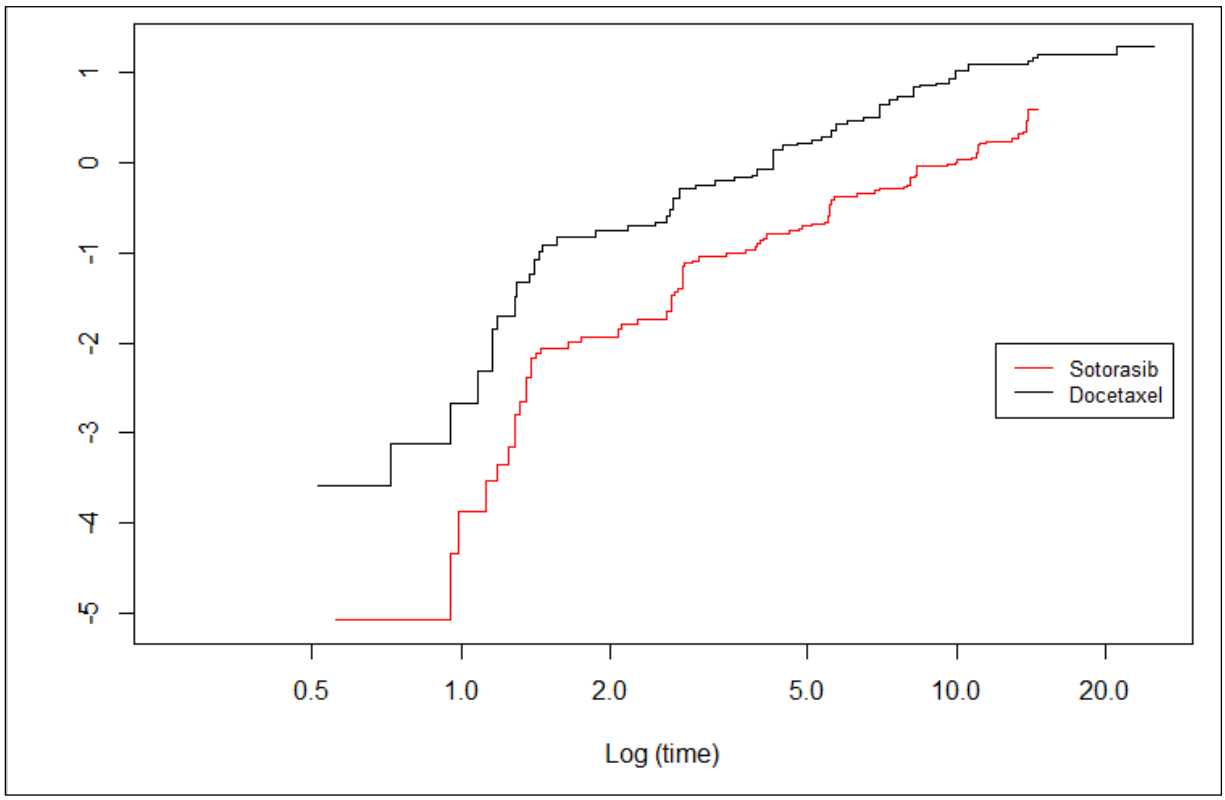
Model	Independent fit – sotorasib		Independent fit – docetaxel		Joint fit (unrestricted)		Joint fit (restricted)	
	AIC	BIC	AIC	BIC	AIC	BIC	AIC	BIC
Exponential	562.5	565.3	1166.5	1170.0	1729.0	1736.9	1729.0	1736.9
Gompertz	561.8	567.4	1166.9	1174.0	1728.6	1744.4	1730.9	1742.7
Weibull	558.4	564.0	1160.6	1167.7	118.9	1734.7	1717.8	1729.6
Generalized Gamma	554.3	562.7	1099.5	1110.1	1653.8	1677.4	1655.3	1671.1
Log-logistic	556.5	562.1	1113.5	1120.6	1670.0	1685.7	1670.1	1682.0
Log-normal	552.4	558.0	1105.7	1112.8	1660.2	1675.9	1658.2	1670.0

Key: AIC, Akaike information criterion; BIC, Bayesian information criterion.
Note: Underlined values indicate the best statistically fitting parametric distribution.

Diagnostics (Proportional Hazards, Schoenfeld residuals and QQ Plots)

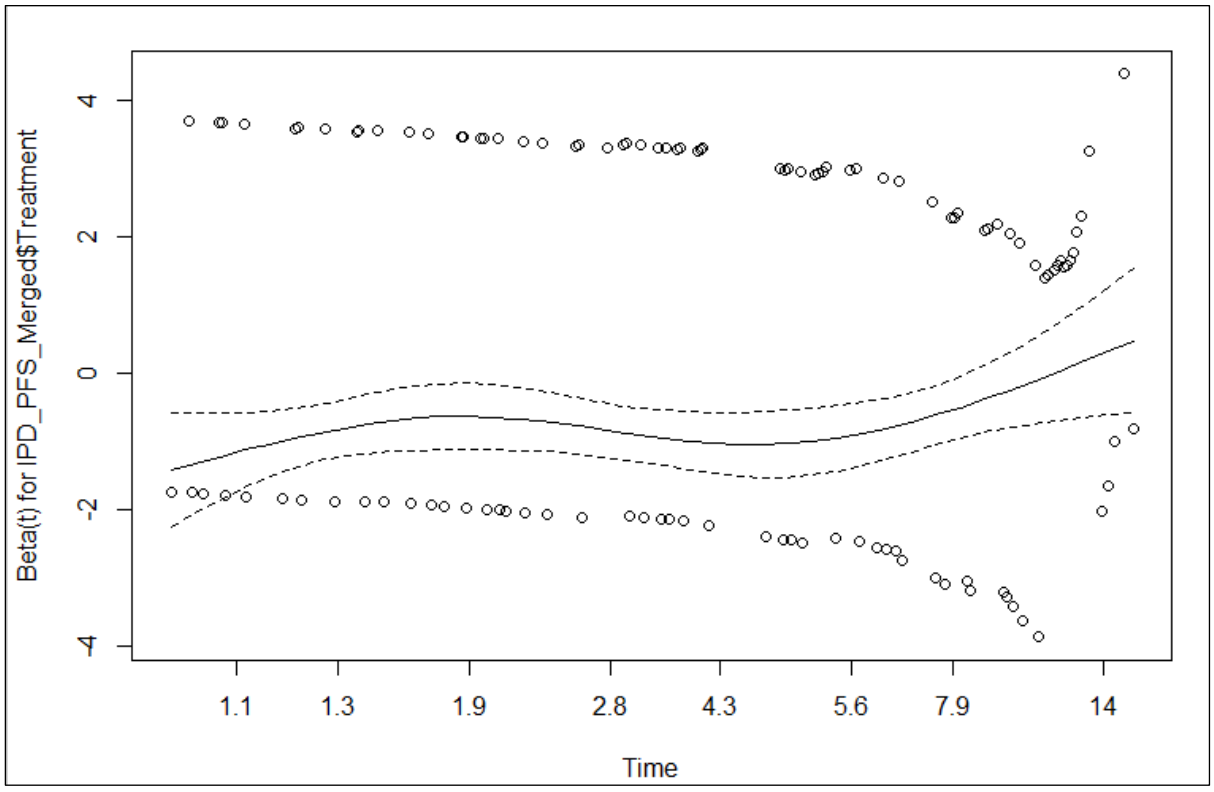
As for OS, the assumption of proportional hazards between the two datasets for independent fits was assessed using the log-cumulative hazards plot (Figure 10) and the Schoenfeld residuals plot (Figure 11). The log-cumulative hazards and the Schoenfeld residuals plot for sotorasib and docetaxel indicated that the proportional hazards assumption did not hold: the log-cumulative hazards plot demonstrated the convergence of the sotorasib and docetaxel curves in the first 2 months, which diverged at around 3 months and then remained parallel beyond 4 months. Likewise, the confidence bands of the scaled Schoenfeld residuals did not include zero for most of the time horizon. The QQ plot, however, indicated that the accelerated failure time assumption was sufficiently valid (Figure 12). Despite some deviations that may as well be sample-size driven, overall, the QQ-plot indicated a straight line.

Figure 10. Log-cumulative hazards plot for PFS using Base-case MAIC



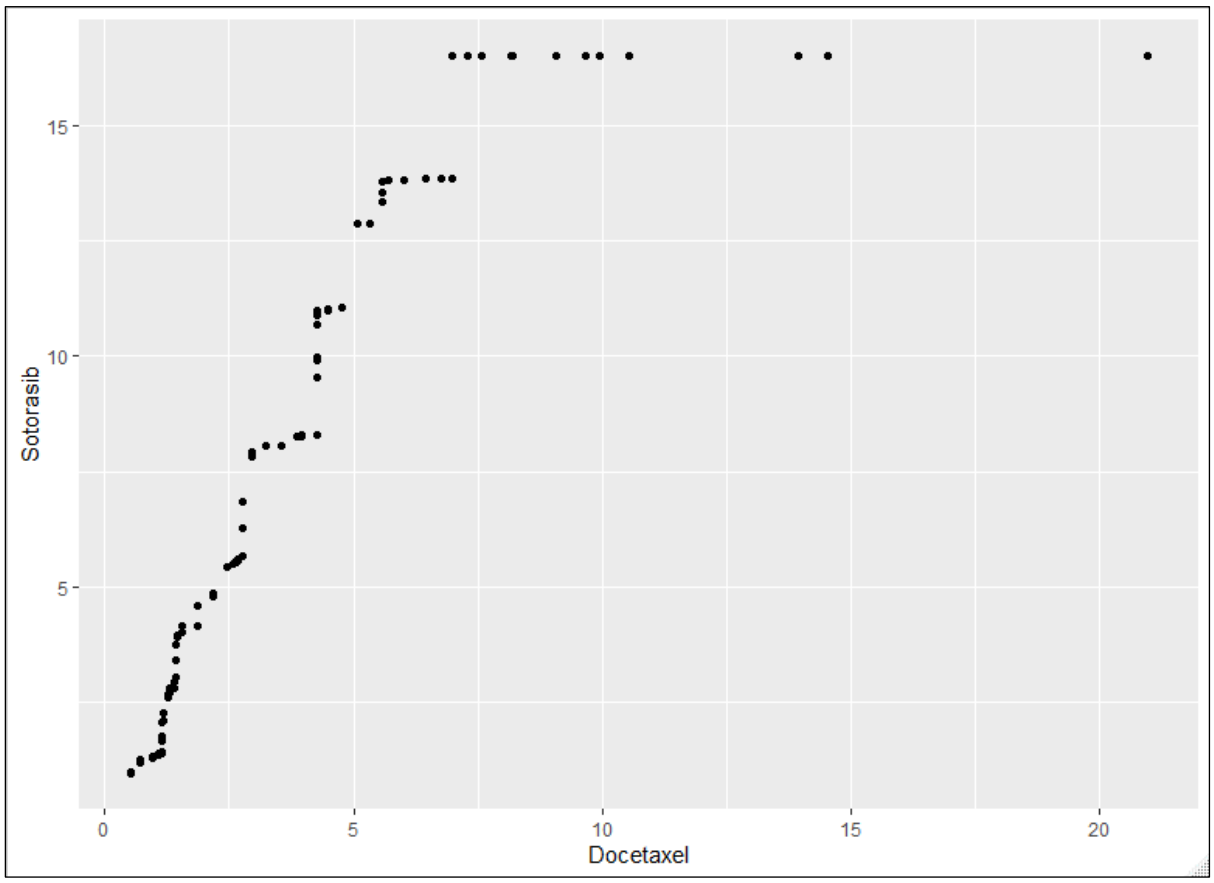
Key: MAIC, matching-adjusted indirect comparison; PFS, progression-free survival.

Figure 11. Schoenfeld residuals plot for PFS using base-case MAIC



Key: MAIC, matching-adjusted indirect comparison; PFS, progression-free survival.

Figure 12. QQ plot for PFS using base-case MAIC



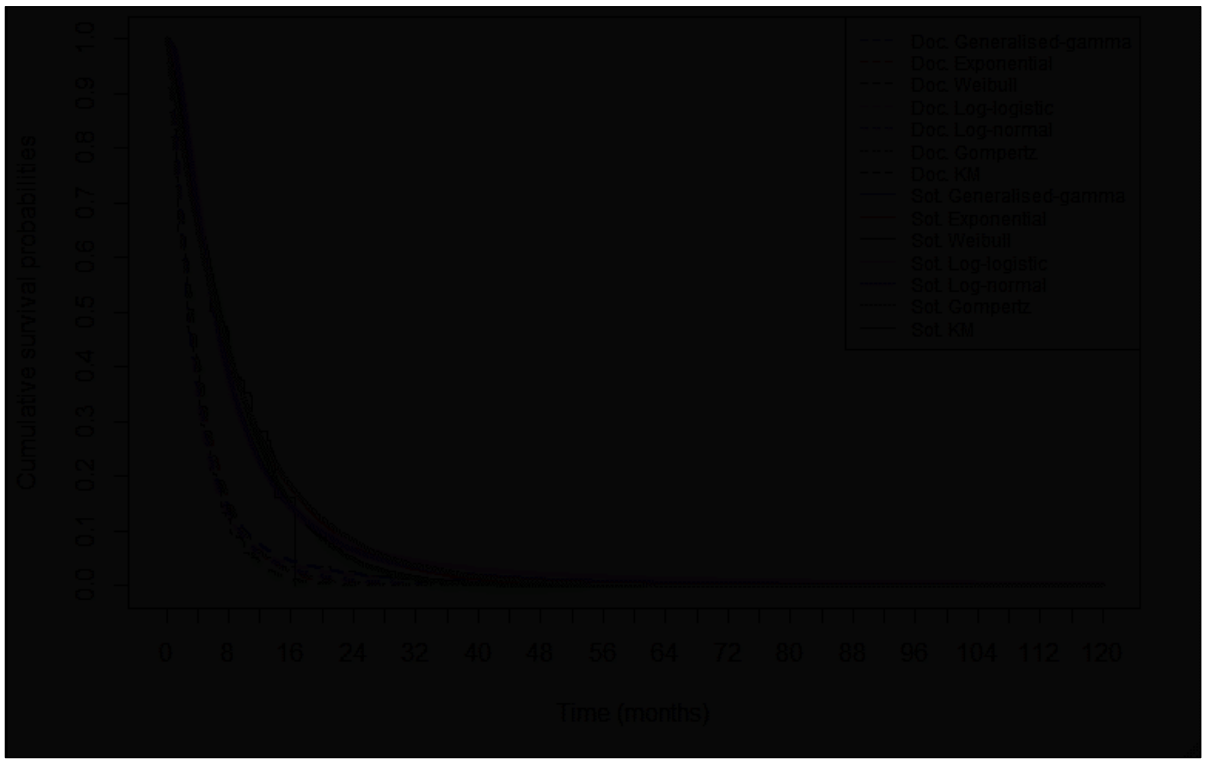
Key: MAIC, matching-adjusted indirect comparison; PFS, progression-free survival.

In summary, there was evidence to suggest the proportional hazards assumption was not valid. The accelerated failure time assumption, however, appeared sufficiently valid. In terms of the selected distribution function, consistent with the approach taken in OS, the restricted log-normal model has been applied for treatment extrapolation.

Visual inspection of observed data

A plot of jointly fitted parametric distributions fitted to the MAIC-adjusted PFS KM curve for sotorasib and the unadjusted PFS KM curve for docetaxel is shown below (**Error! Reference source not found.**). Visual inspection of the plots indicates that the extrapolated data based on the log-normal distribution matched the KM plots well (**Error! Reference source not found.**). All extrapolations for sotorasib indicate improved PFS of sotorasib compared to docetaxel.

[redacted]



Key: KM, Kaplan-Meier; MAIC, matching-adjusted indirect comparison; PFS, progression-free survival.

[redacted]

	[redacted]					
[redacted]						
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
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[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]						

Base-case parametric survival curve selection

In summary, although selecting the most appropriate distribution to model PFS was less clear than OS, the goodness-of-fit statistics indicated that the log-normal approach to PFS extrapolation was the best statistically fitting distribution, with the Weibull, Exponential and Gompertz performing relatively poorly. Further, the diagnostic plots suggest that the proportional hazards assumption is likely to be violated and that an accelerated failure time model is appropriate.

One factor adding to the difficulty of fitting a parametric curve to PFS was that PFS data were not being collected at a truly continuous level. As progression was not continuously assessed, but only measured at certain points

of times, the Kaplan–Meier curves were less smooth than those for OS. However, the Kaplan–Meier curves, did not provide justification for assuming different parametric functions or for fitting curves independently.

Therefore, PFS was modeled based on a jointly fitted restricted model with log-normal distribution which is consistent with the distribution selected for OS and supported by the visual inspection versus the observed data. The 2nd and 3rd best performing distributions (jointly fitted [restricted] generalized gamma and log-logistic, respectively) were considered for sensitivity analyses.

Clinical plausibility of long-term extrapolations

The clinical plausibility of the long-term extrapolations used in the economic analysis was evaluated by considering the predicted PFS landmark results at timepoints of 1-year, 3-years, and 5-years, and the shape of the underlying hazard function was assessed.

Clinical experts consulted by Amgen considered docetaxel and sotorasib projections based on the selected log-normal distribution to be appropriate, clinically valid and reflect the expected survival of the population under consideration. Furthermore, similar to the conclusions on the hazard function shape for OS, the clinical experts considered a non-monotonic hazard function was appropriate to model long-term PFS.

8.3.4 Scenario analysis for survival outcomes

Scenario analyses were conducted where alternative parametric distributions and models were applied. The additional analyses included using alternative MAIC models, independent parametric fitting models, applying the unadjusted analyses (no MAIC), application of a single HR (as the proportional hazards assumption was unclear), and use of KM curves before extrapolation. These are detailed as follows:

- Use a restricted generalized gamma distribution for both PFS and OS, the second best-fitting distribution
- Use a restricted log-logistic distribution for both PFS and OS, the third best-fitting distribution
- Using the unrestricted model (still based on the log-normal assumption) for PFS
- Parametric fit based on unadjusted analyses (restricted model, log-normal distribution)
- Parametric fit based on unadjusted analyses (restricted model, log-normal distribution) using ATT-adjusted Flatiron data for docetaxel
- MAIC using all available variables (same parametric assumptions as in base-case)
- Using the MAIC-adjusted TTD curve from CodeBreak 100 for sotorasib
- No treatment effect of sotorasib vs. Docetaxel after 5 years
- Application of MAIC-adjusted HR applied to docetaxel to get sotorasib
- MAIC-adjusted KM curve from CodeBreak 100 vs. unadjusted KM curve from SELECT-1, followed by a restricted log-normal distribution

Details of the sensitivity analyses conducted, with assumptions and rationale are presented elsewhere in this report (**Appendix K - MAIC**).

8.3.5 Treatment duration

8.3.5.1 Sotorasib

Sotorasib treatment duration was modeled using an HR applied to PFS. The HR was estimated from CodeBreak 100 (75) using a Cox model with the effect estimated between time to treatment discontinuation (TTD) and PFS ([redacted] The HR approach only depends on CodeBreak 100 data and methodology wise is a valid approach for any option of modeling OS and PFS..

Additionally, it was considered that it was appropriate to anchor TTD to PFS for long term extrapolation, as the two outcomes were found to be correlated, which was expected given the “treat to progression” nature of sotorasib. **Error! Reference source not found.** compares the modelled TTD curve to the actual TTD KM curve

from CodeBreaK 100, safety analysis set, 15MAR2021 dco. PFS is modelled with a lognormal distribution and TTD is modelled applying a HR of [redacted]) to the modelled PFS curve.

The modeling of TTD by applying a HR to the PFS curve was validated by comparing the obtained TTD curve to the actual TTD KM curve from the sotorasib arm in CodeBreaK 100: the modelled TTD showed good concordance with the KM curve (**Error! Reference source not found.**).

To account for the expected important correlation between PFS and TTD, clusters based on subject ID were introduced in the Cox model. Clusters are used to take into account correlation in the observations, and also trigger the computation of a robust variance for the model.

The R code used to estimate the HR of TTD vs PFS is provided below.

[redacted]

[redacted]

[redacted]

Key: PFS, progression-free survival; TTD, time to treatment discontinuation.

An alternative approach to modelling sotorasib treatment duration considered applying MAIC weights to the CodeBreak 100 TTD data and fitting parametric models to estimate treatment duration. This approach, however, compared to the HR approach, is more complex but less accurate: The HR approach is based on a single parameter from a single trial. In contrast to OS and PFS, where time-to-event data of two trials are being combined, for TTD SELECT-1 based KM curves do not exist. Adding MAIC weights across trials would add complexity but not accuracy. Furthermore, more degrees of freedom plus the selection of a parametric distribution would be required. The HR approach better reflects the high causal relationship between PFS and TTD, as most patients discontinue treatment at progression. Independently fitted curves may unnecessarily yield misalignment. And given that more than 80% of patients had discontinued sotorasib by the March 2021 data cut snapshot there is low uncertainty related to the estimate

We believe there is a strong statistical case to “tether” TTD to PFS and this is consistent with the clinical use of sotorasib. Therefore, the HR approach sufficiently accounts for the strong relationship between TTD and PFS. These two curves should not be modelled independently. Comparing the modelled curves with the corresponding KM curves shows the approximated relationship is reasonable.

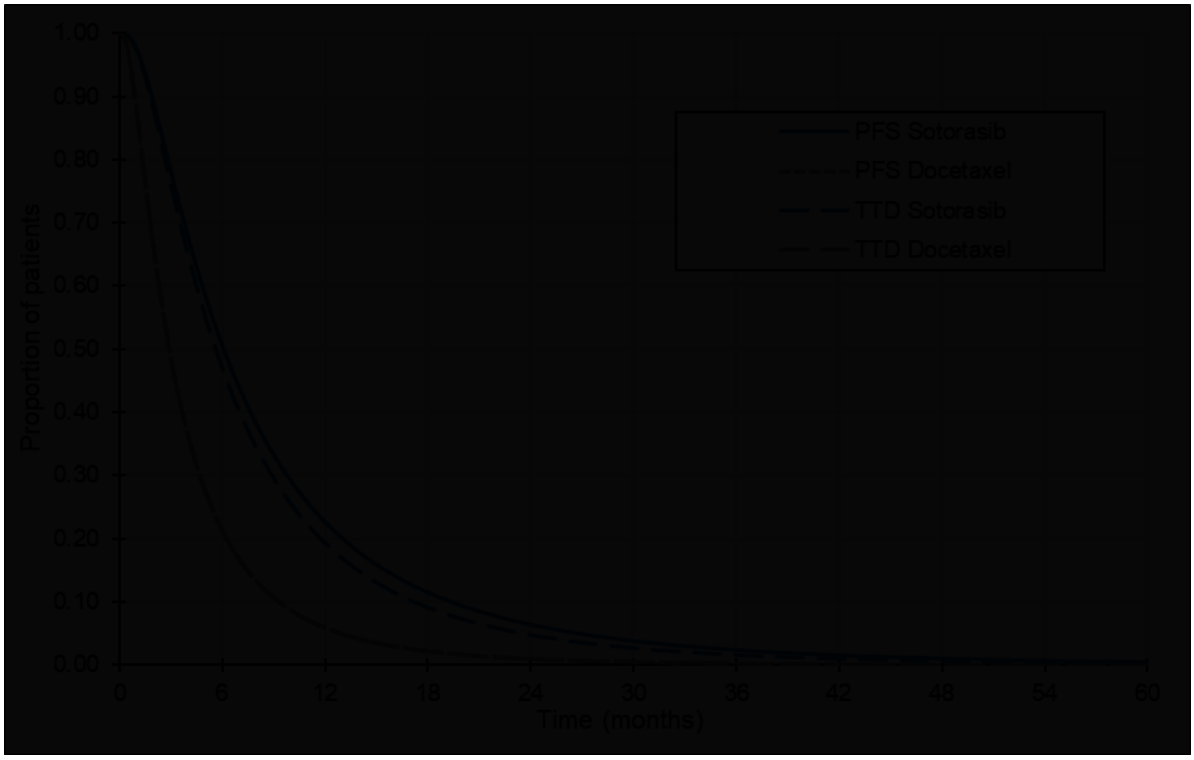
Furthermore, There is a strong precedent based on previous NICE submissions (and acceptance by appraisal committees) for methods that “tether” TTD to PFS for oncology medicines where this reflects how the treatment will be used – i.e. where TTD tends to be around PFS but not the same. For example:

- In NSCLC it is common to assume TTD=PFS if this is in-line with the licence and SmPC wording or otherwise tether TTD to PFS by either applying a HR or adding a mean number of cycles of treatment at progression in the model (i.e. if TTD is slightly higher than PFS). For example, see NICE TA628, NICE TA670 and NICE TA406.

8.3.5.2 Docetaxel

There was no robust data to inform treatment duration for docetaxel. Furthermore, as the cost of docetaxel is small, the effect of docetaxel treatment duration on the results was expected to be negligible and have a minor impact on the incremental results. Docetaxel treatment duration was, therefore, assumed to be equal to PFS in

SELECT-1. A plot showing treatment duration for docetaxel and sotorasib is shown below (**Error! Reference source not found.**).



Key: PFS, progression-free survival; TTD, time to treatment discontinuation.

8.3.6 Time to event data – summarized:

Please refer to sections 8.3.2, 8.3.3, and 8.3.5 for information on time to event data.

8.4 Documentation of health-related quality of life (HRQoL)

8.4.1 Overview of health state utility values (HSUV)

HRQoL data were collected in CodeBreak 100 using the EQ-5D-5L questionnaire before any clinical assessments and before receiving study medication. The questionnaires were administered at the beginning of each three-week treatment cycle for the first seven cycles, and every six weeks subsequently for as long as the patient remained on treatment. The EQ-5D-5L questionnaire was also administered at end of the treatment visit as well as at the safety follow-up visit (~ 30 days after the last dose of sotorasib).

An analysis was conducted using the Danish EQ-5D-5L utility value set (86).

Two analyses were performed in the value sets including (i) a descriptive analysis of the index score by visit and change from baseline and (ii) a mixed model with repeated measures (MMRM) fitted to estimate the impact of (a) time to death category for > 6 months, 3 to 6 months, 1 to 3 months and < 1 month before death and (b) health state based on disease progression. Details of the methods used in the analysis are presented in **Appendix M - HRQoL statistical methodology**.

8.4.1.1 Descriptive analysis of CodeBreak 100 EQ-5D-5L

Descriptive statistics by visit are provided for the mean EQ-5D utility index score by visit using the Danish tariffs (**Error! Reference source not found.**).

The mean change in utility index score from baseline is presented in **Error! Reference source not found.**. Mean change from Baseline in Denmark Utility Index scores ranged from [redacted] indicating stability in health.

[redacted]

Key: Danish EQ-5D-5L index (86).
Note: Analysis based on CodeBreak 100 reported EQ-5D-5L from 15MAR2021 data cut.

[redacted]

Key: Danish EQ-5D-5L index (86)
Note: Analysis based on CodeBreak 100 reported EQ-5D-5L from 15MAR2021 data cut.

8.4.1.2 Mixed models for repeated measures analysis

MMRMs were used to assess the change of utility from baseline without covariates, as described in **Error! Reference source not found.**. Denmark Utility Index scores (**Error! Reference source not found.**) were also

stable across timepoints, decreasing [redacted]. This did not change meaningfully and remained within the Denmark Index MID threshold (0.080), except for Cycle 17, Cycle 19, and Cycle 21. LS mean change from Baseline estimates was not significantly different from zero across all visits (as indicated by the 95% Cis). Available subject observations out of the EQ-5D-5L analysis population had decreased by over half at Cycle 4.

[redacted]

[redacted]	[redacted]	[redacted]
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[redacted]	[redacted]	[redacted]
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[redacted]

8.4.2 Health state utility values used in the health economic model

8.4.2.1 Base-case (health state utilities)

For the base-case, utilities based on health state occupation was used, as it both reflects the health status of patients following the structure of the clinical trial and the partitioned survival model.

Health state utilities by progression status are presented using the Danish EQ-5D-5L value set(86) (**Error! Reference source not found.**), Utilities are age-adjusted in the model according to the DMC guidelines. For the Danish EQ-5D-5L value set(86), the progression health state utility was lower than pre-progression and was statistically significant [redacted] (**Error! Reference source not found.**).

[redacted]

[redacted]						
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	
[redacted]		[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

[redacted]

8.4.2.2 Time to death utilities

Utilities by time to death using the Danish EQ-5D-5L value set (86) are presented in **Error! Reference source not found.**. For the Danish EQ-5D-5L value set, time to death at 3 to 6 months was lower than more than 6 months (although this was not statistically significant ([redacted]). Both 1 to 3 months prior to death and 1 month prior to death

were lower and statistically significant ([redacted] (**Error! Reference source not found.**). The impact of time to death utilities has been explored in scenario analyses.

[redacted]

8.4.3 Adverse reactions and treatment modality disutility

Grade 3+ adverse events with an incidence of ≥ 0.5% in any of the comparator arms (sotorasib and docetaxel) are included in the model. Table 25 presents the disutility per episode for each of the included AEs consistent with sources used in previous appraisals in this disease area at NICE. As disutility values could not be identified for all AEs, a disutility value of 0 was assumed in these cases. This assumption could potentially be conservative given the generally increased frequency of these AEs in the comparator arms versus sotorasib.

For each included AE the disutility was applied in the first model and the duration of each adverse event was assumed to be 4 weeks, with a lower bound of 3.2 weeks and upper bound of 4.8 weeks.

Finally, direct use of reported utility data from CodeBreak 100 likely underestimates the true utility decrement associated with docetaxel given increased cytotoxicity of these agents and the implications of hospital-based intravenous (IV) administration, compared with a targeted oral therapy such as sotorasib. Clinical experts consulted for the NICE appraisal by Amgen verified that a treatment-specific disutility for docetaxel and would be appropriate to capture in the base-case analysis. To inform this, a previous study in advanced NSCLC was used which identified a 0.025 utility decrement associated with IV versus oral administration (89).

Table 25. Adverse event disutilities

Adverse event	Mean (95% CI)*	Source
Decreased neutrophils [a]	0.000	NICE TA484 [assumption](90)
Diarrhea [a]	0.047 (0.016, 0.077)	Nafees 2008(91)
Fatigue [a]	0.073 (0.037, 0.110)	Nafees 2008(92)
Increased ALT [a]	0.050 (0.040, 0.060)	NICE TA 347, 520, and 484 [assumption] (82, 90, 91)
Increased AST [a]	0.000	NICE TA484 [assumption](90)
Neutropenia [a]	0.090 (0.059, 0.120)	Nafees 2008(93)
Decreased white blood cell count	0.050 (0.040, 0.060)	Assumption, value used in NICE TA 347, 520, and 484
Dyspnea	0.050 (0.026, 0.074)	Doyle 2008 (8)
Febrile neutropenia	0.090 (0.058, 0.122)	Nafees 2008(91)
Pleural effusion	0.000 (0.000, 0.000)	Assumption, value used in NICE TA484
Pneumonia	0.008 (0.006, 0.010)	Marti 2013 (93)

Key: ALT, alanine aminotransferase, AST, aspartate aminotransferase.
Note: *, confidence intervals calculated using normal distribution
[a], adverse events included in base-case analysis

8.5 Resource use and costs

8.5.1 Intervention and comparators' costs and resource use

The drug acquisition cost per treatment is presented in Table 26 below, with the unit costs for comparators sourced from Medicinpriser.dk (94). The sotorasib dose of 960mg per day is consistent with the license and the dosing regimen in CodeBreak 100 (73, 95, 96).

Estimation of the monthly cost of treatment is inclusive of the relative dose intensity observed in the respective clinical trial programs. This ensures that efficacy estimates remain internally consistent with drug utilization assumptions. Furthermore, with respect to sotorasib, the inclusion of relative dose intensity (RDI) in drug utilization calculations would best reflect clinical practice given the ability to implement dose reductions and the single-strength formulation of sotorasib packs as per SmPC.

Table 26. Unit drug costs

Drug	Unit	Unit cost (DKK)	Reference	Dose	Relative dose intensity	Cost per month (DKK)[d]
Sotorasib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Docetaxel "Accord"	80 mg per vial	150	170823 - Medicinpriser.dk(94)	75 mg/m^2 on day of treatment	90.3%[b]	333[d]

Note:
[a] CodeBreak 100 CSR (01March2021), Table 14b-5.1, Exposure to sotorasib (AMG510)
[b] Jänne, 2017(97)
[c] Docetaxel cycle cost is based on cost per mg x dose per administration (75 mg/m^2) x body surface area (1.81 m2)
[d] calculated from CEM

8.5.2 Health-state unit costs and resource use

8.5.2.1 Administration costs

The costs of treatment administration for sotorasib and docetaxel are shown in Table 27. As sotorasib is an oral drug, it is assumed that the patients receive training on how to administer the drugs at the first visit, thus a one-off cost has been applied to the first administration. The following visits will be visits related to dispensing the drug, and therefore no administration costs have been assumed for these visits. According to the SmPC, the time required per administration of docetaxel is 60 minutes every 3 weeks(92). Following consultation with two Danish clinical experts, it was confirmed that administration of docetaxel at their departments was coded using the DRG code, 27MP21 – Kemoterapi, kompleks, at the departments(2, 3). Therefore, the administration of docetaxel was costed using the one-day tariff (27MP21) in the model.

Table 27. Administration costs

Drug	Cost (DKK)	Source
Sotorasib (first visit)	1,732	DRG code, 04MA98 – MDC04 1-dagsgruppe, pat. Mindst 7 år; Diagnosis code, DC349 Kræft i Lunge, Treatment code, BTPD5 Indøvning af administration af egen medicin(98)
Docetaxel (per admin)	17,556	DRG code, 27MP21 – Kemoterapi, kompleks; Diagnosis code, DC349 Kræft i Lunge; Treatment code, BWHA208 Behandling med docetaxel(98)

Key: admin, administration; DRG, diagnosis related group.

8.5.2.2 Monitoring and disease management costs

Given the limited published literature that explores the resource use associated with previously treated locally advanced or metastatic NSCLC, monitoring and disease management costs are largely informed from assumptions used and accepted in previous DMC submissions and validated with Danish clinical experts.

Disease monitoring and management costs were aligned with the model structure and reflect resource utilization in both progression-free and post-progression health states.

A summary of the blood sample cost used in the economic model is presented in Table 28, and the unit cost of other disease management is presented in Table 29. A summary of the frequencies and cost per cycle used in the economic model are presented in Table 30.

Table 28. Blood sample cost

Blood sample	Unit cost (DKK)	Source

Hb	31	https://labportal.rh.dk/LabPortal.asp?Mode=View&Id=2403
L+D (DIFFMAS)	90	https://labportal.rh.dk/LabPortal.asp?Mode=View&Id=5154
Creatinine	24	https://labportal.rh.dk/LabPortal.asp?Mode=View&Id=3766
Calcium	24	https://labportal.rh.dk/LabPortal.asp?Mode=View&Id=5247
Albumin	24	https://labportal.rh.dk/LabPortal.asp?Mode=View&Id=5246
Liver (ALAT)	24	https://labportal.rh.dk/LabPortal.asp?Mode=View&Id=5701
Liver (ASAT)	24	https://labportal.rh.dk/LabPortal.asp?Mode=View&Id=3994
Total	**241**	

Table 29. Disease management unit cost

Units	Cost per unit (DKK)	Source
Outpatient consultation	1,732	DRG 2021, 04MA98: MDC04 1-dagsgruppe, pat. Mindst 7 år, Diagnosis: DC349: Kræft i lunge UNS(98).
CT-scan	2,007	DRG 2021, 30PR06: CT-scanning, kompliceret, Diagnosis: DC349: Kræft i lunge UNS Procedure: UXCC00 CT-skanning af thorax(98).
Blood samples	241	See Table 28.

Table 30. Disease management costs per model cycle

Units	Health states		
	First cycle – progression-free (frequency per cycle)	Progression-free – subsequent cycles (frequency per cycle)	Post-progression (frequency per cycle)
Outpatient consultation	1.00	0.25	0.25
CT-scan	1.00	0.08	0.08
Blood samples	1.00	0.25	0.25
Total cycle cost (DKK)	**3,980**	**660.5**	**660.5**

8.5.2.3 Subsequent treatment cost

Currently, no standard treatment is defined for 3L treatment of NSCLC patients (2, 6). Based on clinical expert input, patients with ECOG PS 0 or 1 will often be referred to a phase 1 or 2 trial investigating an experimental treatment(2). It is assumed that no cost associated with experimental treatment will be held by the hospitals, therefore subsequent treatment cost has been omitted from this health economic analysis.

8.5.2.4 Biomarker testing

As described in section 5.3, KRAS testing is part of the current NGS panel for NSCLC patients in Denmark and no additional tests beyond those used in the routine diagnostic workup and management of patients with NSCLC are required. This has been confirmed by two Danish clinical experts(2, 3). Therefore, no cost associated with biomarker testing have been included in the model.

8.5.2.5 Adverse reaction unit costs and resource use

The AEs included in the economic model are previously described in Section 8.2.2.5. The unit costs related to the management of AEs events were derived from the Danish DRG tariff list using the DRG grouper 'Interaktiv DRG'(98). AE costs used in the base-case analysis are summarized in Table 31.

Table 31. Adverse events and associated costs

Adverse event	Cost (DKK)	Source [a]
Decreased neutrophils	3,114	DRG 2021, 16MA98: MDC16 1-dagsgruppe, pat. Mindst 7 år, Diagnosis: DD728: Anden forstyrrelse i hvide blodlegemer
Diarrhea	5,130	DRG 2021, 06MA11: Malabsorption og betændelse i spiserør, mave og tarm, pat. Mindst 18 år, u. kompl. Bidiag., Diagnosis: DK529B: Ikke-infektiøs diaré UNS
Fatigue	3,987	DRG 2021, 23MA03: Symptomer og fund, u. kompl. Bidiag., Diagnosis: DR539A: Udmattelse
Increased ALT	1,626	DRG 2021, 23MA98: MDC23 1-dagsgruppe, pat. Mindst 7 år, Diagnosis: DR740: Transaminase- og laktatdehydrogenaseforhøjelse
Increased AST	1,626	DRG 2021, 23MA98: MDC23 1-dagsgruppe, pat. Mindst 7 år, Diagnosis: DR740: Transaminase- og laktatdehydrogenaseforhøjelse
Neutropenia	3,114	DRG 2021, 16MA98: MDC16 1-dagsgruppe, pat. Mindst 7 år, Diagnosis: DD709: Neutropeni UNS
Decreased white blood cell count	3,114	DRG 2021, 16MA98: MDC16 1-dagsgruppe, pat. mindst 7 år, Diagnosis: DD728: Anden forstyrrelse i hvide blodlegemer
Dyspnea	1,732	DRG 2021, 04MA98: MDC04 1-dagsgruppe, pat. mindst 7 år, Diagnosis: DR060: Dyspnø
Febrile neutropenia	3,114	DRG 2021, 16MA98: MDC16 1-dagsgruppe, pat. mindst 7 år, Diagnosis: DD709A: Neutropeni og agranulocytose forårsaget af lægemiddel
Pleural effusion	34,259	DRG 2021, 04MA09: Pleuritis exsudativa, Diagnosis: DJ919: Pleuraeffusion ved sygdom klassificeret andetsteds
Pneumonia	36,514	DRG 2021, 04MA13: Lungebetændelse og pleurit, pat. mindst 60 år, Diagnosis: DJ189: Pneumoni UNS

Key: ALT, alanine aminotransferase; AST, aspartate aminotransferase.
Note: [a], all costs derived from the Danish DRG tariff list using the Danish DRG grouper 'Interaktiv DRG'**(98)**.

8.5.2.6 Patient and transportation cost

Productivity costs (defined as patient costs in DMC guidelines) and transportation costs are included in the model in line with the DMC method guidelines(85). The unit cost per patient hour is assumed to be DKK 179 and the transportation cost per visit was assumed to be DKK 100 in line with the DMC guidelines(99) (see **Table 32**). Patient and transportation costs were applied at every visit to the hospital, e.g., training for administration of sotorasib, IV administration and disease management. To estimate patient costs, time usage was assumed, see Table 33.

Table 32. Unit cost for estimation of patient cost and transportation cost

Resource	Unit cost (DKK)	Source
Average hourly wage	179	Medicinrådet – "Værdisætning af enhedsomkostninger"(99)
Transportation cost per visit	100	Medicinrådet – "Værdisætning af enhedsomkostninger"(99)

Table 33. Assumed time usage for estimation of patient cost

Resource	Time usage (mins.)	Source
Patient time associated with training of administration with sotorasib	60	60 mins. assumed
Patient time associated with administration of docetaxel	90	Based on SmPC for docetaxel, 90 mins. Is assumed for IV administration of docetaxel(92)
Patient time associated with outpatient consultation	60	60 mins. assumed
Patient time associated with CT-scan	60	60 mins. assumed
Patient time associated with blood samples	30	30 mins. assumed

8.6 Results

8.6.1 Base-case overview

Table 34. Summary of model base-case and rationale

Category	Base-case analysis	Rationale
Model structure	Partitioned survival model with 3 health states: progression-free, progressed, and death	Reflects the three most relevant disease health states which capture the clinical events experienced by patients with NSCLC. The structure is typical of NSCLC and oncology modelling and has been used in several previous DMC assessments.
Time horizon	20-year (lifetime) time horizon	The time horizon was considered sufficient to capture all costs and benefits over the lifetime of the modelled population
Comparator	Docetaxel monotherapy	Docetaxel was described as the second-line therapy in the clinical guidelines for NSCLC(6), and furthermore two consulted Danish clinicians regarded docetaxel as the appropriate standard of care for previously treated (2L+) NSCLC(2, 3).
Population	The population is adults with advanced NSCLC with KRAS G12C mutation and who have progressed after at least one prior line of systemic therapy.	Aligned with the licensed indication. The population is generalizable to Danish clinical practice and reflects a population with minimal treatment options.
Efficacy	MAIC is a valid approach to model efficacy for sotorasib vs. docetaxel monotherapy (SELECT-1)	Given that sotorasib is a single arm trial, an unanchored MAIC offered the most robust method of comparison to account for potential differences in prognostic characteristics. Multiple MAIC models and unadjusted analyses are presented to fully explore the uncertainty of results.
Modelling of TTD	[redacted] Docetaxel: Assumed to be equal to PFS	Most clinically plausible modelling of TTD.
MAIC source	MAIC Adjusted: "all variables of prognostic importance" (SET 1)	Alternative option not feasible due to low effective samples size.

Parametric function for PFS	Sotorasib: Restricted log-normal Docetaxel: Restricted log-normal	Appropriate extrapolation option, clinically plausible extrapolation.
Parametric function for OS	Sotorasib: Restricted log-normal Docetaxel: Restricted log-normal	Appropriate extrapolation option, clinically plausible extrapolation.
Source of utilities	CodeBreak 100	Data specific to the efficacy data and patients in CodeBreak 100 (NSCLC patients with KRAS G12C mutation).
HRQoL	Quality of life is appropriately captured using health-state based utilities	Health-state based utilities have been used in the base-case.
HRQoL	Treatment specific utility decrement for IV docetaxel	Direct use of reported utility data from CodeBreak 100 may underestimate utility decrement associated with a cytotoxic chemotherapy with IV administration. An additional treatment-specific utility decrement identified from the literature is applied to account for this.
Adverse events	Grade 3+ TRAEs	TRAEs are more specific and relevant to capture in the model than treatment emergent adverse events.
Costs	No costs are assumed for KRAS mutation testing	KRAS testing is routinely conducted for NSCLC patients in Denmark and no additional tests beyond those used in the routine diagnostic work up and management of patients with NSCLC are required.
Costs	Disease management costs are generalizable to the Danish clinical setting	Disease management costs are consistent with previous DMC assessments in NSCLC and were considered by Danish clinicians to be reflective of health care resource utilization in this disease area(2, 3).
Costs	Treatment duration approach is appropriate	The treatment duration for sotorasib was applied to PFS using patient level data for simplicity and was reasonable. The treatment duration for docetaxel was set equal to PFS as it is not expected to be a major cost driver.

Key: 2L, second-line; DMC, Danish medicines council; HRQoL, health-related quality of life; IV, intravenous; MAIC, matching-adjusted indirect comparison; NSCLC, non-small-cell lung cancer; PFS, progression-free survival; OS, overall survival; SAF, safety analysis set; TTD, time to treatment discontinuation; TRAE, treatment-related adverse event

8.6.2 Base-case results

In the model base-case where docetaxel is considered the comparator, discounted results are presented in **Error! Reference source not found.**. Using a 20-year time horizon, the incremental total life-year gain of sotorasib versus docetaxel was [redacted] years. The discounted incremental costs of [redacted] DKK and incremental QALYs of [redacted] resulted in an incremental cost-effectiveness ratio (ICER) of [redacted] DKK/QALY versus docetaxel. This would be cost-effective at a willingness-to-pay threshold of DKK 750,000 per QALY.

[redacted]

Key: AE, adverse event; ICER, incremental cost-effectiveness ratio; LY, life-years; NMB, net monetary benefit; WTP, willingness-to-pay; QALY, quality-adjusted life years.

8.7 Sensitivity analyses

8.7.1 Deterministic sensitivity analyses

The results of the DSA comparing sotorasib with docetaxel are presented as tornado plot in **Error! Reference source not found.**. The plot demonstrates the top 10 parameters that had the largest effect on the ICER determined as the difference in the lower and upper bound parameter values. The five parameters which had the largest influence on the ICER were (i) the hazard ratio to derive sotorasib time to treatment discontinuation, (ii) the administration cost of docetaxel, (iii) the relative dose intensity of sotorasib, (iv) the health state utility of progression-free and (v) the hazard ratio to derive docetaxel time to treatment discontinuation.

Key: Admin, administration; AE, adverse event; HR, hazard ratio; IV, intravenous; PFS, progression-free survival; RDI, relative dose intensity; TTD, time-to-treatment-discontinuation.

8.7.2 Scenario analysis

Scenario analyses were conducted to assess the impact of alternative input parameters, settings, or assumptions on the model results. Table 35 summarizes the scenarios considered.

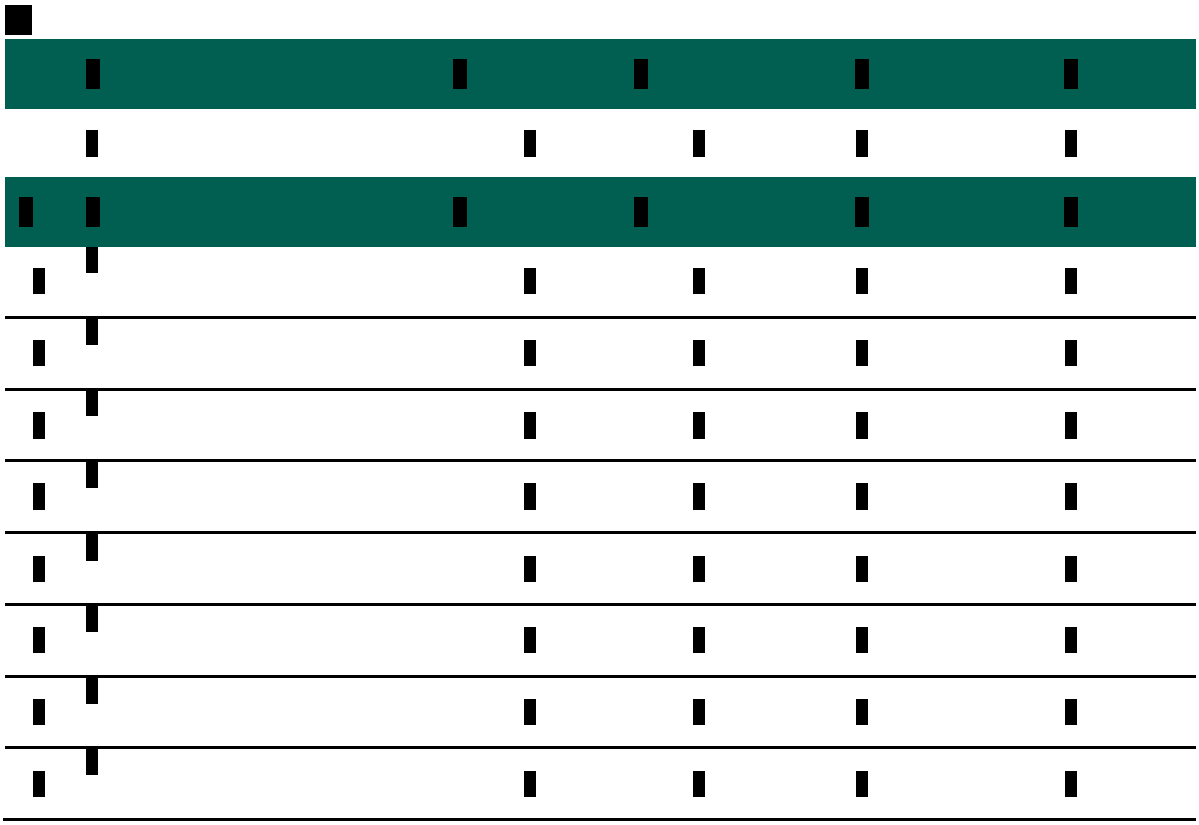
Table 35. Description of scenario analyses

No.	Scenario	Base-case Assumption	Rationale
1	Use 2nd best fitting OS and PFS distribution, generalized gamma.	Restricted model using log-normal distribution.	Effect of choosing the second-best and third-best fitting jointly fitted parametric fits using the restricted model.
2	Use 3rd best fitting OS and PFS distribution, log-logistic.		
3	Unrestricted log-normal distribution for PFS.		Effect of choosing the unrestricted model for PFS, given that there is some uncertainty around which model is the best fitting, using the best fitting log-normal distribution based on BIC.

4	Unadjusted sotorasib from CodeBreak 100 vs. unadjusted docetaxel from SELECT-1.	MAIC uses all variables of prognostic importance.	Effect of using unadjusted outcomes from CodeBreak 100 and SELECT-1.
5	Unadjusted sotorasib from CodeBreak 100 vs. ATT-adjusted docetaxel from Flatiron.	MAIC CodeBreak 100 vs. SELECT-1.	Explore alternative efficacy sources.
6	MAIC using all variables	MAIC using pre-specified important variables (excluding line of therapy and PD(L)-1 expression)	Explore alternative MAIC method
7	MAIC-adjusted TTD curve from CodeBreak 100.	Sotorasib TTD curve derived from hazard ratio applied to PFS	Despite higher complexity and no corresponding data in SELECT-1, the approach is similar to OS and PFS.
8	HR of sotorasib vs. docetaxel = 1 after 5 years.	No time limit on the treatment effect.	Effect of no OS or PFS benefit of sotorasib over docetaxel after 5 years
9	MAIC-adjusted HR for sotorasib vs. docetaxel	Parametric distributions fitted to MAIC-adjusted data from CodeBreak 100	Explore the effect of proportional hazards assumption
10	MAIC-adjusted KM curve from CodeBreak 100 vs. unadjusted KM curve from SELECT-1 followed by restricted log-normal	Parametric distributions fitted to MAIC-adjusted data from CodeBreak 100 and unadjusted data from SELECT-1	Effect of using KM curves directly
11	Apply Time to death utility	.Apply health state utilities by progression status	Effect of modelling HRQOL using time to death utilities
12	15-year time horizon.	20-year time horizon.	Effect of reducing time horizon by 5 years.
13	Include drug wastage.	No drug wastage is assumed.	Drug wastage is explicitly included.
14	Exclude RDI.	Relative dose intensity of drug is taken from clinical trials	Patients are assumed to receive 100% of the drug dosage.

Key: AE, adverse event; ATT, average treatment effect of the treated; BIC, Bayesian information criterion; HR, hazard ratio; KM, Kaplan-Meier; MAIC, matching-adjusted indirect comparison; OS, overall survival; PD-(L)1, programmed death-ligand 1; PFS, progression-free survival; RDI, relative dose intensity; TTD, time to treatment discontinuation.

See results of scenario analysis below in **Error! Reference source not found.**.



[redacted]

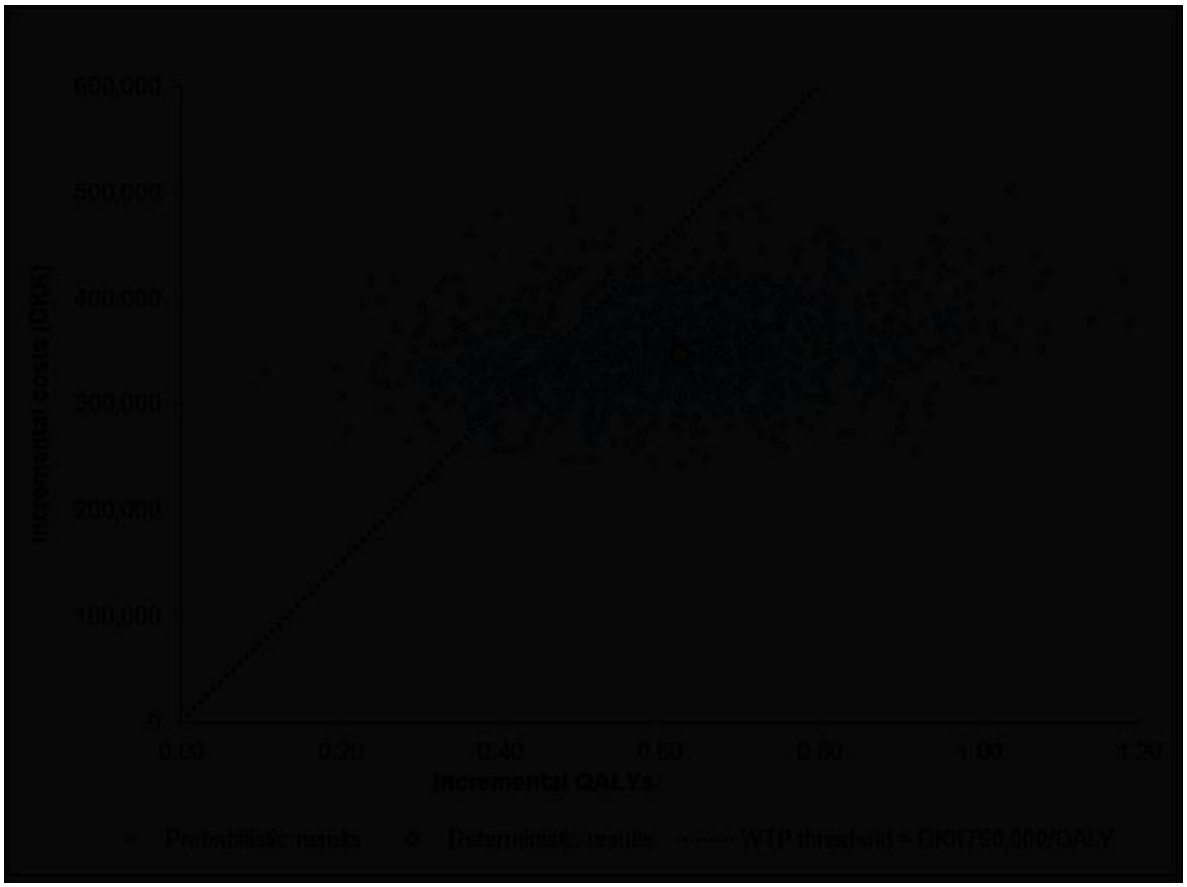
8.7.3 Probabilistic sensitivity analyses

A PSA was undertaken to explore the uncertainty of all model parameters and their associated impact on cost-effectiveness results. 1,000 iterations were used to ensure convergence. The total costs and QALYs were recorded for each iteration and averaged. PSA results for the comparison to docetaxel are presented in **Error! Reference source not found.**. The deterministic ICER for sotorasib compared to docetaxel ([redacted] DKK/QALY) is in line with the PSA results of ([redacted] DKK/QALY) confirming that the results are robust to parameter uncertainty.

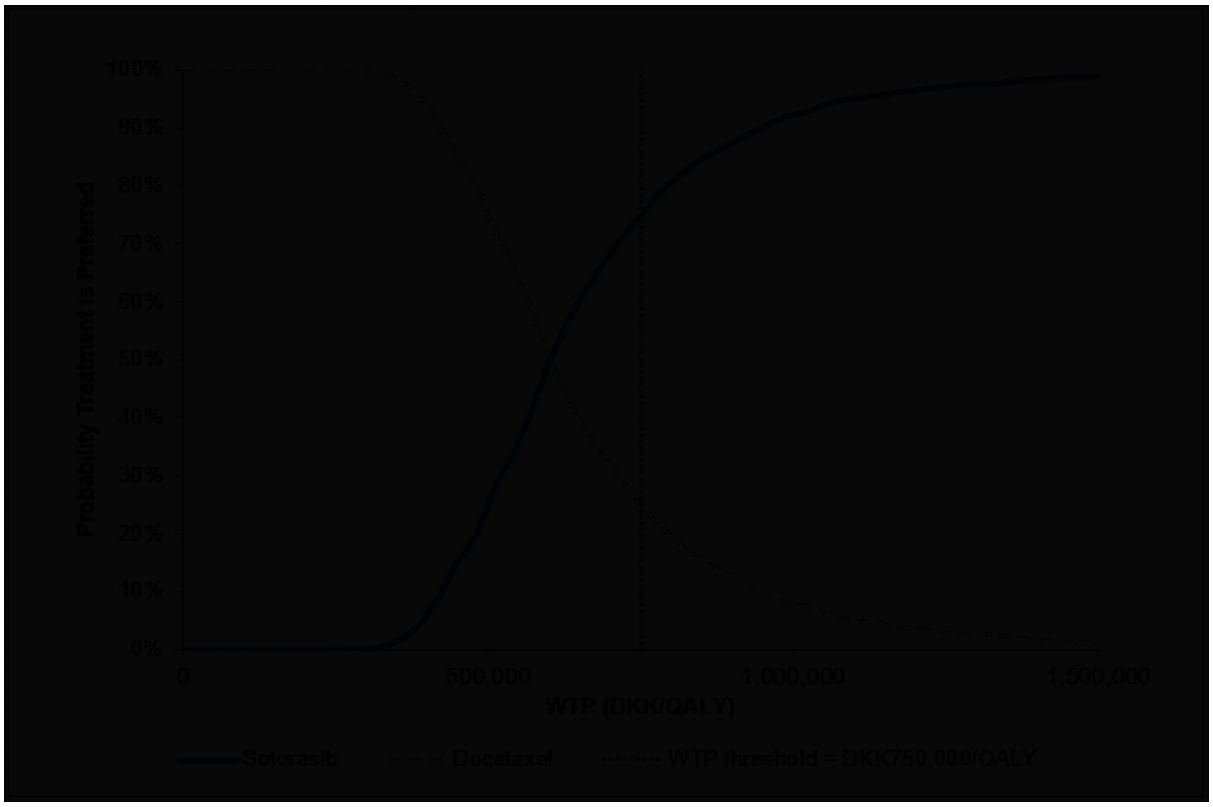
[redacted]

Key: ICER, incremental cost-effectiveness ratio; Incr., incremental; QALY, quality-adjusted life year.

Error! Reference source not found. represents the scatter plot of the incremental costs and QALYs from the PSA results based on 1,000 iterations. As shown in the cost-effectiveness acceptability curve (**Error! Reference source not found.**), sotorasib has a [redacted]% probability of being cost-effective versus docetaxel considering the DKK 750,000 WTP threshold.



Key: QALY, quality-adjusted life year; WTP, willingness-to-pay.



Key: QALY, quality-adjusted life year; WTP, willingness-to-pay.

9. Budget impact analysis

The budget impact model (BIM) was developed to estimate the expected budget impact of recommending sotorasib as a possible standard treatment in Denmark. The budget impact was estimated per year for the first 5 years after the introduction of sotorasib in Denmark.

The budget impact model was partially nested within the cost-effectiveness model, and therefore any changes in the settings of the cost-effectiveness model would affect the results of the BIM. The budget impact result is representative of the population in the cost-effectiveness model and the survival outcome of this population

The analysis was developed by comparing the costs for the Danish regions per year over five years in the scenario where sotorasib is recommended as standard treatment and the scenario where sotorasib is not recommended as standard treatment in the relevant treatment comparison. The total budget impact per year is the difference between the two scenarios.

9.1 Number of patients and market uptake

As described in section 5.1.5, between 110-140 patients with KRAS G12C-mutated NSCLC are expected to be eligible for 2nd line treatment each year. For this budget impact analysis, 125 patients have been assumed each year. Scenario analyses will be conducted on the outer bounds of the patient number estimate.

In the scenario, where sotorasib is not recommended, it is assumed that sotorasib will have a minimal market uptake of 5%, as sotorasib may be administered for a small number of patients based on the medical assessment by the physician. The remaining 95% is assumed to receive docetaxel in 2nd line in the scenario. See Table 36 for the patient numbers in this scenario.

In the scenario, where sotorasib is recommended, it is assumed that sotorasib will have 100% market uptake, as it is the superior treatment option compared to docetaxel, both in terms of efficacy and safety. See Table 37 for the patient numbers in this scenario.

Table 36. Number of patients expected to be treated over the next five-year period - if sotorasib is not recommended as standard treatment

	Year 1	Year 2	Year 3	Year 4	Year 5
Sotorasib	6	6	6	6	6
Docetaxel	119	119	119	119	119
Total number of patients	125	125	125	125	125

Table 37. Number of patients expected to be treated over the next five-year period - if sotorasib is recommended as standard treatment

	Year 1	Year 2	Year 3	Year 4	Year 5
Sotorasib	125	125	125	125	125
Docetaxel	0	0	0	0	0
Total number of patients	125	125	125	125	125

9.2 Budget impact

Based on the base-case settings, the estimated budget impact of recommending sotorasib as standard treatment in Denmark was DKK [redacted] in year 1 and DKK [redacted] in year 5 as shown in Error! Reference source not found..

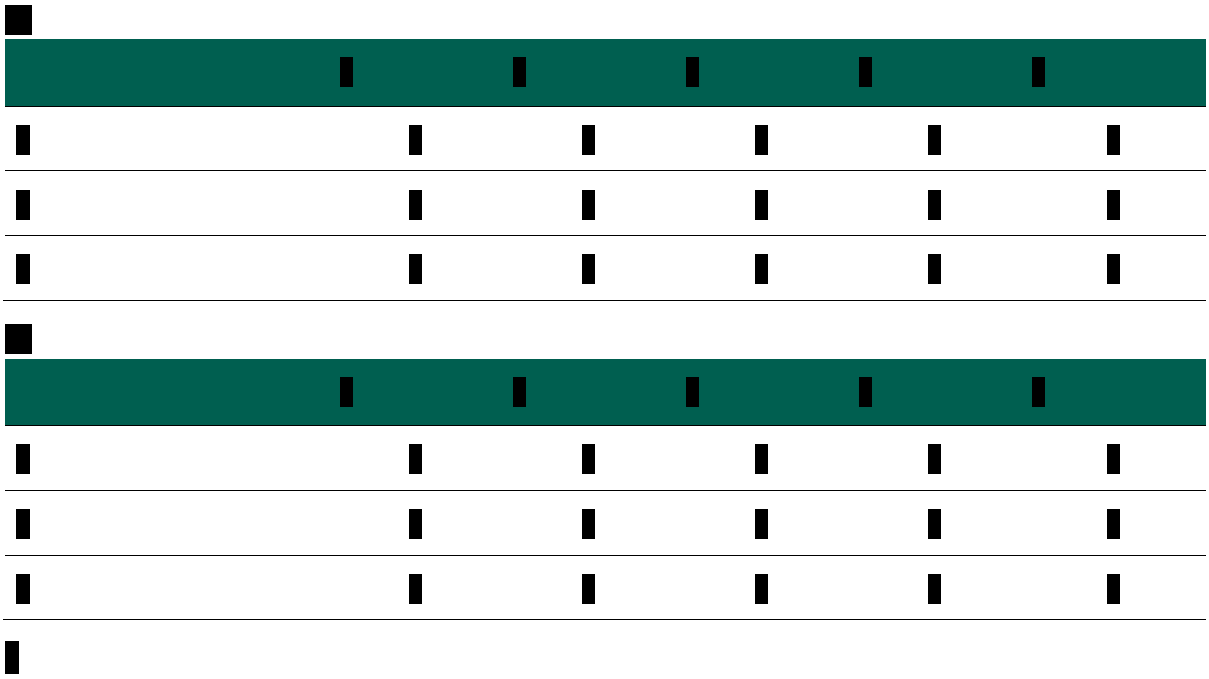
[redacted]

9.3 Scenario analysis

To test impact of the patient number estimate on the budget impact of recommending sotorasib, scenario analyses have been conducted on two scenarios:

- Scenario 1, where 110 patients are eligible for 2nd line treatment each year.
- Scenario 2, where 140 patients are eligible for 2nd line treatment each year.

The budget impact results of recommending sotorasib for scenario 1 has been reported in **Error! Reference source not found.** and for scenario 2 in Error! Reference source not found..



10. Discussion on the submitted documentation

Sotorasib is a highly innovative, first-in-class targeted therapy, which has received positive opinion by CHMP/EMA for the indication "*as monotherapy is indicated for the treatment of adults with advanced non-small cell lung cancer (NSCLC) with KRAS G12C mutation and who have progressed after at least one prior line of systemic therapy.*" Although data are currently limited to a phase 2 single-arm trial and indirect treatment comparisons, this collective early evidence indicates that sotorasib is highly effective, well tolerated and provides superior survival outcomes (PFS and OS) compared with the current primary non-targeted standard of care therapy. Sotorasib should therefore be made available as early as possible to address the high and urgent unmet needs of these patients, as real-world evidence suggests that the current prognosis for these patients is poor.

As the standard 2L treatment of advanced *KRAS G12C*-mutated NSCLC in Denmark, docetaxel was selected as the appropriate comparator.

Sotorasib was investigated in a single-arm clinical trial, CodeBreak 100. No direct head-to-head evidence was available to compare the clinical efficacy of sotorasib and docetaxel. In such circumstances, the relative efficacy of two treatments can often be estimated using indirect treatment comparison methods for OS and PFS. In this analysis, the relative efficacy was assessed using an unanchored MAIC. This method allows assessment of efficacy between treatments when a common comparator is missing by adjusting for population-level differences present in different data sources (74).

The MAIC used data from two clinical studies: the CodeBreak 100 trial for sotorasib, and the SELECT-1 trial for docetaxel. Comparability of the data sources, and hence the feasibility and appropriateness of performing a MAIC, was assessed through a review of the design and population profiles of the studies involved in the analyses.

Clinical outcomes

The clinical value of sotorasib compared to docetaxel is demonstrated by the survival outcome measures, PFS and OS. The results from the MAIC for PFS, demonstrate that sotorasib provides a [redacted] gain in median PFS compared with docetaxel monotherapy ([redacted]), exceeding the minimal clinically important difference of 3 months in median

PFS(7). For OS, matching adjustment indicates that sotorasib provides a [redacted] gain in median OS compared with the primary comparator docetaxel monotherapy ([redacted]), exceeding the minimal clinically important difference of 3 months in median OS(7).

Safety outcomes were compared narratively and were limited by incomparable exposure times between sotorasib and docetaxel evidence. The median duration of treatment varied from 5.5 months for sotorasib to 2.4 months for docetaxel. Sotorasib presented a lower rate of treatment discontinuations due to AEs (8.7% vs. 14.5%), and lower occurrence of grade 3 or worse TRAEs (20.6% vs 30.0%). Sotorasib is expected to be safer and more tolerable compared to docetaxel, aligning with the clinical expectation of safety of a targeted therapy compared to chemotherapies.

Strengths

The CodeBreak 100 trial provides an early indication of the efficacy and safety of targeted therapy with sotorasib. The trial recruited patients who are reflective of those in Danish clinical practice (as observed in the retrospective registry study described in section 5.1.5) and assessed relevant outcomes using the dose regimen approved by the EMA. Results from indirect comparisons using the most plausible method available to derive relative efficacy estimates between sotorasib and docetaxel was used. In the context of a disease with no other targeted therapies, high and urgent unmet needs, and with limited available data, the evidence in support of sotorasib is compelling. The evidence strongly indicates that sotorasib has a superior efficacy and safety profile compared with the current standard of care systemic cytotoxic chemotherapy.

Limitations

Given the context of a disease with no other targeted therapies, high and urgent unmet needs, and with limited available data with which to make comparisons, there are limitations to the current evidence base. The lack of a direct trial comparison between sotorasib and docetaxel, necessitates the need to conduct an unanchored MAIC to estimate the relative treatment effect. An unanchored MAIC is based around a strong assumption that all effect modifiers and prognostic factors can be accounted for.

The proportion of patients with stable brain metastases (both trials excluded patients with active brain metastases) was not reported in SELECT-1 and was 21% in CodeBreak 100 pre-matching (18% post matching). The analysis is potentially conservative for the comparative efficacy of sotorasib vs. docetaxel in this regard, as the presence of brain metastases is a negative prognostic factor, whereas in other previously treated NSCLC RCTs, the proportion of patients with stable brain metastases was consistently lower than in CodeBreak 100, suggesting there were potentially fewer patients with brain metastases in the SELECT-1 trial.

As PFS and OS outcomes are likely to be worse for patients with each successive line of therapy, the comparison is likely to be biased in favor of docetaxel due to the differences in the patient population between CodeBreak 100 and SELECT-1. The SELECT-1 trial only included patients with one previous line of therapy. This compares with 57% of patients having had more than one line of therapy in CodeBreak 100. Furthermore, there is limited data for either sotorasib or docetaxel in patients with squamous *KRAS G12C*-mutated cancer. The CodeBreak 100 trial excluded patients at or above ECOG performance status 2, who would be particularly likely to benefit from sotorasib's superior safety profile compared with docetaxel.

Health economics

A cohort-based partitioned survival model was developed in Microsoft Excel® to evaluate the cost-effectiveness of sotorasib vs. docetaxel from a Danish restrictive societal perspective over a lifetime horizon (20 years).

The health economic analysis demonstrates that sotorasib is a novel and clinically effective treatment option for 2L+ NSCLC patients with the KRAS G12C mutation, which significantly improves life-years and QALYs compared with docetaxel. In the base-case analysis, the ICER for sotorasib versus docetaxel was [redacted] DKK/QALY and on life-years, the ICER was [redacted] DKK/LY. This would be cost-effective at a willingness-to-pay threshold of DKK 750,000 per

QALY. Results of the probabilistic sensitivity analyses are consistent with the base-case results, indicating that the base-case results are robust to parameter uncertainty. The PSA estimated a [redacted]% probability that sotorasib is cost-effective compared to docetaxel at the given threshold of DKK 750,000 per QALY. The BIM suggested that the estimated budget impact of recommending sotorasib as standard treatment in Denmark was [redacted] million DKK in year 1 and [redacted] million DKK in year 5, when assuming 125 new patients would be eligible for treatment with sotorasib each year.

The most clinically plausible extrapolations of PFS and OS data were selected for the base-case analysis and extensive scenario analyses were conducted to assess the impact of alternative modeling choices with only a small impact on the results of the analyses.

A key strength of the analysis is that given the similarity of patient populations, the risk of bias is expected to be low. However, due to the highly pre-treated population of CodeBreak 100, the potentially remaining bias most likely favors docetaxel. Therefore, the outcomes of the MAIC analysis can be considered conservative. Secondly, the model appears to be robust to parameter uncertainty and structural uncertainty. The ICER exceed the willingness-to-pay threshold of DKK 750,000 per QALY in only one scenario.

Conclusion

In summary, CodeBreak 100 suggests that sotorasib is a highly effective and tolerable therapy for NSCLC patients with KRAS G12C mutation. The indirect treatment comparison suggests that sotorasib provides a superior treatment option for these patients compared to docetaxel, providing PFS and OS gains which exceed the minimally clinical important differences of 3 months, previously defined by the lung cancer expert committee at DMC(7).

Health economic analysis demonstrates that sotorasib is a more effective and more costly treatment option compared to docetaxel that would be cost-effective at a willingness-to-pay threshold of 750,000 DKK per QALY.

The interpretation of the current clinical evidence is somewhat limited by the current lack of a direct comparison between sotorasib and docetaxel. This limitation will be addressed in the future with results of the ongoing phase 3 randomized, active-controlled CodeBreak 200 study, where sotorasib and docetaxel are compared head-to-head. Survival and additional clinical benefits of sotorasib will be confirmed in this trial. Similar or perhaps better efficacy estimates may be seen in the ongoing Phase III study.

11. List of experts

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12. References

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

A SLR was conducted to identify RCTs that report clinical effectiveness and safety of United States and EU licensed second-line therapies. Randomized controlled trials (phase II - IV) of adults (18 years) with locally advanced and unresectable or metastatic (stage IIIB-IV) NSCLC who had received at least 1 prior systemic therapy were eligible for inclusion. Outcomes of interest include overall survival (OS), progression-free survival (PFS) and event-free survival (65), time to progression (TTP), time to next treatment (TTNT), response rates, disease control rate, treatment duration and adverse events. Studies were identified by searching electronic databases, reference lists of relevant articles, conference proceedings and other supplementary sources.

The SLR conformed to published guidelines issued by the Cochrane Collaboration (1) and the Centre for Reviews & Dissemination (CRD; York, UK) and followed the methodological requirements of the National Institute for Health and Care Excellence (NICE), UK, the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (66), and the Consolidated Standards of Reporting Trials (CONSORT) and statements (66-70). The SLR search was conducted in June 2020. An updated search was conducted on 26 January 2021.

Searches were conducted in Embase, Medline and The Cochrane Central Register of Controlled Trials (CENTRAL), for the original and updated searches.

Search Strategies

This SLR search strategy was based on that used in a recently published SLR by Schulz et al. (2019), which was conducted in the pretreated NSCLC population(100). Unlike Schulz et al. the current review set out to include only those publications reporting outcome data for a KRASm population or subgroup in line with the objectives of this SLR. The current review therefore included any studies identified as relevant by Schulz et al, regardless of publication date, and all relevant studies published during or after 2015 identified by replicating the Schulz et. al (2019) search strategy (100). The replicated searches were run in June 2020 and updated again 26th January 2021.

The following electronic databases were searched via the OVID platform:

- Embase, 1980 to present day
- MEDLINE®, incorporating:
    - MEDLINE®, 1946 to present day
    - MEDLINE® In Process & Other Non-Indexed Citations
    - MEDLINE® Epub Ahead of Print and MEDLINE® Daily
- The Cochrane Library, incorporating;
    - the Cochrane Database of Systematic Reviews (Cochrane Reviews)
    - the Cochrane Central Register of Controlled Trials (CENTRAL)

The database search strings identified relevant studies (full papers or conference abstracts) indexed in Embase, and were modified to perform the searches in MEDLINE, and the Cochrane Library, to account for differences in syntax and thesaurus headings. Searches include terms for free text and Medical Subject Heading (MeSH) terms. The search strategy for each database, and associated number of hits, are presented below for the June 2020 and the January 2021 update.

Search strategies for RCTs

Embase – original search

Embase <1980 to present>: accessed 25th June 2020

	Searches	Results
1	exp non small cell lung cancer/	98821
2	lung cancer/ and non small cell.ti,ab.	14730
3	nsclc.ti,ab.	81646
4	non small cell.ti,ab.	102425
5	(carcinom$ or cancer$ or neoplas$).ti,ab.	3177270
6	lung$.ti,ab.	933416
7	1 or 2 or 3 or (4 and 5 and 6)	156582
8	crossover-procedure/ or double-blind procedure/ or randomized controlled trial/ or single-blind procedure/	690342
9	(random$ or factorial$ or crossover$ or cross over$ or cross-over$ or placebo$ or (doubl$ adj blind$) or (singl$ adj blind$) or assign$ or allocat$ or volunteer$).ti,ab.	2272961
10	8 or 9	2372831
11	(animal$ not human$).sh,hw.	4395903
12	10 not 11	2158432
13	7 and 12	16155
14	limit 13 to conference abstracts	6524
15	13 not 14 [Full texts only]	9631
16	limit 14 to yr="2017 -Current"	2485
17	limit 15 to yr="2015 -Current"	3950
18	16 or 17	6435

Medline – original search

Ovid MEDLINE(R) and Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Daily and Versions(R) <1946 to June 11, 2020>: accessed 12 June 2020

#	Searches	Results
1	exp non small cell lung cancer/	52621
2	lung cancer/ and non small cell.ti,ab.	43793
3	nsclc.ti,ab.	42066
4	non small cell.ti,ab.	62661
5	(carcinom$ or cancer$ or neoplas$).ti,ab.	2292005
6	lung$.ti,ab.	650840
7	1 or 2 or 3 or (4 and 5 and 6)	76000
8	crossover-procedure/ or double-blind procedure/ or randomized controlled trial/ or single-blind procedure/	507382
9	(random$ or factorial$ or crossover$ or cross over$ or cross-over$ or placebo$ or (doubl$ adj blind$) or (singl$ adj blind$) or assign$ or allocat$ or volunteer$).ti,ab.	1677369
10	8 or 9	1766178
11	(animal$ not human$).sh,hw.	4664148
12	10 not 11	1593110
13	7 and 12	7727
14	limit 13 to yr="2015 -Current"	2731

Cochrane – original search

The Cochrane Library including Cochrane Central Register of Controlled Trials (CENTRAL), Cochrane Database of Systematic Reviews (Cochrane Reviews): accessed 12 June 2020

#	Searches	Results
1	exp non small cell lung cancer/	4213
2	lung cancer/ and non small cell.ti,ab.	3559
3	nsclc.ti,ab.	9389
4	non small cell.ti,ab.	11599
5	(carcinom$ or cancer$ or neoplas$).ti,ab.	169791
6	lung$.ti,ab.	51312
7	1 or 2 or 3 or (4 and 5 and 6)	13703
8	crossover-procedure/ or double-blind procedure/ or randomized controlled trial/ or single-blind procedure/	137
9	(random$ or factorial$ or crossover$ or cross over$ or cross-over$ or placebo$ or (doubl$ adj blind$) or (singl$ adj blind$) or assign$ or allocat$ or volunteer$).ti,ab.	1118684
10	8 or 9	1118699
11	(animal$ not human$).sh,hw.	2072
12	10 not 11	1117419
13	7 and 12	9466
14	limit 13 to yr="2015 -Current"	4281
15	exp non small cell lung cancer/	4213
16	lung cancer/ and non small cell.ti,ab.	3559
17	nsclc.ti,ab.	9389
18	non small cell.ti,ab.	11599

19	(carcinom$ or cancer$ or neoplas$).ti,ab.	169791
20	lung$.ti,ab.	51312
21	15 or 16 or 17 or (18 and 19 and 20)	13703
22	crossover-procedure/ or double-blind procedure/ or randomized controlled trial/ or single-blind procedure/	137
23	(random$ or factorial$ or crossover$ or cross over$ or cross-over$ or placebo$ or (doubl$ adj blind$) or (singl$ adj blind$) or assign$ or allocat$ or volunteer$).ti,ab.	1118684
24	22 or 23	1118699
25	(animal$ not human$).sh,hw.	2072
26	24 not 25	1117419
27	21 and 26	9466
28	limit 27 to yr="2015 -Current"	4281

Embase - 2021 update

Embase <1980 to 2021 Week 03>: accessed 26 January 2021

	Searches	**Results**
1	exp non small cell lung cancer/	105188
2	lung cancer/ and non small cell.ti,ab.	14842
3	nsclc.ti,ab.	85349
4	non small cell.ti,ab.	106532
5	(carcinom$ or cancer$ or neoplas$).ti,ab.	3202195
6	lung$.ti,ab.	930054
7	1 or 2 or 3 or (4 and 5 and 6)	163414
8	crossover-procedure/ or double-blind procedure/ or randomized controlled trial/ or single-blind procedure/	708522

9	(random$ or factorial$ or crossover$ or cross over$ or cross-over$ or placebo$ or (doubl$ adj blind$) or (singl$ adj blind$) or assign$ or allocat$ or volunteer$).ti,ab.	2312465
10	8 or 9	2412281
11	(animal$ not human$).sh,hw.	4232620
12	10 not 11	2193742
13	7 and 12	16797
14	limit 13 to conference abstracts	6842
15	13 not 14 [Full texts only]	9955
16	limit 14 to yr="2017 -Current"	2796
17	limit 15 to yr="2015 -Current"	4278
18	16 or 17	7074
19	(Sep* 2020 or Oct* 2020 or Nov* 2020 or Dec* 2020 or Jan* 2021).dp.	230158
20	limit 18 to dd=20200901-202101026	383
21	18 and 19	265
22	20 or 21	505

Medline – 2021 update

Ovid MEDLINE(R) and Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Daily and Versions(R) <1946 to January 25, 2021>: 26 January 2021

#	Searches	Results
1	exp non small cell lung cancer/	55228
2	lung cancer/ and non small cell.ti,ab.	45910
3	nsclc.ti,ab.	45567
4	non small cell.ti,ab.	67103
5	(carcinom$ or cancer$ or neoplas$).ti,ab.	2409018
6	lung$.ti,ab.	682052
7	1 or 2 or 3 or (4 and 5 and 6)	81120
8	crossover-procedure/ or double-blind procedure/ or randomized controlled trial/ or single-blind procedure/	521393
9	(random$ or factorial$ or crossover$ or cross over$ or cross-over$ or placebo$ or (doubl$ adj blind$) or (singl$ adj blind$) or assign$ or allocat$ or volunteer$).ti,ab.	1761165
10	8 or 9	1851358
11	(animal$ not human$).sh,hw.	4737364
12	10 not 11	1672953
13	7 and 12	8154
14	(2020 Sep* or 2020 Oct* or 2020 Nov* or 2020 Dec* or 2021 Jan*).dp.	589177
15	13 and 14	230
16	limit 13 to ed=20200901-20210126	149
17	15 or 16	358

Cochrane – 2021 update

The Cochrane Library including Cochrane Central Register of Controlled Trials (CENTRAL), Cochrane Database of Systematic Reviews (Cochrane Reviews): accessed 26 January 2021

#	Searches	Results
1	exp non small cell lung cancer/	4365
2	lung cancer/ and non small cell.ti,ab.	3663
3	nsclc.ti,ab.	9820
4	non small cell.ti,ab.	12057
5	(carcinom$ or cancer$ or neoplas$).ti,ab.	178044
6	lung$.ti,ab.	54134
7	1 or 2 or 3 or (4 and 5 and 6)	14278
8	crossover-procedure/ or double-blind procedure/ or randomized controlled trial/ or single-blind procedure/	137
9	(random$ or factorial$ or crossover$ or cross over$ or cross-over$ or placebo$ or (doubl$ adj blind$) or (singl$ adj blind$) or assign$ or allocat$ or volunteer$).ti,ab.	1178914
10	8 or 9	1178929
11	(animal$ not human$).sh,hw.	2106
12	10 not 11	1177616
13	7 and 12	9948
14	limit 13 to yr="2020 -Current"	517

In addition, the following sources were hand searched:

- ***Conference proceedings***

To identify further studies not captured in the electronic database searches, proceedings of the following conferences held between January 2017 – January 2021 inclusive were searched via the conferences' online platforms, or via downloadable abstract books:

- American Society of Clinical Oncology (ASCO)
- European Society for Medical Oncology (ESMO)

- International Association for the Study of Lung Cancer (IASLC) World congress on lung cancer
- American Association of Cancer Research (AACR).

In addition, conference abstracts indexed in Embase were also considered for inclusion.

- ***Clinical trial registries***

To obtain details of potentially relevant clinical trials, the following clinical trial registry databases were searched (January 2017 – January 2021):

- clinicaltrials.gov
- National Cancer Institute (NCI) clinical trial database: https://www.cancer.gov/
- International Standard Randomized Controlled Trial Number (ISRCTN) Register: https://www.isrctn.com/
- United Kingdom Coordinating Committee on Cancer Research (UKCCCR) Register of Cancer Trials: http://www.ctu.mrc.ac.uk/ukcccr/
- European Organization for Research and Treatment of Cancer (EORTC): http://www.eortc.org/
- UK Clinical Trials Gateway: https://www.ukctg.nihr.ac.uk/
- metaRegister of Controlled Trials (mRCT): http://www.isrctn.com/page/mrct

- ***Reference lists***

Reference lists of included publications and relevant SLRs/NMAs were scanned.

Search strategies for single-arm trials

The electronic databases and congresses below were originally searched for single arm trials in patients with *KRAS G12C-mutated* NSCLC on 24 July 2019 (covering the period 2014 to 2019). These searches were first re-screened to extend the population inclusion criterion to patients with KRAS mutant NSCLC. The searches were then updated 10 March 2021 to identify single arm trials in patients with KRAS mutant NSCLC in the period 2019 to 2021.

- MEDLINE® Epub Ahead of Print, In-Process & Other Non-Indexed Citations, MEDLINE® Daily and Ovid MEDLINE® 1946 to present
- Embase, 1974 to present
- Cochrane Library, comprising:
    - Cochrane Database of Systematic Reviews (CDSR)
    - Database of Abstracts of Reviews of Effects (DARE)
    - Cochrane Central Register of Controlled trials (CENTRAL)
    - Cochrane Methodology Register (CMR)
    - NHS Economic Evaluations Database (NHS EED)
    - Health Technology Assessment Database
    - American College of Physicians (ACP) Journal Club
- Clinical trials registers:
    - National Institutes of Health (NIH) https://www.nih.gov/
    - ClinicalTrials.gov http://www.clinicaltrials.gov/

    - World Health Organization International Clinical Trials Registry Platform (ICTRP) http://www.who.int/ictrp/en/
    - Australian New Zealand Clinical Trials Registry (ANZCTR) http://www.anzctr.org.au/
    - European Clinical Trials Register (EU CTR) https://www.clinicaltrialsregister.eu/
- Conference proceedings covering 2017 to 2021:
    - American Society of Clinical Oncology (ASCO) Annual meeting: https://www.asco.org/
    - European Society for Medical Oncology (ESMO): http://www.esmo.org/
    - World Conference on Lung Cancer (WCLC): https://wclc2019.iaslc.org/
    - European Lung Cancer Congress (ELCC): https://www.esmo.org/Conferences/ELCC-2019-European-Lung-Cancer-Congress
    - American Society of Clinical Oncology GastroIntestinal Congress (ASCO) https://www.asco.org/

The initial SLR focused on only populations with *KRAS G12C-mutated* NSCLC; however, as this yielded very few hits, this was rescreened to expand the inclusion to patients with any KRAS mutant NSCLC. The search strategies for each database, and associated number of hits, are presented below for the initial July 2019 searches and the March 2021 update.

- ***Embase – original search: 24 July 2019***

#	Searches	Results
1	exp lung non small cell cancer/	80 585
2	(nsclc or non-small cell lung cancer).ti,ab.	96 745
3	1 or 2	132 161
4	limit 3 to yr="2014 -Current"	71 463
5	exp colon cancer/ or exp rectum cancer/ or colorectal tumor/	301 005
6	((colorect$ or rectal$ or rectum$ or colon$ or sigma$ or sigmo$ or rectosigm$ or bowel$ or anal or anus) adj3 (cancer$ or neoplas$ or oncolog$ or malignan$ or tumo?r$ or carcinoma$ or adenocarcinoma$ or metasta$ or meta-sta$ or sarcoma$ or adenom$ or lesion$)).ti,ab.	323 534
7	5 or 6	391 666
8	limit 7 to yr="2009 -Current"	247 336
9	4 or 8	314 073
10	k ras oncogene/	9909

11	((k ras or kras or k-ras or V-Ki-ras$ or V-K-ras or V-Ki-ras or v ki ras or c-ki-ras or c-k-ras or ki-ras or ki ras or Kras1 or Kras2 or KRAS1P or RASK or RASK1 or RASK2 or Kirsten RAS) adj5 (mutation$ or mutant$ or mutated or status or exon or gene$ or translocation$ or rearrangement$ or oncogene$ or fusion$ or expression$ or over?expression$ or amplification$ or inversion$ or deletion$)).ti,ab.	26 944
12	10 or 11	30 660
13	epidemiology/ or epidemiology.ti,ab,kw.	418 811
14	incidence/ or incidence.ti,ab,kw.	1 108 289
15	prevalence/ or prevalence.ti,ab,kw.	974 387
16	overall survival/ or (disease specific survival* or long term survival* or overall survival* or prolong$ survival* or survival anal$).ti,ab,kw.	434 023
17	progression free survival/ or (progression free survival or progression-free survival).ti,ab,kw.	106 597
18	(overall response rate or ORR).mp.	33 752
19	(duration of response or time to response or TTR).mp.	22 485
20	adverse drug reaction.fs.	1 200 009
21	or/13-20	3 683 830
22	Case study/	62 816
23	Case report.tw.	388 029
24	Letter/	1 024 171
25	or/22-24	1 465 246
26	21 not 25	3 497 123
27	9 and 12 and 26	4845
28	(animal$ not human$).sh,hw.	4 222 885
29	27 not 28	4770
30	limit 29 to english language	4680

31	limit 30 to (editorial or erratum or letter or note or patent or reports or "review" or short survey or tombstone)	569
32	systematic review/ or "systematic review (topic)"/ or systematic review.mp. or meta-analysis/ or "meta analysis (topic)".mp. or meta-analysis.mp.	406 496
33	31 not 32	491
34	30 not 33	4189
35	remove duplicates from 34	4064

- ***MEDLINE – original search: 24 July 2019***

#	Searches	Results
1	exp Carcinoma, Non-Small-Cell Lung/	48 644
2	(nsclc or non-small cell lung cancer).ti,ab.	56 422
3	1 or 2	67 049
4	limit 3 to yr="2014 -Current"	29 081
5	exp colon cancer/ or exp rectum cancer/ or colorectal tumor/	184 107
6	((colorect$ or rectal$ or rectum$ or colon$ or sigma$ or sigmo$ or rectosigm$ or bowel$ or anal or anus) adj3 (cancer$ or neoplas$ or oncolog$ or malignan$ or tumo?r$ or carcinoma$ or adenocarcinoma$ or metasta$ or meta-sta$ or sarcoma$ or adenom$ or lesion$)).ti,ab.	224 916
7	5 or 6	264 155
8	limit 7 to yr="2009 -Current"	127 847
9	4 or 8	156 290
10	k ras oncogene/	12 293
11	((k ras or kras or k-ras or V-Ki-ras$ or V-K-ras or V-Ki-ras or v ki ras or c-ki-ras or c-k-ras or ki-ras or ki ras or Kras1 or Kras2 or KRAS1P or RASK or RASK1 or RASK2 or Kirsten RAS) adj5 (mutation$ or mutant$ or mutated or status or exon or gene$ or translocation$ or rearrangement$ or oncogene$ or fusion$ or expression$ or over?expression$ or amplification$ or inversion$ or deletion$)).ti,ab.	14 621

12	10 or 11	22 786
13	epidemiology/ or epidemiology.ti,ab,kw.	172 050
14	incidence/ or incidence.ti,ab,kw.	805 391
15	prevalence/ or prevalence.ti,ab,kw.	660 077
16	Survival Analysis/ or (disease specific survival* or long term survival* or overall survival* or prolong$ survival* or survival anal$).ti,ab,kw.	313 126
17	progression free survival/ or (progression free survival or progression-free survival).ti,ab,kw.	39 360
18	(overall response rate or ORR).mp.	18 412
19	(duration of response or time to response or TTR).mp.	13 580
20	adverse effects.fs.	1 660 331
21	or/13-20	3 220 374
22	Case study/	2 033 482
23	Case report.tw.	291 514
24	Letter/	1 035 818
25	or/22-24	2 916 737
26	21 not 25	2 783 864
27	9 and 12 and 26	1613
28	(animal$ not human$).sh,hw.	4 559 823
29	27 not 28	1610
30	limit 29 to english language	1561
31	limit 30 to (editorial or review)	184
32	systematic review/ or "systematic review (topic)"/ or systematic review.mp. or meta-analysis/ or "meta analysis (topic)".mp. or meta-analysis.mp.	251 075

33	31 not 32	131
34	30 not 33	1430
35	remove duplicates from 34	1427

- ***Cochrane – original search: 24 July 2019***

#	Searches	Results
1	exp Carcinoma, Non-Small-Cell Lung/	3982
2	(nsclc or non-small cell lung cancer).ti,ab.	12 273
3	1 or 2	12 686
4	limit 3 to yr="2014 -Current" [Limit not valid in DARE; records were retained]	5674
5	exp colon cancer/ or exp rectum cancer/ or colorectal tumor/	7717
6	((colorect$ or rectal$ or rectum$ or colon$ or sigma$ or sigmo$ or rectosigm$ or bowel$ or anal or anus) adj3 (cancer$ or neoplas$ or oncolog$ or malignan$ or tumo?r$ or carcinoma$ or adenocarcinoma$ or metasta$ or meta-sta$ or sarcoma$ or adenom$ or lesion$)).ti,ab.	21 675
7	5 or 6	22 605
8	limit 7 to yr="2009 -Current" [Limit not valid in DARE; records were retained]	15 130
9	4 or 8	20 698
10	k ras oncogene/	65
11	((k ras or kras or k-ras or V-Ki-ras$ or V-K-ras or V-Ki-ras or v ki ras or c-ki-ras or c-k-ras or ki-ras or ki ras or Kras1 or Kras2 or KRAS1P or RASK or RASK1 or RASK2 or Kirsten RAS) adj5 (mutation$ or mutant$ or mutated or status or exon or gene$ or translocation$ or rearrangement$ or oncogene$ or fusion$ or expression$ or over?expression$ or amplification$ or inversion$ or deletion$)).ti,ab.	1176
12	10 or 11	1193
13	epidemiology/ or epidemiology.ti,ab,kw.	14 636
14	incidence/ or incidence.ti,ab,kw.	108 348
15	prevalence/ or prevalence.ti,ab,kw.	35 425
16	Survival Analysis/ or (disease specific survival* or long term survival* or overall survival* or prolong$ survival* or survival anal$).ti,ab,kw.	91 780
17	progression free survival/ or (progression free survival or progression-free survival).ti,ab,kw.	20 488
18	(overall response rate or ORR).mp.	24 732
19	(duration of response or time to response or TTR).mp.	4872
20	adverse effects.fs.	2083
21	or/13-20	239 399
22	Case study/	0
23	Case report.tw.	2133

24	Letter/	0
25	or/22-24	2133
26	21 not 25	238 919
27	9 and 12 and 26	651
28	(animal$ not human$).sh,hw.	2033
29	27 not 28	651
30	limit 29 to english language [Limit not valid in ACP Journal Club,CDSR,DARE,CLCMR; records were retained]	521
31	limit 30 to (editorial or review) [Limit not valid in ACP Journal Club,CDSR,DARE,CLEED,CLHTA,CLCMR; records were retained]	9
32	systematic review/ or "systematic review (topic)"/ or systematic review.mp. or meta-analysis/ or "meta analysis (topic)".mp. or meta-analysis.mp.	76 701
33	31 not 32	0
34	30 not 33	521
35	remove duplicates from 34	507

- ***Embase – updated search: 10 March 2021***

#	Searches	Results
1	exp lung non small cell cancer/	106879
2	(nsclc or non-small cell lung cancer).ti,ab.	116340
3	1 or 2	160606
4	limit 3 to yr="2019 -Current"	34076
5	exp colon cancer/ or exp rectum cancer/ or colorectal tumor/	339744
6	((colorect$ or rectal$ or rectum$ or colon$ or sigma$ or sigmo$ or rectosigm$ or bowel$ or anal or anus) adj3 (cancer$ or neoplas$ or oncolog$ or malignan$ or tumo?r$ or carcinoma$ or adenocarcinoma$ or metasta$ or meta-sta$ or sarcoma$ or adenom$ or lesion$)).ti,ab.	367191
7	5 or 6	442830
8	limit 7 to yr="2019 -Current"	62540
9	4 or 8	94311
10	k ras oncogene/	11065

11	((k ras or kras or k-ras or V-Ki-ras$ or V-K-ras or V-Ki-ras or v ki ras or c-ki-ras or c-k-ras or ki-ras or ki ras or Kras1 or Kras2 or KRAS1P or RASK or RASK1 or RASK2 or Kirsten RAS) adj5 (mutation$ or mutant$ or mutated or status or exon or gene$ or translocation$ or rearrangement$ or oncogene$ or fusion$ or expression$ or over?expression$ or amplification$ or inversion$ or deletion$)).ti,ab.	31465
12	10 or 11	35639
13	epidemiology/ or epidemiology.ti,ab,kw.	463878
14	incidence/ or incidence.ti,ab,kw.	1249736
15	prevalence/ or prevalence.ti,ab,kw.	1124407
16	overall survival/ or (disease specific survival* or long term survival* or overall survival* or prolong$ survival* or survival anal$).ti,ab,kw.	523163
17	progression free survival/ or (progression free survival or progression-free survival).ti,ab,kw.	132750
18	(overall response rate or ORR).mp.	42707
19	(duration of response or time to response or TTR).mp.	26376
20	adverse drug reaction.fs.	1261807
21	or/13-20	4119933
22	Case study/	76518
23	Case report.tw.	442402
24	Letter/	1118459
25	or/22-24	1625849
26	21 not 25	3912144
27	9 and 12 and 26	1245
28	(animal$ not human$).sh,hw.	4494444
29	27 not 28	1204
30	limit 29 to english language	1191

31	limit 30 to (editorial or erratum or letter or note or patent or reports or "review" or short survey or tombstone)	104
32	systematic review/ or "systematic review (topic)"/ or systematic review.mp. or meta-analysis/ or "meta analysis (topic)".mp. or meta-analysis.mp.	511387
33	31 not 32	90
34	30 not 33	1101
35	remove duplicates from 34	1049

- ***MEDLINE – updated search: 10 March 2021***

#	Searches	Results
1	exp Carcinoma, Non-Small-Cell Lung/	55698
2	(nsclc or non-small cell lung cancer).ti,ab.	66758
3	1 or 2	78455
4	limit 3 to yr="2019 -Current"	15154
5	exp colon cancer/ or exp rectum cancer/ or colorectal tumor/	199364
6	((colorect$ or rectal$ or rectum$ or colon$ or sigma$ or sigmo$ or rectosigm$ or bowel$ or anal or anus) adj3 (cancer$ or neoplas$ or oncolog$ or malignan$ or tumo?r$ or carcinoma$ or adenocarcinoma$ or metasta$ or meta-sta$ or sarcoma$ or adenom$ or lesion$)).ti,ab.	251120
7	5 or 6	291930
8	limit 7 to yr="2019 -Current"	37673
9	4 or 8	52497
10	k ras oncogene/	12466
11	((k ras or kras or k-ras or V-Ki-ras$ or V-K-ras or V-Ki-ras or v ki ras or c-ki-ras or c-k-ras or ki-ras or ki ras or Kras1 or Kras2 or KRAS1P or RASK or RASK1 or RASK2 or Kirsten RAS) adj5 (mutation$ or mutant$ or mutated or status or exon or gene$ or translocation$ or rearrangement$ or oncogene$ or fusion$ or expression$ or over?expression$ or amplification$ or inversion$ or deletion$)).ti,ab.	16640

12	10 or 11	24918
13	epidemiology/ or epidemiology.ti,ab,kw.	198048
14	incidence/ or incidence.ti,ab,kw.	888464
15	prevalence/ or prevalence.ti,ab,kw.	745199
16	Survival Analysis/ or (disease specific survival* or long term survival* or overall survival* or prolong$ survival* or survival anal$).ti,ab,kw.	361241
17	progression free survival/ or (progression free survival or progression-free survival).ti,ab,kw.	50329
18	(overall response rate or ORR).mp.	21857
19	(duration of response or time to response or TTR).mp.	15139
20	adverse effects.fs.	1778356
21	or/13-20	3535848
22	Case study/	2158984
23	Case report.tw.	328403
24	Letter/	1123553
25	or/22-24	3123899
26	21 not 25	3073118
27	9 and 12 and 26	430
28	(animal$ not human$).sh,hw.	4750851
29	27 not 28	429
30	limit 29 to english language	426
31	limit 30 to (editorial or review)	23
32	systematic review/ or "systematic review (topic)"/ or systematic review.mp. or meta-analysis/ or "meta analysis (topic)".mp. or meta-analysis.mp.	317308

33	31 not 32	19
34	30 not 33	407
35	remove duplicates from 34	407

- ***Cochrane – updated search: 10 March 2021***

#	Searches	Results
1	exp Carcinoma, Non-Small-Cell Lung/	4656
2	(nsclc or non-small cell lung cancer).ti,ab.	14347
3	1 or 2	14819
4	limit 3 to yr="2019 -Current" [Limit not valid in DARE; records were retained]	2010
5	exp colon cancer/ or exp rectum cancer/ or colorectal tumor/	8922
6	((colorect$ or rectal$ or rectum$ or colon$ or sigma$ or sigmo$ or rectosigm$ or bowel$ or anal or anus) adj3 (cancer$ or neoplas$ or oncolog$ or malignan$ or tumo?r$ or carcinoma$ or adenocarcinoma$ or metasta$ or meta-sta$ or sarcoma$ or adenom$ or lesion$)).ti,ab.	25271
7	5 or 6	26344
8	limit 7 to yr="2019 -Current" [Limit not valid in DARE; records were retained]	3676
9	4 or 8	5654
10	k ras oncogene/	66
11	((k ras or kras or k-ras or V-Ki-ras$ or V-K-ras or V-Ki-ras or v ki ras or c-ki-ras or c-k-ras or ki-ras or ki ras or Kras1 or Kras2 or KRAS1P or RASK or RASK1 or RASK2 or Kirsten RAS) adj5 (mutation$ or mutant$ or mutated or status or exon or gene$ or translocation$ or rearrangement$ or oncogene$ or fusion$ or expression$ or over?expression$ or amplification$ or inversion$ or deletion$)).ti,ab.	1344
12	10 or 11	1362
13	epidemiology/ or epidemiology.ti,ab,kw.	12994

14	incidence/ or incidence.ti,ab,kw.	123869
15	prevalence/ or prevalence.ti,ab,kw.	41883
16	Survival Analysis/ or (disease specific survival* or long term survival* or overall survival* or prolong$ survival* or survival anal$).ti,ab,kw.	105477
17	progression free survival/ or (progression free survival or progression-free survival).ti,ab,kw.	25533
18	(overall response rate or ORR).mp.	29151
19	(duration of response or time to response or TTR).mp.	5931
20	adverse effects.fs.	2083
21	or/13-20	272783
22	Case study/	0
23	Case report.tw.	2708
24	Letter/	0
25	or/22-24	2708
26	21 not 25	272193
27	9 and 12 and 26	76
28	(animal$ not human$).sh,hw.	2133
29	27 not 28	76
30	limit 29 to english language [Limit not valid in ACP Journal Club,CDSR,DARE,CLCMR; records were retained]	66
31	limit 30 to (editorial or review) [Limit not valid in ACP Journal Club,CDSR,DARE,CLEED,CLHTA,CLCMR; records were retained]	1
32	systematic review/ or "systematic review (topic)"/ or systematic review.mp. or meta-analysis/ or "meta analysis (topic)".mp. or meta-analysis.mp.	33812
33	31 not 32	1

34	30 not 33	65
35	remove duplicates from 34	65

Study eligibility criteria and selection for the SLR of RCTs

Two reviewers independently screened the titles and abstract against the eligibility criteria in Appendix A Table 1, with discrepancies resolved by a third reviewer. Given that evidence specifically in patients with *KRAS G12C-mutated* NSCLC was anticipated to be limited, the eligibility criteria included patients with any KRAS mutant NSCLC. Furthermore, for the same reasons, the eligibility criteria included any interventions and comparators; however, as the relevant comparators for sotorasib in this appraisal are docetaxel monotherapy, and as the aim of the SLR was to explore the possibility of conducting indirect comparisons for sotorasib.

Appendix A Table 1. Eligibility criteria for the SLR of RCTs

Criteria	Include	Exclude
Population	Adults (18 years) with KRAS mutated locally advanced and unresectable or metastatic (stage IIIB-IV) NSCLC who had received at least 1 prior systemic therapy. Studies with non-adult participants if information specific to adults was reported separately¶. Subgroups of particular interest including but not limited to: • PD-L1 expression • Prior PD-(L)1 therapies • Early vs. late progressors	• Paediatric and adolescent (<18 years) patients • Patients with cancers other than NSCLC • Early-stage NSCLC patients (Stage<IIIB) • Trials studying safety and efficacy of treatment administered in adjuvant setting • Treatment naïve patients
Intervention/comparator	Any therapies licensed in the United States or European Union for the second or later line treatment of patients with NSCLC *Retreatment with Immuno-oncology therapies will be considered as is in scope even if not a specified retreatment post progression on an anti PD-(L)1*	Treatments specifically targeting EGFR/ALK or ROS 1 mutations Or other targetable mutation
Outcomes	**Efficacy** • Overall survival (OS)§ • Progression-free survival (PFS)§ • Progression after next line of therapy (PFS2) § • Time to progression (TTP)§ • Time to next treatment (TTNT) • Event-free survival§	Non-clinical outcomes

Criteria	Include	Exclude
	• Objective response rate (ORR) • Partial response (PR) • Complete response (CR) • Odds ratio for response rates • Duration of response • Disease control rate or clinical benefit rate • Treatment duration and dosing (median duration, mean duration, mean number of doses, cumulative doses, etc.) **Safety and tolerability:** • All-grade treatment-emergent AEs • Treatment related grade 3 or 4 AEs • Treatment related SAEs • Tolerability: dose reductions and interruptions, discontinuation (any reason), discontinuation (due to AEs)	
Study design/setting	Phase II – IV randomised controlled trials	• Trials with a phase I component only • Non-randomized clinical trials • Studies with <10 participants
Language of publication	English language publications (English language abstracts of foreign language publications will be considered for inclusion.)	Non-English language publications without an English abstract.
Date of publication	For the replicated searches, full papers published during or after 2015‡ Conference abstracts published during or after 2017‡	• Studies published prior to 2015‡ • Conference abstracts published prior to 2017
Countries	No restriction	-

Study eligibility criteria and selection for the SLR of RCTs

Two reviewers independently screened the titles and abstract against the eligibility criteria in Appendix Table 2, with discrepancies resolved by a third reviewer. Given that evidence specifically in patients with *KRAS G12C-mutated* NSCLC was anticipated to be limited, the eligibility criteria included patients with any KRAS mutant NSCLC. However, there was a specific interest in studies providing data in patients with *KRAS G12C-mutated* NSCLC. Furthermore, for the same reasons, the eligibility criteria included any interventions.

Appendix Table 2. Eligibility criteria for the SLR of single-arm trials

Eligibility criteria	Inclusion Criteria	Exclusion Criteria
Population	Patients with NSCLC (any stage, any line of treatment) carrying a *KRAS*^{G12C} mutation or any other KRAS mutation (*KRASm*)	Tumor types other than NSCLC
Interventions	Any anti-cancer drugs, any line of treatment or no treatment	Radiotherapy or surgery (unless a relevant comparator arm)
Comparator	Any or none	NA
Outcomes	Outcome reported by *KRASm* mutation status *Clinical evidence* • Overall survival • Progression-free survival • Adverse events • Overall response rate • Time to response • Duration of response *HRQoL evidence* Note, search strings were limited by outcomes and do not include HRQoL terms. However, if HRQoL data from SAT studies were identified in the NSCLC SLR Update and SLR Rescreen, data will be included	
Study design	Only single-arm trials (experimental/interventional, not observational)	Exclude animal/*in vitro* studies, case studies and case reports
Date restrictions	1) SLR Update: Published since 2019 Congress abstract searches limited to the past 3 year and clinical trials (to cover *KRASm*) 2) SLR Rescreen: Published from 2014 to 2019 (to cover *KRASm*)	
Language restrictions	English language	

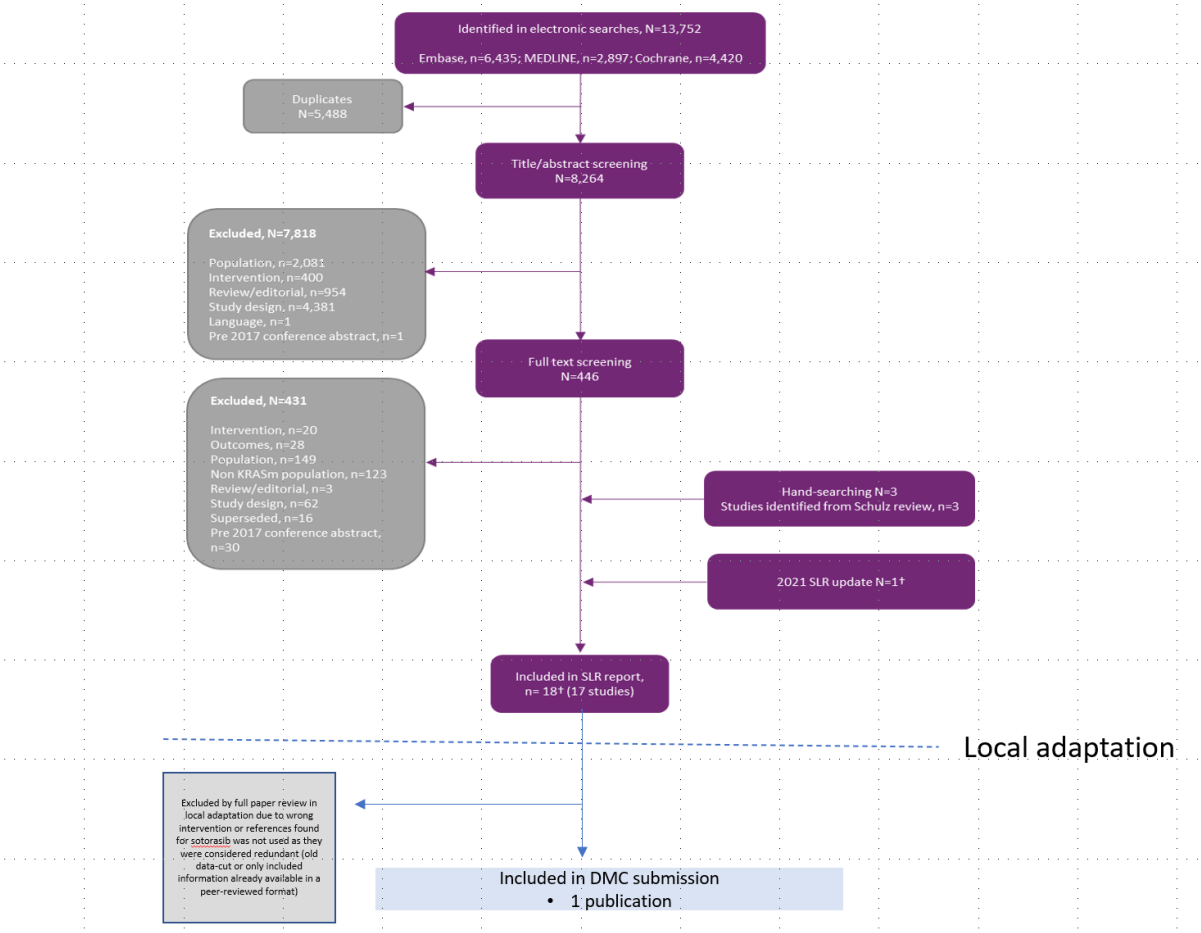
Publication type	All publication types, except editorials and reviews, but including systematic reviews*	
Country	Not restricted	

Results of the SLRs

Results of the SLR of RCTs

The PRISMA flow diagram illustrating the number of studies meeting the inclusion criteria, and the exclusion of irrelevant RCTs, is provided in Appendix Figure 1. The electronic database search identified 13,752 citations, of which 5,488 were identified as duplicates and excluded. The remaining 8,264 citations were screened on the basis of title and abstract, and 7,818 were then excluded leaving 446 citations to be screened on the basis of the full publications. During full text screening, 431 publications were subsequently excluded resulting in 18 included publications relating to 17 unique studies reported on a KRAS population or subgroup. The search update conducted on 26th January 2021 identified a further 1,380 citations, of which 105 were screened on the basis of the full publication. One study published as a full paper was included to supersede a previously identified conference abstract from the same trial (JUNIPER). No additional references were identified through hand searching of conference abstracts.

Appendix Figure 1. Study flow of included and excluded RCTs



† The publication identified in the 2021 update search, superseded a conference abstract identified in the original search, therefore total included studies are less than the total of the original and update search.

The list of the 17 studies meeting the broad eligibility criteria is provided in Appendix Table 3. Of these 17 studies meeting the broad inclusion criteria, 7 were conducted specifically in KRAS mutant NSCLC patients (see Appendix Table 3). Of these, 5 provided outcomes data specifically in patients harboring the KRAS G12C mutation (see Appendix Table 4).

The SLR confirmed there are currently no published RCTs of sotorasib or other KRASG12C inhibitors.

Regarding the relevant comparators for sotorasib in this submission, 3 of these 5 studies included docetaxel monotherapy as an intervention or comparator arm (NCT01362296 (Blumenschein et al 2015) (7); SELECT-1 (Janne et al 2017) (10); and TAILOR (Rulli et al 2015 (12)). Of these, SELECT-1 was by far the largest and provided the most robust PFS and OS data in the subgroup of NSCLC patients harboring the KRAS G12C mutation, and sufficient data on the baseline characteristics of enrolled patients to allow its consideration as a data source in indirect comparative analyses with sotorasib; the other 2 studies were much smaller and were more limited in their data. On this basis, the SELECT-1 trial was the only viable candidate as a data source for docetaxel monotherapy in the indirect comparisons described in section 7.2.1 and Appendix K - MAIC.

The full list of studies excluded following screening the full publications, along with the rationale for their exclusion, is provided in the following Microsoft Excel files:

Studies excluded after full text review (n=431)

8489 List of 431 excluded studies.xls

Studies excluded after full text review 2021 update (n=105)

8876 NSCLC 2021 update_list of 105 e:

Of these 17 studies meeting the broad inclusion criteria, 7 were conducted specifically in KRAS mutant NSCLC patients (see Appendix Table 3). Of these, 5 provided outcomes data specifically in patients harboring the *KRAS G12C* mutation (see Appendix Table 4).

The SLR confirmed there are currently no published RCTs of sotorasib or other $KRAS^{G12C}$ inhibitors.

Regarding the relevant comparators for sotorasib in this submission, 3 of these 5 studies included docetaxel monotherapy as an intervention or comparator arm (NCT01362296 Blumenschein et al 2015 (101); SELECT-1 Janne et al 2017 (72); TAILOR Rulli et al 2015 (102)). Of these, SELECT-1 was by far the largest and provided the most robust PFS and OS data in the subgroup of NSCLC patients harboring the *KRAS G12C* mutation, and sufficient data on the baseline characteristics of enrolled patients to allow its consideration as a data source in indirect comparative analyses with sotorasib; the other 2 studies were much smaller and were more limited in their data. On this basis, the SELECT-1 trial was the only viable candidate as a data source for docetaxel monotherapy in the indirect comparisons described in **Appendix K - MAIC.**

Appendix Table 3. Overview of 17 RCTs meeting the broad eligibility criteria (not necessarily patients harboring the KRAS G12C mutation)

							Included in Danish submission and reason
Studies specifically reporting data for KRASm patients							
Blumenschein et al 2015(101) NCT01362296 Phase 2	International study (France, Greece, Hungary, Italy, Republic of Korea, Netherlands, Spain, United States) conducted between September 2011 and July 2012	Trametinib 2 mg orally once daily (n=86) Docetaxel 75 mg/m^2 IV every 3 weeks (n=43)	1) Patients must have received only one prior approved platinum-containing chemotherapy regimen for advanced stage/metastatic NSCLC	1) Patients aged ≥18 years with histologically or cytologically confirmed adenocarcinoma stage IV NSCLC with a positive mutational status for KRAS, NRAS, BRAF, or MEK1, and an ECOG performance status of 0–1	1) Patients who had received any previous treatment with a BRAF or MEK inhibitor or a docetaxel-containing regimen 2) Patients at risk of retinal vein occlusion or central serous retinopathy 3) Patients with unstable/untreated brain metastases	1°: PFS 2°: Safety and tolerability, RR, DOR, OS and steady-state PKs of trametinib	**Excluded** Docetaxel arm too small and does not hold sufficient data on the baseline characteristics of enrolled patients to allow its consideration as data source in indirect comparative analyses with sotorasib.
Carter et al 2016 (103) NCT01229150; CTEP: 8444 Phase 2	USA study conducted between March 2010 and May 2013	Single agent selumetinib 75 mg orally twice per day (n=11) Combination of erlotinib 100 mg orally once daily + selumetinib 150 mg orally once daily (n=30)	1) Patients were treated (or had refused treatment with) with a platinum-containing doublet chemotherapy regimen. Patients who received >2 prior systemic therapies were excluded	1) Histologically proven advanced NSCLC, were greater than 18 years of age, had an ECOG performance status of 0–2, adequate organ function 2) Treated brain metastases were allowed if not requiring steroid or antiepileptic medications.	1) Uncontrolled disease unrelated to the primary malignancy and a history of prior EGFR TKI (erlotinib) or an MEK inhibitor.	1°: ORR	**Excluded** No relevant interventions
Gerber et al 2018(104) NCT01395758 Phase 2	USA study conducted between July	Erlotinib,150 mg orally once daily in combination with	1) Patients had received at least one prior line of chemotherapy	1) Patients with inoperable locally advanced or metastatic (stage III–IV) NSCLC (all histologies) harbouring	1) Patients with known activating EGFR mutations were excluded.	1°: PFS 2°: OS, radiographic response	**Excluded** No relevant interventions

							Included in Danish submission and reason
	2011 and June 2013	tivantinib, 360 mg orally twice daily (n=51) Investigator's choice chemotherapy (gemcitabine 1250 mg/m^2 days 1 and 8 every 21 days, docetaxel 75 mg/m^2 day 1 every 21 days, or pemetrexed 500 mg/m^2 day 1 every 21 days) (n=45)		a documented KRAS mutation. 2) ECOG PS 0–2)	2) Patients with unstable/untreated brain metastases		
Goldman et al 2020 (105) NCT02152631 Phase 3	International study conducted in October 2011 (still active at time of writing – December 2020)	Abemaciclib 200 mg PO twice a day (n=270) Erlotinib 150 mg PO once daily (n=183)	1) Patients who progressed after platinum-based chemotherapy (with or without maintenance therapy) and received one additional therapy which may have included an immune checkpoint inhibitor or other anti-cancer therapy for advanced and/or metastatic disease OR was judged by the physician as ineligible for further standard second-line chemotherapy. 2) Patients who had received treatment with a	1) Patients with metastatic (stage IV) NSCLC with detectable mutations in codons 12 or 13 of the KRAS oncogene and ECOC PS of 0–1 2) Patients must have discontinued all previous therapies for cancer (including chemotherapy, radiotherapy, immunotherapy, and investigational therapy) for at least 21 days for myelosuppressive agents or 14 days for non-myelosuppressive	1) Patients with unstable/untreated brain metastases	1°: OS 2°: PFS, ORR, and safety and tolerability	**Excluded** No relevant interventions

							Included in Danish submission and reason
			prior CDK4 and CDK6 inhibitors were excluded	agents prior to receiving study drug			
Janne et al 2017 (72) NCT01933932 SELECT-1 Phase 3	International study conducted between October 2013 and January 2016	75 mg of selumetinib (hydrogen sulphate) twice daily + 75 mg/m^2 of docetaxel intravenously on day 1 of every 21-day cycle (n=254) Matched placebo plus docetaxel (same schedule) (n=256)	1) Patients had previously received at least 1 prior anticancer drug regimen for advanced or metastatic NSCLC 2) Patients who had received more than 1 prior anticancer drug regimen for advanced or metastatic NSCLC, or prior treatment with an MEK inhibitor or any docetaxel-containing regimen were excluded	1) Patients 18 years or older, with histologically or cytologically confirmed locally advanced or metastatic NSCLC (stage IIIB–IV). 2) Patients had failure of 1 previous line of therapy for advanced disease, a centrally confirmed KRAS-mutant tumor 3) With WHO performance status of 0 or 1	1) Mixed small cell and non–small cell lung cancer histology and presence of brain metastases or spinal cord compression (unless asymptomatic, treated, stable, and off steroids and anti-convulsants for ≥4 weeks prior to screening).	1°: PFS 2°: OS, ORR, DOR, TTP, safety and tolerability,	**Included** in application
Papadimitrakopoulo et al 2016 (106) BATTLE-2 Phase 2	US study	Arm 1, erlotinib 150 mg once daily (n=22) Arm 2, erlotinib 150mg once per day and the AKT inhibitorMK-2206 135mg once weekly (n=42) Arm 3, MEK inhibitor AZD6244	1) Patients refractory to more than one prior therapy were randomly assigned, stratified by KRAS status	1) Patients aged ≥18 years with pathologically confirmed advanced or incurable stage IIIB or stage IV NSCLC who had failed at least one front-line metastatic NSCLC chemotherapy regimen or EGFR TKI, and had and an ECOG performance status of 0–2.	1) Subjects whose tumor harbours the EML4-ALK fusion gene (unless the patient has failed treatment with ALK inhibitor) 2) Subjects whose tumor harbours an EGFR mutation (unless the subject failed treatment with EGFR TKIs in which case they could be randomized to Arms 2, 3, and 4)	1°: 8-week disease control rate 2°: OS, PFS, ORR and toxicity	**Excluded** No relevant interventions

							Included in Danish submission and reason
		100 mg per day, and AKT inhibitor MK-2206 100 mg once weekly (n=75) Arm 4, sorafenib 400 mg orally twice daily (n=61)			3) Patients with unstable/untreated brain metastases		
Rulli et al 2015 (102) NCT00637910 TAILOR	Italian study conducted between October 2007 to March 2012 (cut-off January 2013)	Docetaxel Given IV at either 75 mg/m² every 21 days, or 35 mg/m² on days 1, 8, and 15, every 28 days (n=25) Erlotinib 150 mg once daily (n=26)	1) Patients who had recurrence or progression after failing platinum-based chemotherapy 2) Patients who had received taxanes or anti-EGFR agents were excluded	1) Patients with advanced or metastatic NSCLC with EGFR wt and ECOG PS 0–2	1) Patients with EGFRm	1) Efficacy between treatments	**Excluded** No relevant interventions
Studies using chemotherapy as a comparator							
Borghaei et al 2015 (107) NCT01673867	International study (United States, Argentina,	Nivolumab 3 mg/kg every 2 weeks	1) Patients who had received one prior	1) Patients aged ≥ 18 years with stage IIIB or IV or recurrent non-	1) Patients with autoimmune disease, symptomatic interstitial	1°: OS	**Excluded**

							Included in Danish submission and reason
Phase 3	Australia, Austria, Brazil, Canada, Chile, Czechia, France, Germany, Hong Kong, Hungary, Italy, Mexico, Norway, Peru, Poland, Romania, Russian Federation, Singapore, Spain, Switzerland) conducted between November 2012 and December 2013.	(n=292) Docetaxel 75 mg/m^2 every 3 weeks (n=290)	platinum-based doublet chemotherapy regimen. Patients who received prior treatment with immune-stimulatory antitumor agents including checkpoint-targeted agents, and prior use of docetaxel were excluded	squamous NSCLC after radiation therapy or surgical resection and ECOG PS 0 or 1 2) Patients with known EGFR mutation or ALK translocation could receive or be receiving an additional line of TKI therapy, and a continuation of or switch to maintenance therapy with pemetrexed, bevacizumab, or erlotinib was allowed in all patients.	lung disease, systemic immunosuppression. 2) Patients with unstable/untreated brain metastases	2°: PFS, ORR, efficacy according to tumor PD-L1 expression level	Population with no relevant mutation
Bradbury et al 2018 (108) NCT01708993 CCTG IND211 Phase 2	Canadian study conducted between October 2012 and August 2015	Arm A, pemetrexed 500 mg/m^2 IV over 10 min on day one, every 21 days, and pelareorep 4.5×10^{10} TCID50 IV over 60 min on days 1–3 every 21 days (n=38) Arm B, pemetrexed, 500 mg/m^2, IV over 10 min on day one, every 21 days (n=37)	1) Patients received must have received one regimen of palliative first-line platinum containing combination which may not have contained docetaxel. 2) Patients may have received other therapies including immunotherapy, or with signal transduction inhibitors, including EGFR inhibitors. 3) Prior adjuvant chemotherapy was permissible providing patients had completed at least 1 year prior to relapse/recurrence of	1) Patients aged ≥18 years with clinically and/or radiologically documented diagnosis of NSCLC and ECOG PS 0–1	1) Concurrent treatment with other investigational drugs or anti-cancer therapy 2) Patients with untreated brain metastases, untreated spinal cord compression or meningeal metastases	1°: PFS 2°: OS, ORR, exploratory translational analyses	**Excluded** Population with no relevant mutation

							Included in Danish submission and reason
		Arm C, docetaxel 75 mg/m^2, IV over 60 min on day one, every 21 days and pelareorep 4.5×10^{10} TCID50 IV over 60 min on days 1–3, every 21 days (n=39) Arm D, docetaxel 75 mg/m^2, IV over 60 min on day one, every 21 days and pelareorep 4.5×10^{10} TCID50 IV over 60 min on days 1–3, every 21 days (n=38)	disease and the patient had received one regimen of palliative first-line chemotherapy.				
Ciuleanu et al 2012 (109) NCT00556322 TITAN Phase 3	International study conducted between April 10, 2006 and Feb 24, 2010	Erlotinib 150 mg/day (n=203) Chemotherapy (single-agent docetaxel or pemetrexed) (n=221)	1) Patients who had received first-line platinum doublet chemotherapy 2) Patients with previous exposure to anti-human-EGFR-directed drugs or drugs directed at pemetrexed molecular targets, previous chemotherapy or systemic anti-neoplastic therapy other than the permitted platinum-based regimens were excluded.	1) Patients aged ≥18 years with locally advanced, recurrent, or metastatic NSCLC, who had progressed during four cycles of a standard platinum-based chemotherapy doublet in the SATURN study, and ECOG PS 0–2	1) Patients with uncontrolled or untreated brain metastasis; or spinal cord compression or other malignancies within the past 5 years (except carcinoma in situ)	1°: OS 2°: PFS, TTP	**Excluded** Population with no relevant mutation

							Included in Danish submission and reason
Pillai et al 2020 (110) NCT01798485 GALAXY-2 Phase 3	International study conducted between April 2013 and December 2015	Ganetespib 150 mg/m² IV on days 1 and 15 + Docetaxel 75 mg/m² IV on day 1 (n=335) Docetaxel 75 mg/m² IV on day 1 (n=337)	1) Patients who had progressed following platinum doublet chemotherapy, with allowance for maintenance chemotherapy	1) Patients with stage IIIB or IV adenocarcinoma with EGFR wt and ALK wt, and ECOG PS of 0–1	1) Patients with unstable brain metastases	1°: OS 2°: PFS, OS in patients with elevated screening LDH levels	**Excluded** Population with no relevant mutation
Ramalingam et al 2015 (111) GALAXY-1 Phase 2	International study (North America, eastern Europe, Western Europe) conducted between July 2011 and May 2013	Ganetespib 150 mg/m² IV on days 1 and 15 + Docetaxel 75 mg/m² on IV day 1 every 3 weeks (n=42) Docetaxel 75 mg/m² IV on day 1 every 3 weeks (n=47)	1) Patients who had received systemic therapy for advanced disease 2) Prior maintenance therapy was allowed.	1) Patients with stage IIIB or IV NSCLC, ECOG PS of 0 or 1, and disease progression following first-line therapy	1) Patients with unstable brain metastases.	1°: PFS 2°: PFS, OS in adenocarcinoma patients, safety, and tumor response rate	**Excluded** Population with no relevant mutation
Rittmeyer et al 2017 (112) NCT02008227 OAK Phase 3	International study conducted between March 11, 2014 and April 29, 2015	Atezolizumab 1200 mg IV every 3 weeks (n=425) Docetaxel 75 mg/m² IV every 3 weeks (n=425)	1) Patients had received ≥1 platinum-based combination therapy for stage IIIB or IV NSCLC 2) Patients who had received previous treatments with docetaxel, CD137 agonists, anti-CTLA4, or	1) Patients aged ≥18 years with squamous or non-squamous NSCLC and an ECOG PS of 0–1 2) Patients with EGFR mutations or an ALK fusion oncogene were additionally required to	1) Patients with unstable brain metastases and a history of autoimmune disease	1°: OS 2°: PFS, ORR, DOR, and safety	**Excluded** Population with no relevant mutation

							Included in Danish submission and reason
			therapies targeting the PD-L1 and PD-1 pathway were excluded	have received previous TKI therapy			
Studies using erlotinib as a comparator							
Karampeazis et al 2013 (113) NCT00440414 HORG Phase 3	International study conducted between January 2006 and April 2010	Pemetrexed 500 mg/m² over 1-hour as IV infusion on day 1, every 3 weeks (n=178) Erlotinib 150 mg/day orally (n=179)	1) Patients who had received taxane or platinum based regimen (not mandatory for older patients) Patients who had received prior pemetrexed and TKI were excluded	1) Patients aged <65 years with stage IIIB or IV NSCLC who had experienced disease progression after 1 or 2 lines of chemotherapy and ECOG PS 0–2	1) Patients with squamous cell histology, a second primary tumor, active infection, severe heart disease and uncontrolled diabetes mellitus. 2) Patients with unstable brain metastasis	1°: TTP 2°: PFS, OS, ORR, safety	**Excluded** No relevant intervention
Scagliotti et al 2015 (114) NCT01244191 MARQUEE Phase 3	International study (Europe and Russia, the United States, Latin America, Canada, and Australia) conducted between January 2011 and July 2012 (cut-off December 15, 2012)	Erlotinib 150 mg once daily orally + Tivantinib 360 mg twice daily orally (n=526) Placebo + erlotinib 150 mg once daily orally (n=522)	1) Patients who had received 1–2 prior systemic anticancer regimens, including prior platinum-based chemotherapy, without prior exposure to EGFR inhibitors, tivantinib, or any other MET inhibitor	1) Patients aged ≥18 years with stage IIIb to IV non-squamous NSCLC, ECOG PS of 0–1 and adequate bone marrow, liver, and kidney functions 2) Archival or fresh tissue samples for biomarker analyses and EGFR mutation status were mandatory for all patients.	1) Patients with clinically unstable brain metastases or history of cardiac disease, uncontrolled hypertension, or other active malignancies.	1°: OS 2°: PFS and safety	**Excluded** No relevant intervention
Spigel et al 2017 (115) OAM4971g (METLung) NCT01456325	International study conducted between January 2012 and August 2013 (cut-off	Onartuzumab 15 mg/kg IV on day 1 of each 21-day cycle +	1) Patients who had received platinum-based chemotherapy	1) Patients with stage IIIB to IV locally advanced or metastatic NSCLC determined to be	1) Patients with untreated/unstable brain metastases	1°: OS 2°: PFS, ORR, biomarker analysis and safety.	**Excluded** No relevant intervention

							Included in Danish submission and reason
Phase 3	October 26, 2013).	daily oral erlotinib 150 mg (n=250) Placebo IV + erlotinib 150 mg orally (n=249)	2) Patients who had received prior treatment with an EGFR inhibitor were excluded	MET positive with ECOG PS of 0 –1 2) Patients with progressive disease after one previous line of platinum-based chemotherapy but had not received more than two prior lines of treatment	2) Patients with interstitial lung disease, pleural effusion, pericardial fluid or ascites, serious active infection, uncontrolled GI inflammatory disease, uncontrolled diabetes mellitus, major surgery 2 weeks before random assignment, and history of other invasive malignancy or cardiac disease		
Studies assessing other interventions							
Ciuleanu et al 2017 (116) NCT01186861 Phase 2	International study conducted in July 2013 (data cut-off).	Linsitinib 150 mg orally once daily + erlotinib 150 mg once daily for 21 days (n=102) Placebo twice daily. + erlotinib 150 mg for 21 days (n=103)	1) Patients who had received prior IGF-1R therapy or concurrent maintenance bevacizumab were excluded	1) Patients with advanced NSCLC stages IIIB or IV following completion of first-line platinum-based chemotherapy, ECOG PS 0–1, a fasting glucose ≤150 mg/dL and adequate haematopoietic, hepatic and renal function	1) Patients with diabetes mellitus requiring insulinotropic or insulin therapy, a history of poorly controlled GI disorders or significant cardiovascular disease 2) Patients with disease progression at the time of study entry	1°: PFS 2°: OS, ORR, CR, PR, DCR	**Excluded** No relevant intervention

Appendix Table 4. Baseline characteristics from 5 RCTs that provided data in patients with KRAS G12C-mutated NSCLC

Trial name, NCT ID, Study names	Treatment arm (n)	Age, median, years (range) [95% CI]	Male, n (%)	Smoking status, n (%)	Histology, n (%)		Clinical staging , n (%)	Mutation status, n (%)		Included in DMC application, reason for exclusion
					Squamous cell carcinoma	Non-squamous cell carcinoma		PD-L1 expression, n (%)	KRAS	
Blumenschein et al 2015 (101) NCT01362296 Phase 2	Trametinib (n=86)	63.0 (40–79)	46 (53)	Current: 13 (15) Former: 67 (78)	0 (0)	-	86 (100)	-	KRASm: 86 (100) KRASmG12C: 31 (35)	**Excluded** Docetaxel arm too small and does not hold sufficient data on the baseline characteristics of enrolled patients to allow its consideration as data source in indirect comparative analyses with sotorasib.
	Docetaxel (n=43)	63.0 (34–79)	23 (53)	Current: 13 (30) Former: 23 (53)	1 (2)	-	43 (100)	-	KRASm: 43 (100) KRASmG12C: 18 (40)	
Carter et al 2016 (103) NCT01229150; CTEP: 8444 Phase 2	Selumetinib (n=11)	64 (50–83)	4 (36)	Current: 0 (0) Former: 11 (100)	0 (0)	-	-	-	KRASm: 11 (100) KRASmG12C: 4 (36)	**Excluded** Not relevant comparators
	Erlotinib+ selumetinib (n=30)	66 (58-82)	14 (47)	Current: 9 (30) Former: 21 (70)	0 (0)	-	-	-	KRASm: 30 (100) KRASmG12C: 8 (27)	
Gerber et al 2018 (104) NCT01395758 Phase 2	Erlotinib + tivantinib (n=51)	64 (IQR, 55–70)	18 (35)	Current: 3 (6) Former: 43 (84)	-	-	-	-	KRASm: 51 (100) KRASmG12C: 26 (51)	**Excluded** Not relevant comparators
	Investigator's choice	67	15 (33)	Current: 2 (4)	-	-	-	-	KRASm: 45 (100)	

Trial name, NCT ID, Study names	Treatment arm (n)	Age, median, years (range) [95% CI]	Male, n (%)	Smoking status, n (%)	Histology, n (%)		Clinical staging, n (%)	Mutation status, n (%)		Included in DMC application, reason for exclusion
					Squamous cell carcinoma	Non-squamous cell carcinoma		PD-L1 expression, n (%)	KRAS	
	chemotherapy, gemcitabine, docetaxel or pemetrexed (n=45)	(58–71)		Former: 40 (89)					KRASmG12C: 18 (40)	
Janne et al 2017 (72) NCT01933932 SELECT-1 Phase 3	Selumetinib + docetaxel (n=254)	62 (36-85)	158 (62)	Current: 52 (21) Former: 186 (73)	14 (6)	240 (95)	-	<5%: 224 (44) ≥5%: 161 (32) Unknown: 125 (25)	KRASm: Codon 12 or 13: 237 (93) Codon 61: 16 (6) KRASmG12C: 98 (39)	Included Docetaxel arm holds correct population and sufficient reporting to allow for MAIC with sotorasib
	Matched placebo plus docetaxel (n=256)	61 (34–81)	145 (57)	Current: 62 (24) Former: 173 (68)	14 (6)	242 (95)	-		KRASm: Codon 12 or 13: 244 (95) Codon 61: 12 (5) KRASmG12C: 104 (41)	
Rulli et al 2015 (102) NCT00637910 TAILOR	Docetaxel (n=25) and erlotinib (n=26) combined	34 (56–71)	37 (73)	Current: 44 (86) Former: 0 (0)	-	-	-	-	-	**Excluded** Docetaxel arm too small and does not hold sufficient data on the baseline characteristics (e.g. KRASm) of enrolled patients to allow its

Trial name, NCT ID, Study names	Treatment arm (n)	Age, median, years (range) [95% CI]	Male, n (%)	Smoking status, n (%)	Histology, n (%)		Clinical staging , n (%)	Mutation status, n (%)		Included in DMC application, reason for exclusion
					Squamous cell carcinoma	Non-squamous cell carcinoma		PD-L1 expression, n (%)	KRAS	
										consideration as data source in indirect comparative analyses with sotorasib.

D1.1.3.2 Results of the SLR for single-arm trials

The PRISMA flow diagram illustrating the number of studies meeting the inclusion criteria, and the exclusion of irrelevant RCTs, is provided in Appendix Figure 2.

As described previously, this SLR had two parts: SLR update and SLR rescreen. In total, 1240 relevant publications were identified from electronic searches as part of the SLR update and 522 as part of the SLR re-screen. We included 626 publications for double-blind full text review from SLR Update and SLR Rescreen combined. Additionally, 8 abstracts from congress searches and 5 clinical trials met the inclusion criteria.

As a result, 38 publications and 5 clinical trials identified through electronic and supplementary searches were included for data extraction. These 44 included records are summarized in Appendix Table 5, with a complete list of included and excluded publications from the electronic searches provided in the excel file below.

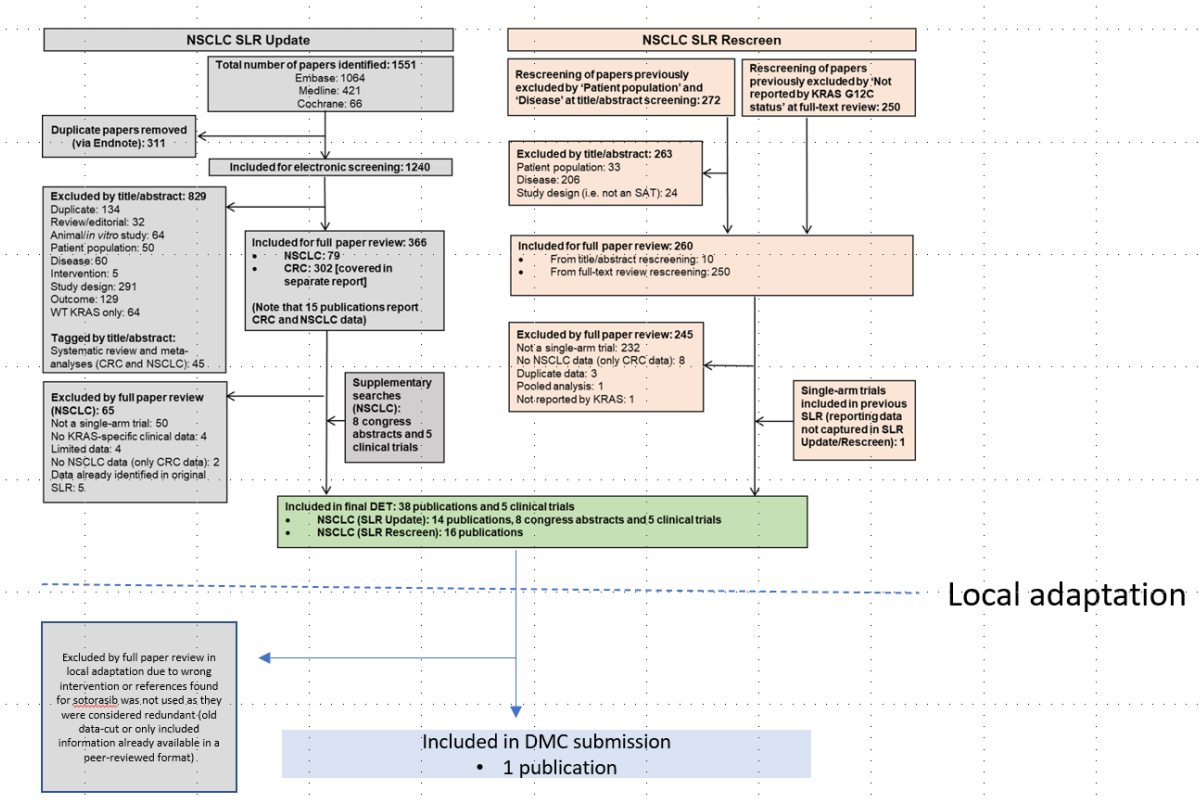
Local adaptation

Only the publication by Skoulidis 2021 qualified for inclusion concerning sotorasib as monotherapy in the correct population with the latest data-cut of as of 15 March 2021.

Included and excluded publications from electronic searches.

AMSR001B_NSCLC KRASm SAT_FTR Decis

Appendix Figure 2.Study flow of included and excluded single-arm trials



Appendix Table 5. Summary of 44 included single-arm studies – global SLR –

Articles marked X was not used as source documentation in this DMC submission due to wrong intervention or references found for sotorasib was not used as they were considered redundant (old data-cut or only included information already available in a peer-reviewed format). Articles used are marked X.

Author Country	NCT ID, Study Name, Phase of Study	Dates	Intervention Number of Patients with NSCLC in Total	Prior Therapy LoT Median (Range), Number or n (%)	Key Inclusion Criteria	Key Exclusion Criteria	Key Primary and Secondary Endpoints/Objectives
KRAS^{G12C} Inhibitors: 6 publications							
Govindan, 2019 International	NCT03600883 Phase 1	Data cutoff: 4 Apr 2019	Sotorasib 14	> 2 (including anti-PD-[L]1 therapies)	Histologically confirmed, locally advanced or metastatic cancer with the *KRAS*^{G12C} mutation; an ECOG PS of 0 - 2; measurable disease per RECIST v1.1; for patients with NSCLC, previous platinum-based combination therapy, targeted therapies, or both	Active (untreated) brain metastases; systemic antitumor therapy within 28 days before initiation of sotorasib therapy; and radiation therapy within 2 weeks before initiation of sotorasib therapy, myocardial infarction within 6 months	Primary: safety, including the incidence of a DLT Secondary: PK, ORR, DoR, DCR, PFS, duration of SD
Govindan, 2019 International	NCT03600883 Phase 1	Data cutoff: 4 Apr 2019	Sotorasib 13	3 (1 - 5)			
Hong, 2020 International	NCT03600883 CodeBreak 100 Phase 1	Data cutoff: 25 March 2020	Sotorasib 40	≥ 2: 31 (77.5) ≥ 3: 19 (47.5)			
Hong, 2020 International	NCT03600883 CodeBreak 100 Phase 1	Data cutoff: 01 Jun 2020	Sotorasib 59	3 (0 - 11)			
Li, 2020 International	NCT03600883 CodeBreak 100 Phase 2	Data cutoff: 1	Sotorasib 126	Anti-PD-(L)1: 91.3% Platinum-based CHT			

Author Country	NCT ID, Study Name, Phase of Study	Dates	Intervention Number of Patients with NSCLC in Total	Prior Therapy LoT Median (Range), Number or n (%)	Key Inclusion Criteria	Key Exclusion Criteria	Key Primary and Secondary Endpoints/Objectives
		Sept 2020		and anti-PD-(L)1: 81.0%			
Skoulidis,2021	NCT03600883 CodeBreak 100 Phase 2	Data-cutoff date 15, March 2021.	Sotorasib 126	Anti-PD-(L)1: 91.3% Platinum-based CHT and anti-PD-(L)1: 81.0%			
Riely, 2021 USA	NCT03785249 KRYSTAL-1 Phase 1/2	Data cutoff: 30 Aug 2020	Adagrasib 79	CHT and an anti-PD-(L)1	Advanced or metastatic NSCLC with *KRAS*^{G12C} mutation; prior treatment with CHT and anti-PD-(L)1	NR	NR
Inhibitors of EGFR/MAPK Signaling Pathway: 27 publications							
2005-005393-73 Germany	EudraCT: 2005-005393-73 Phase 2	Enrollment: Sept 2007 to Sept 2009; completion: 18 Oct 2010	Erlotinib 34	No prior systemic treatment for advanced NSCLC	At least one measurable target lesion; ECOG PS 0 - 2; no prior systemic treatment for advanced NSCLC	NR	PET with both FDG and FLT for accuracy of early prediction of non progression following erlotinib therapy

Author Country	NCT ID, Study Name, Phase of Study	Dates	Intervention Number of Patients with NSCLC in Total	Prior Therapy LoT Median (Range), Number or n (%)	Key Inclusion Criteria	Key Exclusion Criteria	Key Primary and Secondary Endpoints/Objectives
NCT02774278 International	NCT02774278 Phase 2	Jul 2005 to Jun 2009	Erlotinib 264	NR	Advanced NSCLC; tumor accessible for biopsy by bronchoscopy; progression after standard CHT, or unwilling/unable to undergo CHT	Unstable systemic disease; other malignancies in the last 5 years; brain metastases; prior treatment with anti-EGFR therapy	Primary: number of differentially expressed genes associated with clinical benefit (including *KRASm*) Secondary: ORR, CBR
Tarhini, 2017 USA	NR Phase 1/2	NR	Rilotumumab and erlotinib 45	Median: 2	Recurrent or progressive advanced NSCLC; at least 1 and a maximum of 2 prior CHT regimens	Prior erlotinib, other EGFR TKIs, or antibodies targeting EGFR	Primary: safety, RP2D, efficacy (target DCR of 70%) Secondary: OS, PFS
Zhao, 2015 China	NCT00816868 C-TONG0807 Phase 2	Enrollment: Feb 2009 to Sept 2009	Erlotinib and capecitabine 58	None, all naïve to lung cancer treatment	Over 65 years; measurable metastatic or stage IIIB adenocarcinoma NSCLC; naïve to lung cancer treatment; ECOG PS ≤ 2; life expectancy ≥ 12 weeks	Malabsorption, inability to take oral medication, active peptic ulcer, renal disease, newly diagnosed CNS metastasis, unstable systemic disease	Primary: 12-week nonprogression rate Secondary: ORR, toxicity, PFS, and OS.

Author Country	NCT ID, Study Name, Phase of Study	Dates	Intervention Number of Patients with NSCLC in Total	Prior Therapy LoT Median (Range), Number or n (%)	Key Inclusion Criteria	Key Exclusion Criteria	Key Primary and Secondary Endpoints/Objectives
Leighl, 2017 Canada	IND.196 Phase 1	Jan 2010 to Jan 2013	Foretinib and erlotinib 31	Median 2 CHT: 31 (100) Radiation: 18 (58) Other: 9 (29)	Histologically or cytologically confirmed NSCLC; 1 failed CHT for advanced disease; eligible to receive erlotinib; archival tissue available for analysis; measurable disease per RECIST v1.1; ECOG PS ≤ 2	Untreated or uncontrolled cardiovascular conditions; > 2 prior CHT regimens for metastatic disease; prior treatment with anti-EGFR agents; symptomatic or untreated brain metastasis	Primary: RP2D Secondary: descriptive statistics of safety, DLT, response, DoR, PK and PD
Gerber, 2015 USA	NCT01302808 Phase 1	2009 to 2014[a]	Romidepsin and erlotinib 17	3 (1 - 5)	Histologically or cytologically confirmed previously treated advanced NSCLC; measurable disease per RECIST v1.0; ECOG PS 0 or 1; no limit of prior LoTs including erlotinib	Active cardiac disease, QTc prolongation, or other clinically significant ECG abnormalities; prior exposure to romidepsin; pregnancy or lactation	Primary: safety, tolerability, MTD Secondary: efficacy and PK
Ho, 2019 USA	NCT02047344 Phase 2	Oct 2013 to Dec 2018[a]	Antroquinonol 30	≥ 2 prior CHT: 73%	Cytologically or histologically confirmed non-	NR	Primary: PFS Secondary: PK, PD, DCR, ORR, OS

Author Country	NCT ID, Study Name, Phase of Study	Dates	Intervention Number of Patients with NSCLC in Total	Prior Therapy LoT Median (Range), Number or n (%)	Key Inclusion Criteria	Key Exclusion Criteria	Key Primary and Secondary Endpoints/Objectives
NCT02047344 International	NCT02047344 Phase 2	Oct 2013 to 7 Dec 2018	Antroquinonol Efficacy Analysis set: 30 Safety set: 31	More than or equal to 2, but less than or equal to 4, prior lines of systemic anti cancer therapy	squamous NSCLC (stage IV); disease progression after 2 prior LoTs (at least 1 platinum-based) or patients who refused treatment with approved treatments; at least 1 measurable target lesion per RECIST v1.1; fresh or archival biopsy tissue available; ECOG PS 0 - 2	Chemo-, hormone- or immunotherapy, within 4 weeks, radiotherapy within 2 weeks prior to study start; prior treatment with a histone deacetylase inhibitor or an EGFR inhibitor within at least 4 weeks prior to treatment; brain metastases	
Paik, 2020 USA	NCT02417701 Phase 2	6 Oct 2016 to 28 Dec 2020[a]	TAK228 21	Median: 2	Stage IV LUSC with NFE2L2 or KEAP1 mutation and ADCL with *KRAS* + *KEAP1* co-mutation	NR	Primary: ORR Secondary: PFS
Gerber, 2020 USA	NR Phase 2	Enrollment: Sept 2013 to Jun 2016	Defactinib 55	4 (1 - 8)	Inoperable advanced NSCLC; documented *KRASm*; at least 1 prior platinum-based CHT; measurable disease per RECIST v1.1; no	Leptomeningeal metastasis	Primary: 12-week PFS rate Secondary: PFS, OS, ORR, and safety

Author Country	NCT ID, Study Name, Phase of Study	Dates	Intervention Number of Patients with NSCLC in Total	Prior Therapy LoT Median (Range), Number or n (%)	Key Inclusion Criteria	Key Exclusion Criteria	Key Primary and Secondary Endpoints/Objectives
					prior treatment with a FAK inhibitor; ECOG PS 0 or 1.		
Nokihara, 2019 Japan	NCT01553656 Phase 1	Enrollment: 28 March 2011 to 9 Jun 2014	Cabozantinib 20	≥ 3: 20 (100) CHT: 20 (100) BEV: 10 (50) Nivolumab: 1 (5) TKI: 19 (95) Crizotinib: 1 (5) Erlotinib: 10 (50) Gefitinib: 13 (65) Vandetanib: 1 (20)	Advanced or metastatic solid tumors; standard of care ineffective or inappropriate; ≥ 20 years old; ECOG PS ≤ 2; no significant comorbidities. NSCLC expansion: pathologically or cytologically confirmed NSCLC (IIIb or IV); measurable disease per RECIST v1.0; one of the following: *EGFR* mutation (plus prior treatment with an EGFR inhibitor); *KRASm*; gene fusion of RET, ROS1, or ALK (prior treatment with an ALK inhibitor)	NR	Primary: MTD and/or RP2D of capsule and tablet formulations Safety and efficacy analyses were conducted in all patients who received ≥ 1 dose of cabozantinib.

Author Country	NCT ID, Study Name, Phase of Study	Dates	Intervention Number of Patients with NSCLC in Total	Prior Therapy LoT Median (Range), Number or n (%)	Key Inclusion Criteria	Key Exclusion Criteria	Key Primary and Secondary Endpoints/Objectives
NCT02642042 USA	NCT02642042 Phase 2	18 Jul 2016 to 15 May 2019	Docetaxel and trametinib 54	1:16 (29.6) 2: 38 (70.4) *KRAS*^{G12C} 1: 6 (31.6) 2: 13 (68.4) *KRASm* Non-G12C 1:10 (28.6) 2: 25 (71.4)	*KRASm* and known *KRASm* subtype; NSCLC IV or recurrent; measurable disease per RECIST 1.1; at least 1 but no more than 2 LoTs for lung cancer (at least 1 platinum-based CHT)	NR	Primary: ORR in all *KRASm* Secondary: ORR, OS, and PFS in *KRAS*^{G12C} and *KRASm* Non-G12C; grade 3 - 5 AE
Gandara, 2017 USA	NCT01192165 Phase 1b	14 Sept 2010 to 7 Oct 2013[a]	Trametinib and docetaxel plus growth factor (granulocyte colony-stimulating factor [G-CSF]) or trametinib and pemetrexed 95	0 - 4 lines of prior CHT	ECOG PS ≤ 1; histologically or cytologically confirmed metastatic NSCLC; measurable disease per RECIST v1.1, and no more than 2 prior LoT	Prior anticancer therapy within 3 weeks of first study dose; symptomatic or untreated leptomeningeal or brain metastases; history or evidence/risk of retinal vein occlusion. Central serous retinopathy; history of interstitial lung disease or pneumonitis; severe	Primary (part 1): RP2D Primary (expansion cohort): ORR

Author Country	NCT ID, Study Name, Phase of Study	Dates	Intervention Number of Patients with NSCLC in Total	Prior Therapy LoT Median (Range), Number or n (%)	Key Inclusion Criteria	Key Exclusion Criteria	Key Primary and Secondary Endpoints/Objectives
						or uncontrolled systemic diseases	
Barbie, 2018 USA	NCT02258607 NR Phase 1b	Conducted: March 2015 to March 2017	Momelotinib and trametinib 21	1 or more	*KRASm*; metastatic NSCLC; disease progression after ≥ 1 platinum-based CHT regimen, or if disease progression occurred ≥ 6 months after completion of adjuvant therapy for stage I to IIIA; measurable disease per RECIST v1.1; and ECOG PS 0 or 1	Any treatment (21 days) or immunotherapy (28 days) for NSCLC prior to study enrollment; prior exposure to JAK, MEK, or TBK1 pathway inhibitors	Primary: incidence of DLTs during first 28-day cycle Secondary: DCR at week 8; ORR; PFS, OS
Huijberts, 2020 Netherlands	NCT02230553 Phase 1	Oct 2014 to Dec 2019[a]	Lapatinib and trametinib 15	≥ 2: 85% (all cancers)	ECOG PS 0 or 1; life expectancy ≥ 3 months; measurable disease per RECIST v1.1; no treatment within 4 weeks prior to the first dose of study treatment	Symptomatic or untreated leptomeningeal disease; symptomatic brain metastasis; history of interstitial lung disease, pneumonitis, or retinal vein	Primary: RP2R Secondary: safety and tolerability, preliminary anti-tumor activity, PD, and PK

Author Country	NCT ID, Study Name, Phase of Study	Dates	Intervention Number of Patients with NSCLC in Total	Prior Therapy LoT Median (Range), Number or n (%)	Key Inclusion Criteria	Key Exclusion Criteria	Key Primary and Secondary Endpoints/Objectives
						occlusion; previous treatment with combinations of targeted agents known to interfere with EGFR, HER2, HER3, HER4, or MAPK and PI3K pathway components	
Bedard, 2015 5 countries: USA, Canada, and Europe.	NCT01155453 Phase 1b	Enrollment: May 2010 to Jan 2013	All cancers Buparlisib and trametinib 17	All cancers 3 (1 - 14)	Dose-escalation part: adults with advanced solid tumors (RAS or BRAF mutations) Dose-expansion part: measurable disease per RECIST v1.0; advanced NSCLC, ovarian, or pancreatic cancer; WHO PS 0 - 2; adequate organ function	Anxiety assessed as grade ≥ 3; ocular/retinal comorbidities associated with increased risk of central serous retinopathy or retinal vein occlusion	Primary: incidence rate of DLT in cycle 1 Secondary: safety, PK; efficacy, and predictive/PD biomarkers

Author Country	NCT ID, Study Name, Phase of Study	Dates	Intervention Number of Patients with NSCLC in Total	Prior Therapy LoT Median (Range), Number or n (%)	Key Inclusion Criteria	Key Exclusion Criteria	Key Primary and Secondary Endpoints/Objectives
Bardia, 2020 International	NCT01363232 Phase 1b	15 Aug 2011 to 24 March 2014 (data cutoff)	Binimetinib and buparlisib 27	All cancers 3 (1 - 12)	Advanced solid tumors; disease progression after standard therapy and/or no effective standard therapy available; evaluable disease per RECIST v1.1; ECOG PS 0 to 2.	Diabetes mellitus; impaired cardiovascular function; clinically significant cardiovascular diseases, history of depression, ocular disease and ophthalmopathy	Primary: safety and MTD Secondary: efficacy, PK, PD
Froesch, 2020 Switzerland	NCT02964689 Phase 1b	Enrollment: May 2017 to Dec 2019	Binimetinib, pemetrexed and cisplatin 18	NR	Stage III - IV NSCLC unsuitable for curative treatment; PS 0 to 1, *KRASm*; no prior systemic therapy	NR	NR
Desai, 2020 Australia & New Zealand	NR Phase 1	Conducted: 20 Nov 2013 to 19 Oct 2017	Lifirafenib 19 (9 dose escalation + 10 dose expansion)	All cancers: ≥ 3 (inc. B-RAF inhibitor treatment) 50% prior surgery ≥ 75%	Histologically or cytologically confirmed advanced/metastatic solid tumors; ECOG PS ≤ 1; no effective standard therapy available; locally assessed *BRAF, NRAS*,	Untreated leptomeningeal or brain metastases; major surgery within 28 days or radiotherapy within 14 days of enrollment; unresolved toxicity	Primary during dose escalation: safety and tolerability, including DLT and TEAEs. Secondary: PK, ORRs, PFS, DoR, duration of SD

Author Country	NCT ID, Study Name, Phase of Study	Dates	Intervention Number of Patients with NSCLC in Total	Prior Therapy LoT Median (Range), Number or n (%)	Key Inclusion Criteria	Key Exclusion Criteria	Key Primary and Secondary Endpoints/Objectives
					or *KRAS* mutation-positive solid tumors	grade ≥ 1 from prior cancer therapy	
van Geel, 2020 Netherlands	NCT02039336 Phase 1	Enrollment: Apr 2014 to Apr 2018	Dacomitinib/PD-0325901 11	At least 2: antineoplastic therapy for advanced disease	Histologically or cytologically confirmed advanced CRC, NSCLC or pancreatic cancer; documented *KRASm* and *PIK3CA* wild-type status; ECOG PS < 2; life expectancy ≥ 3 months; measurable disease per RECIST v1.1.	Anti-cancer or any treatment with investigational drugs within 4 weeks prior to study treatment; prior therapy containing targeted drug combinations against EGFR, HER2, HER3, HER4 or MAPK and PI3K pathway	Primary: RP2D and schedule Secondary: safety and tolerability, antitumor activity, PK
Nogova, 2020 Germany	NR Phase 1	Enrollment: Oct 2009 to Dec 2013	Everolimus and sorafenib 16	All cancers Surgery: 1 (0 - 4) Radiation: 1 (0 - 4) CHT: 2.5 (0 - 6) Targeted therapy: 0 (0 - 2)	Solid tumors (expansion part NSCLC with *KRASm*); measurable disease per RECIST v1.1; ECOG PS 0 - 2.	Any concomitant uncontrolled condition; brain metastases if they required permanent treatment	Primary: dose finding Secondary: safety, PK, PD using FDG-PET, objective response
NCT00098254, 2021 USA	NCT00098254 Phase 2	Dec 2004 to Jan 2011	BAY 43-9006 (Sorafenib) 37	NR	Recurring or progressive NSCLC after 1 regimen of CHT	NR	Primary: ORR, PFS, number of participants with AEs Secondary: OS,

Author Country	NCT ID, Study Name, Phase of Study	Dates	Intervention Number of Patients with NSCLC in Total	Prior Therapy LoT Median (Range), Number or n (%)	Key Inclusion Criteria	Key Exclusion Criteria	Key Primary and Secondary Endpoints/Objectives
							correlation of response with *KRASm*
Tolcher, 2015 NR	NCT01021748 NR Phase 1	23 Nov 2009 to 16 Jul 2014, dates from ClinicalTrials.gov	MK-2206 and selumetinib 19	All cancers: 3 (1 - 10)	NR	NR	Dose finding: MTD in patients with locally advanced or metastatic solid tumors MTD expansion: confirm the MTD in a select cohort of patients with *KRASm* NSCLC
Lopez-Chavez, 2015 USA	NCT01306045 CUSTOM Phase 2	Enrollment and molecular profiling: Feb 2011 to Dec 2012	Selumetinib monotherapy for *KRAS*, *HRAS*, *NRAS*, or *BRAF* mutations[b] 481	NR	Histologically confirmed recurrent or advanced NSCLC, SCLC (including lung neuroendocrine tumors), or thymic malignancies	NR	Primary: ORR 40% Secondary: OS, PFS
Huijberts, 2020 Netherlands	NCT2450656 Phase 1	Jun 2015 to Dec 2019, dates from	Afatinib and selumetinib 6	NR	NR	NR	Primary: RP2R Secondary: anti-tumor activity PK and PD

Author Country	NCT ID, Study Name, Phase of Study	Dates	Intervention Number of Patients with NSCLC in Total	Prior Therapy LoT Median (Range), Number or n (%)	Key Inclusion Criteria	Key Exclusion Criteria	Key Primary and Secondary Endpoints/Objectives
		ClinicalTrials.gov					
Zimmer, 2014 12 European sites	NR Phase 1	Enrollment: March 2011 to Sept 2012; data cutoff: 21 Sept 2012	RO4987655 24	1: 2 (8) 2: 12 (50) ≥ 3: 10 (42)	Histological or cytological evidence of NSCLC with *KRASm*; ECOG PS ≤ 1; life expectancy ≥ 12 weeks; measurable disease per RECIST v1.1; ≤ 3 prior LoTs for NSCLC	History of retinal vein occlusion, glaucoma, central serous retinopathy, corneal erosion, or risk factors for these ocular disorders	NR, phase 1 expansion study assessed safety, PD, and antitumor activity
Immune Checkpoints Inhibitors: 8 publications							
Peters, 2017 International	NCT02031458 BIRCH Phase 2	Screening and enrollment: 16 Jan 2014 to 4 Dec 2014; data	Atezolizumab 667	Cohort 1: none Cohort 2: 1 Cohort 3: ≥ 2	Histologically or cytologically confirmed IIIB or IV or recurrent NSCLC; tumor PD-L1 expression; ECOG PS 0 or 1; measurable	CNS metastases, history of pneumonitis, autoimmune diseases, or chronic viral diseases; prior treatment with	Primary: ORR Secondary: DoR, ORR, PFS, OS, safety

Author Country	NCT ID, Study Name, Phase of Study	Dates	Intervention Number of Patients with NSCLC in Total	Prior Therapy LoT Median (Range), Number or n (%)	Key Inclusion Criteria	Key Exclusion Criteria	Key Primary and Secondary Endpoints/Objectives
		cutoff: 1 Dec 2015			disease per RECIST v1.1.	CD137 agonists or ICIs	
Eberhardt, 2017 Unclear	NCT02031458 BIRCH Phase 2	NR	Atezolizumab 204	None			
Hellmann, 2019 International	NCT01988896 Phase 1b	27 Dec 2013 to 9 May 2016	Atezolizumab and cobimetinib 28	3 (0 - 11)	ECOG PS 0 or 1; measurable disease per RECIST v1.1.	Known or active untreated CNS metastases; autoimmune disease; prior therapy with T-cell-modulating agents; prior intolerance to a MEK inhibitor	Primary: safety and tolerability Secondary: best overall response; DoR, PFS, OS
Pujol, 2020 Unclear	NCT02779751 Phase 1b	14 Nov to 3 Feb 2020 (estimated completion: 29 Oct 2021)[a]	Abemaciclib and pembrolizumab 50	Cohort A: CHT-naïve Cohort B: 68% 1 prior line of CHT	Cohort A CHT-naïve with ≥ 1% TC PD-L1 staining, *KRASm* non-squamous NSCLC Cohort B squamous subtype; ≤ 1 prior platinum-containing CHT regimen	NR	Primary[a]: number of participants with SAEs and non-SAEs Secondary: ORR, DCR, DoR, PFS, OS, PK

Author Country	NCT ID, Study Name, Phase of Study	Dates	Intervention Number of Patients with NSCLC in Total	Prior Therapy LoT Median (Range), Number or n (%)	Key Inclusion Criteria	Key Exclusion Criteria	Key Primary and Secondary Endpoints/Objectives
Gulley, 2017 USA	NCT01772004 JAVELIN Phase 1b	Enrollment and treatment initiation: 10 Sept 2013 to 24 Jun 2014	Avelumab 184	Carboplatin: 157 (85) Pemetrexed: 100 (54) Paclitaxel: 76 (41) Cisplatin: 46 (25) Gemcitabine: 32 (17) Erlotinib: 20 (11) Docetaxel:18 (10) Vinorelbine: 9 (5)	Confirmed stage IIIB or IV NSCLC; progression after platinum-based doublet CHT for metastatic disease; ECOG PS 0 or 1; life expectancy ≥ 3 months; no active or history of CNS metastases; measurable disease by CT or MRI scan and RECIST v1.1; available material for biomarker analyses	NR	Primary: occurrence of DLT during the first 3 weeks of treatment Secondary: BOR, DoR, PFS, OS, safety and activity according to PD-L1 expression on TC and IC
Rizvi, 2014 USA	NR NR Phase NR	NR	Nivolumab 129	≥ 3 prior therapies: 54%	NR	NR	NR
Reuss, 2020 USA	NCT02259621 Phase 1b/2	Enrollment: Jul 2017 to March 2018	Nivolumab and ipilimumab 9	NR	Resectable stage IB - IIIA treatment-naïve, histologically confirmed NSCLC; ECOG PS 0 – 1ALK	Active autoimmune disease; ongoing immunosuppressive therapy; active concurrent malignancy; history	Primary: safety and feasibility with a planned enrollment of 15 patients Pathologic response was a key secondary endpoint

Author Country	NCT ID, Study Name, Phase of Study	Dates	Intervention Number of Patients with NSCLC in Total	Prior Therapy LoT Median (Range), Number or n (%)	Key Inclusion Criteria	Key Exclusion Criteria	Key Primary and Secondary Endpoints/Objectives
						of symptomatic interstitial lung disease; preoperative CHT; any prior treatment with PD-1 or CTLA-4 inhibitors.	
Crombet, 2020 Unclear	NR Phase 1	NR	CIMAvax and nivolumab 13	1	NR	NR	NR
Proteasome, HSP90 and Autophagy Inhibitors: 3 publications							
Felip, 2018 International	NCT01124864 NR Phase 2	Conducted: Oct 2010 to Nov 2014	AUY922 153	Last therapy, n (%) CHT: *KRASwt* 25 (73.5) *KRASm* 22 (78.6) All 92 (60.1) Hormonal therapy: *KRASwt* 0 *KRASm* 0 (0) All 1 (0.7) Immunotherapy: *KRASwt* 1 (2.9) *KRASm* 1 (3.6) All 3 (2.0)	Histologically or cytologically confirmed, advanced NSCLC; ≥ 2 LoTs, except for less pretreated EGFR cohort (EGFR < 2).	NR	Primary: ORR or no clinical benefit for each stratum Secondary: OS, PFS, safety, PK

Author Country	NCT ID, Study Name, Phase of Study	Dates	Intervention Number of Patients with NSCLC in Total	Prior Therapy LoT Median (Range), Number or n (%)	Key Inclusion Criteria	Key Exclusion Criteria	Key Primary and Secondary Endpoints/Objectives
				Targeted therapy: *KRASwt* 11 (32.4) *KRASm* 6 (21.4) All 64 (41.8) Other: *KRASwt* 1 (2.9) *KRASm* 0 (0) All 3 (2.0)			
Drilon, 2019 USA	NCT 01833143 Phase 2	11 Apr to 28 Aug 2019[a]	Bortezomib 16	2 (1–4)	Advanced NSCLC; *KRASm*; Karnofsky PS ≥ 70%, 1 prior LoT; measurable disease per RECIST v1.1; never smoker or tumor with a $KRAS^{G12D}$ mutation regardless of smoking history	Uncontrolled metastatic disease involving the CNS; at least grade 2 peripheral neuropathy; hypersensitivity to boron or mannitol	Primary: response rate Secondary: PFS, OS, and toxicity
Malhotra, 2018 USA	NCT01649947, NCT00728845 Phase 1b	NR	Carboplatin, paclitaxel (BEV[c]) and hydroxychloroquine 40	None	NR	NR	NR

Amongst the 44 included records, 6 were for $KRAS^{G12C}$ inhibitors. These included 5 records that related to the CodeBreak 100 trial of sotorasib and 1 that related to another adagrasib, which is another $KRAS^{G12C}$ inhibitor that is in development but not yet licensed for use. The other records related to therapies that are not comparators for sotorasib, and so do not inform this appraisal of sotorasib.

Local adaptation:

The global SLR for single-arm trials included 44 references, and in the local adaptation 43 references were excluded marked red in Appendix table 3.

The global SLR for RCT trials included 18 references, and in the local adaptation 17 references were excluded marked red in Appendix table 5.

Additional sources of evidence was added to support the application as some results were not reported in the primary publications of the studies(71).

Eligibility criteria	**Inclusion Criteria**	**Exclusion Criteria**
Population	Patients with NSCLC (any stage, any line of treatment) carrying a *KRAS G12C* mutation or any other KRAS mutation (*KRASm*)	Tumor types other than NSCLC
Interventions	Sotorasib	Radiotherapy or surgery (unless a relevant comparator arm)
Comparator	Docetaxel	All other comparators not used in Denmark
Outcomes	Outcome reported by *KRASm* mutation status *Clinical evidence* • Overall survival • Progression-free survival • Adverse events *HRQoL evidence* Note, search strings were limited by outcomes and do not include HRQoL terms.	
Study design	RCT or single-arm trials (experimental/interventional)	Exclude animal/*in vitro* studies, case studies and case reports
Language restrictions	English language	

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Publication type	All publication types, except editorials and reviews, but including systematic reviews*	
Country	Not restricted	
Other criteria	Sufficient patient population (size) and reporting (baseline characteristics) to allow for MAIC	

Conclusion of the global SLRs and the local adaptation

The SLRs of RCTs and single arm trials confirm that:

- Published data for sotorasib in *KRAS G12C-mutated* NSCLC is currently only available from the CodeBreak 100 single arm trial.
- Published trial data available for the relevant comparators to sotorasib for this appraisal are very limited
    - The SELECT-1 trial is the only trial providing sufficient data for docetaxel monotherapy in patients with KRAS mutant NSCLC (including *KRAS G12C-mutated* NSCLC) to allow a viable exploration of an indirect comparison with sotorasib.
- Outcomes for patients with KRAS mutated NSCLC, including KRAS G12C, are very poor.
- The submission will provide comparative efficacy estimates by conducting an unanchored MAIC using data from CodeBreak 100 trial (sotorasib), and SELECT-1 trial

Author Country	**NCT ID, Study Name, Phase of Study**	**Dates**	**Intervention Number of Patients with NSCLC in Total**	**Prior Therapy** **LoT Median (Range), Number or n (%)**	**Key Inclusion Criteria**	**Key Exclusion Criteria**	**Key Primary and Secondary Endpoints/Objectives**
Skoulidis ,2021	NCT03600883 CodeBreak 100 Phase 2	Data-cutoff date 15, March 2021.	Sotorasib 126	Anti-PD-(L)1: 91.3% Platinum-based CHT and anti-PD-(L)1: 81.0%	Histologically confirmed, locally advanced or metastatic cancer with the *KRAS^{G12C}* mutation; an ECOG PS of 0 - 2; measurable disease per RECIST v1.1; for patients with NSCLC, previous	Active (untreated) brain metastases; systemic antitumor therapy within 28 days before initiation of sotorasib therapy; and radiation therapy within	Primary: safety, including the incidence of a DLT Secondary: PK, ORR, DoR, DCR, PFS, duration of SD

					platinum-based combination therapy, targeted therapies, or both	2 weeks before initiation of sotorasib therapy, myocardial infarction within 6 months	
Janne, 2017	NCT01933932, *SELECT-1,* International study	conducted between October 2013 and January 2016	75 mg of selumetinib (hydrogen sulphate) twice daily + 75 mg/m^2 of docetaxel intravenously on day 1 of every 21-day cycle (n=254) Matched placebo plus docetaxel (same schedule) (n=256)	1) Patients had previously received at least 1 prior anticancer drug regimen for advanced or metastatic NSCLC 2) Patients who had received more than 1 prior anticancer drug regimen for advanced or metastatic NSCLC, or prior treatment with an MEK inhibitor or any docetaxel-containing regimen were excluded	1) Patients 18 years or older, with histologically or cytologically confirmed locally advanced or metastatic NSCLC (stage IIIB–IV). 2) Patients had failure of 1 previous line of therapy for advanced disease, a centrally confirmed KRAS-mutant tumor 3) With WHO performance status of 0 or 1	1) Mixed small cell and non–small cell lung cancer histology and presence of brain metastases or spinal cord compression (unless asymptomatic, treated, stable, and off steroids and anti-convulsants for ≥4 weeks prior to screening).	1°: PFS 2°: OS, ORR, DOR, TTP, safety and tolerability,

Quality assessment

The literature search adhered to the highest standards for conducting and reporting. The SLR was re-fitted for the purpose of the assessment in Denmark using the same methodology.

Unpublished data

The data-on file from CodeBreak 100 **trial** used for this submission were full study report and were developed to support regulatory submissions to EMA/FDA. The data analysis therefore adherers to the most stringent quality criteria.

Table 38 Ongoing studies that may inform the evidence base for sotorasib and comparators

ClinicalTrials.gov Search Results 03/31/2022

	Title	Status	Study Results	Conditions
1	Phase 1/2 Study of VS-6766 + Sotorasib in G12C NSCLC Patients	Recruiting	No Results Available	•Non Small Cell Lung Cancer •KRAS Activating Mutation
2	A Study of Sotorasib (AMG 510) in Participants With Stage IV NSCLC Whose Tumors Harbor a KRAS p.G12C Mutation in Need of First-line Treatment	Recruiting	No Results Available	•Non-small Cell Lung Cancer
3	Combination Study of RMC-4630 and Sotorasib for NSCLC Subjects With KRASG12C Mutation After Failure of Prior Standard Therapies	Recruiting	No Results Available	•Non-Small Cell Lung Cancer
4	RW Efficacy of Sotorasib in KRAS G12C-mutated Metastatic NSCLC	Recruiting	No Results Available	•NSCLC Stage IV •KRAS P.G12C
5	Expanded Access of AMG 510 (Sotorasib)	Available	No Results Available	•Non Small-cell Lung Cancer •Locally Advanced Unresectable NSCLC •Locally Advanced Metastatic NSCLC
6	Study to Compare AMG 510 "Proposed INN Sotorasib" With Docetaxel in Non Small Cell Lung Cancer (NSCLC) (CodeBreak 200).	Active, not recruiting	No Results Available	•KRAS p, G12c Mutated /Advanced Metastatic NSCLC
7	A Phase II Study of Neoadjuvant Sotorasib in Combination With Cisplatin or Carboplatin and Pemetrexed for Surgically Resectable Stage IIA-IIIB Non-Squamous Non-Small Cell Lung Cancer With a KRAS p.G12C Mutation	Not yet recruiting	No Results Available	•Lung Cancer
8	A Study of Anti-Cancer Therapies Targeting the MAPK Pathway in Patients With Advanced NSCLC	Recruiting	No Results Available	•Advanced Non-squamous Non-small-cell Lung Cancer
9	A Phase 1/2, Study Evaluating the Safety, Tolerability, PK, and Efficacy of Sotorasib (AMG 510) in Subjects With Solid Tumors With a Specific KRAS Mutation (CodeBreaK 100)	Recruiting	No Results Available	•KRAS p.G12C Mutant Advanced Solid Tumors
10	Testing the Use of Targeted Treatment (AMG 510) for KRAS G12C Mutated Advanced Non-squamous Non-small Cell Lung Cancer (A Lung-MAP Treatment Trial)	Recruiting	No Results Available	•Lung Adenocarcinoma •Lung Non-Small Cell Carcinoma •Recurrent Lung Non-Squamous Non-Small Cell Carcinoma •Stage IV Lung Cancer AJCC v8 •Stage IVA Lung Cancer AJCC v8 •Stage IVB Lung Cancer AJCC v8

Appendix B - Main characteristics of included studies

Table 39: Main study characteristics of CodeBreak 100

Trial name: CodeBreak 100	NCT number: NCT03600883
Objective	To evaluate safety and efficacy of sotorasib as monotherapy in subjects with KRAS p.G12C-mutated advanced tumors (non-small cell lung cancer [NSCLC])
Publications – title, author, journal, year	- Sotorasib for Lung Cancers with KRAS p.G12C Mutation. F. Skoulidis et al. N Engl J Med. 2021;384:2371-81 (73) - Clinical study report (Data on file) (71)
Study type and design	Phase 2, international, multicenter, open-label study of sotorasib monotherapy in adult patients with locally advanced or metastatic *KRAS p.G12C*-mutated NSCLC. Conducted at 59 study centers in the United States, Canada, France, Belgium, Germany, Switzerland, Austria, Japan, South Korea, Australia, and Brazil
Sample size (n)	ITT, N = 126
Main inclusion and exclusion criteria	Inclusion: • Adults (age ≥ 18 years). • Locally advanced or metastatic NSCLC with the KRAS p.G12C mutation confirmed on central laboratory testing with the use of the therascreen KRAS RGQ PCR Kit. • Disease progression after the receipt of anti–programmed death 1 (PD-1) or anti–programmed death ligand 1 (PD-L1) immunotherapy or platinum-based combination chemotherapy or after the receipt of both immunotherapy and platinum-based combination chemotherapy. • An ECOG performance status score of 0 to 1 (on a scale from 0 to 5). • Measurable disease according to RECIST, version 1.1. Exclusion: • Active untreated brain metastases. • The receipt of more than three previous lines of therapy. • The receipt of systemic anticancer therapy within 28 days before the initiation of sotorasib therapy. • The receipt of therapeutic or palliative radiation therapy within 2 weeks before the initiation of sotorasib therapy. • Previous treatment with a direct KRASG12C inhibitor. • Myocardial infarction within 6 months of study day 1. • Gastrointestinal tract disease causing the inability to take oral medication.
Intervention	Patients received 960 mg sotorasib orally once per day without interruption until the occurrence of progressive disease, the development of unacceptable side effects, or withdrawal of consent.
Comparator(s)	None
Follow-up time	The median follow-up was 15.3 months (range: 1.1 to 18.4+)

Trial name: CodeBreak 100	NCT number: NCT03600883
Is the study used in the health economic model?	Yes
Primary, secondary and exploratory endpoints	Primary • Objective response (complete or partial response) as assessed by blinded, independent, central radiologic review. Tumor response was assessed by independent central review according to RECIST, version 1.1, with the use of contrast-enhanced CT or MRI. Key secondary: • Duration of response • Disease control rate (defined as complete response, partial response, or stable disease, according to RECIST, version 1.1; minimum time interval for the Determination of stable disease, 5 weeks) • Overall survival • Progression-free survival • Time to response Other secondary endpoints: • Safety • Adverse events were graded with the use of the Common Terminology Criteria for Adverse Events, version 5.0. Exploratory endpoints: • Biomarkers were evaluated by means of molecular analysis of blood and tumor-tissue specimens for their association with tumor response to sotorasib therapy. • Changes in cancer-specific symptoms and overall health status using patient-reported outcome measures: (EORTC QLQ-C30, QLQ LC13; NSCLC-SAQ; PGIS; PGIC; PRO-CTCAE; item GP5 of the FACT-G; EQ-5D-5L)
Method of analysis	**ORR**: Percentage of subjects with an objective response summarized with Clopper-Pearson exact 95% CI. **Duration of response**: The median duration of objective response was calculated as of the data-cutoff date for all 46 patients who had an objective response to sotorasib therapy. **Disease control rate**: Summarized as for ORR **Time to response**: Summarized descriptively (responders only) **Progression-free survival**: Summarized with Kaplan-Meier curves, quartiles, and rates at 6 and 9 months **Overall survival**: Summarized as for PFS **PROs and HRQoL**: EORTC QLQ-C30; EORT QLQ-LC13; PGIS; PGIC; FACT-G (GP5); NSCLC-SAQ; PRO-CTCAE; EQ-5D-5L: Summarized descriptively. Changes from baseline over time tested using mixed effects model for repeated measures (MMRM) model
Subgroup analyses	Exploratory biomarkers: • PD-L1 protein expression (< 1%, 1-49% and ≥ 50%) • Co-occurring mutations in TP53, STK11, and KEAP1 • Mutational status in both STK11 and KEAP1

Trial name: CodeBreak 100	NCT number: NCT03600883
Other relevant information	None

Table 40: SELECT-1 – Study Characteristics

Trial name: SELECT-1	NCT number: NCT01933932
Objective	To compare the efficacy of the mitogen-activated protein kinase kinase (MEK) inhibitor selumetinib + docetaxel with docetaxel alone as second-line therapy for advanced *KRAS*-mutant NSCLC.
Publications – title, author, journal, year	Selumetinib Plus Docetaxel Compared With Docetaxel Alone and Progression-Free Survival in Patients With KRAS-Mutant Advanced Non–Small Cell Lung Cancer - The SELECT-1 Randomized Clinical Trial. Pasi A. Jänne, et al. JAMA. 2017;317(18):1844-1853. doi:10.1001/jama.2017.3438.
Study type and design	A multinational randomized clinical trial was conducted at 202 sites across 25 countries from October 2013 through January 2016. Of 3323 patients with advanced NSCLC and disease progression following first-line anticancer therapy tested for a KRAS mutation, 866 were enrolled and 510 were randomized. Patients were randomly assigned to treatment in a 1:1 ratio based on a computer-generated random number, using an interactive voice or web response system. Patients were stratified by WHO performance status (0 or 1) and tumor histology (squamous or non-squamous), and 1 randomization list was made for each of the 4 randomization strata. No cross-over was allowed. The investigators, patients, and sponsors were masked during treatment assignment.
Sample size (n)	Selumetinib + Docetaxel, n = 254 Placebo + Docetaxel, n = 256

Trial name: SELECT-1	NCT number: NCT01933932
Main inclusion and exclusion criteria	**Main inclusion:** • Provision of signed, written, and dated informed consent prior to any study specific procedures • Male or female, aged 18 years or older • Histological or cytological confirmation of locally advanced or metastatic NSCLC (IIIB-IV) • KRAS mutation positive tumor sample as determined by the designated testing laboratory • Failure of 1st line anti-cancer therapy due to radiological documentation of disease progression in advanced disease or subsequent relapse of disease following 1st line therapy **Main exclusion:** • Mixed small cell and non-small cell lung cancer histology. • Received >1 prior anti-cancer drug regimen for advanced or metastatic NSCLC. Patients who develop disease progression while on switch maintenance therapy (maintenance using an agent, not in the first-line regimen) will not be eligible. • Receiving or have received systemic anti-cancer therapy within 30 days prior to starting study treatment • Symptomatic brain metastases or spinal cord compression. Patients with asymptomatic brain metastasis, or treated and stable off steroids and anticonvulsants for at least 1 month prior to entry into the study are eligible • Other concomitant anti-cancer therapy agents except for steroids • Prior treatment with a Mitogen-Activated Protein Kinase (MEK) inhibitor or any docetaxel-containing regimen (prior treatment with paclitaxel is acceptable). • Last radiation therapy within 4 weeks prior starting study treatment, or limited field of radiation for palliation within 7 days of the first dose of study treatment
Intervention	• 75 mg of selumetinib (hydrogen sulfate) twice daily on a continuous oral administration schedule in combination with 75 mg/m2 of docetaxel intravenously on day 1 of every 21-day cycle All patients received granulocyte colony-stimulating factor (G-CSF) or, where available, pegylated G-CSF (pegfilgrastim) starting within 24 hours following each docetaxel administration and not within 14 days before the next docetaxel dose. Patients received assigned study treatment until objective disease progression, intolerable toxicity, or withdrawal of study consent. Patients could continue to receive treatment following disease progression as long as the investigator considered them as continuing to derive clinical benefit in the absence of significant toxicity.
Comparator(s)	• Matched placebo in combination with 75 mg/m2 of docetaxel intravenously on day 1 of every 21-day cycle All patients received granulocyte colony-stimulating factor (G-CSF) or, where available, pegylated G-CSF (pegfilgrastim) starting within 24 hours following each docetaxel administration and not within 14 days before the next docetaxel dose. Patients received assigned study treatment until objective disease progression, intolerable toxicity, or withdrawal of study consent. Patients could continue to receive treatment following disease progression as long as the investigator considered them as continuing to derive clinical benefit in the absence of significant toxicity.

Trial name: SELECT-1	NCT number: NCT01933932
Follow-up time	Median duration of follow-up for overall survival: placebo + docetaxel, 12.2 months (IQR, 8.1-16.8). Median duration of follow-up for progression-free survival: placebo + docetaxel, 4.2 months (IQR, 0.03-11.1)
Is the study used in the health economic model?	Yes
Primary, secondary and exploratory endpoints	**Primary Outcome variable:** PFS using investigator site assessments according to RECIST 1.1 **Secondary Outcome variables:** OS ORR using investigator site assessments according to RECIST 1.1 DoR using investigator site assessments according to RECIST 1.1 Time to symptom progression as measured by the Average Symptom Burden Index (ASBI) score of the Lung Cancer Symptom Scale (LCSS) Symptom improvement rate as measured by the ASBI score of the LCSS **Safety:** • Adverse events • Clinical chemistry, hematology, and urinalysis • Vital signs • ECHO/MUGA • Ophthalmological examination **Exploratory Outcome variables:** • Individual items of the LCSS: Symptom distress and interference with activity levels • SF-36v2 domain scale scores and physical and mental component summary scores • KRAS mutation status of plasma derived DNA from samples collected at screening and treatment discontinuation • KRAS mutation subtype(s) • Host genetic polymorphisms • Biomarkers to response or development of cancer

Trial name: SELECT-1	NCT number: NCT01933932
Method of analysis	PFS is the primary endpoint. However, the study has been sized to characterize the OS benefit of selumetinib 75mg bd in combination with docetaxel. Approximately 500 KRAS mutation positive tumor patients will be randomized between the two treatment arms to obtain approximately 325 death events (65% maturity). The final analysis of PFS will take place on a pre-specified date when it is predicted that 325 death events will have occurred. The exact date will be predicted by modelling the blinded death rate data. If the true OS hazard ratio (HR) for the comparison of selumetinib 75mg bd in combination with docetaxel 75mg/m2 vs. placebo in combination with docetaxel 75mg/m2 is 0.72, this number of events will provide at least 80% power to demonstrate a statistically significant difference for OS, assuming a 2% 1-sided Type I error. This OS HR corresponds to an approximate 2-month improvement in median OS over an estimate of 5.2 months (estimated from D1532C00016) for placebo in combination with docetaxel, assuming proportional hazards and exponential data distribution. A 2-month improvement in median OS is regarded as clinically meaningful. The smallest treatment difference that would be statistically significant at the final analysis is an OS HR of approximately 0.80 (0.796 if exactly 325 OS events). Efficacy data will be analyzed on an intention-to-treat basis using randomized treatment. PFS, OS, and time to symptom progression using the ASBI will be analyzed using a stratified logrank test. The results will be presented in terms of the HR, associated two-sided confidence interval (CI), and p-value. Kaplan-Meier (KM) plots of PFS, OS, and time to symptom progression will also be presented. ORR and symptom improvement rate using the ASBI will be analyzed using a logistic regression adjusted for the stratification factors WHO Performance Status (1/0) and tumor histology (squamous/non-squamous). In order to describe the nature of the benefits of selumetinib treatment, PFS, OS, ORR, time to symptom progression, and symptom improvement rate will be tested at a 2-sided significance level of 5%. However, in order to strongly control the type, I error at 2.5% 1-sided, a multiple testing procedure (MTP) with an alpha-exhaustive recycling strategy (Burman et al 2009) will also be employed across the primary endpoint (PFS) and key secondary endpoints (i.e., OS and ORR). Safety data will be summarised and listed for all patients who received at least one dose of study treatment (selumetinib/placebo) based on the treatment received. No formal statistical testing will be performed on the safety data. Adverse events will be summarised by preferred term and system organ class (using the Medical Dictionary for Regulatory Activities [MedDRA]). Summaries of AEs by causality and CTC grade will also be presented.
Subgroup analyses	Prespecified subgroup analyses will be conducted comparing PFS between treatments in the subgroups of the full analysis set defined by the stratification factors WHO PS and histology, plus the following factors: • Gender (Male vs. Female) • Age at randomisation (< 65 vs. = 65) • Smoking status (smoker vs. non-smoker (never smoker) • Status of disease (Locally advanced vs. Metastatic) The purpose of the subgroup analyses is to assess the consistency of treatment effect across expected prognostic factors but from the results observed in Phase II (D1532C00016) it is not expected that these factors will be predictive factors for a qualitatively different treatment effect. No adjustment to the significance level for testing will be made since all these analyses will be considered supportive of the primary analysis of PFS.

Trial name: SELECT-1	NCT number: NCT01933932
Other relevant information	None

Table 41. Comparison of CodeBreak 100 and SELECT-1 Study Designs

Inclusion Criteria	Sotorasib (CodeBreak 100)	Docetaxel (SELECT-1)
Setting	Multicenter	Multicenter
Blinding	Open-label	Double-blinded
Inclusion criteria	• Adults (age ≥ 18 years) • Histologically confirmed locally advanced or metastatic (stage IIIB - IV) NSCLC • ECOG/WHO PS 0 or 1 • *KRAS p.G12C mutation*-positive	• Adults (age ≥ 18 years) • Histologically/cytologically confirmed locally advanced or metastatic (stage IIIB - IV) NSCLC • ECOG/WHO PS 0 or 1 • *KRAS*-mutation-positive
Exclusion criteria	• Active brain metastases from non-brain tumors. • Myocardial infarction within 6 months of study day 1. • Gastrointestinal tract disease causing the inability to take oral medication.	• Mixed small cell and non-small cell lung cancer histology • Active brain metastases • ≥ 1 prior therapy for advanced or metastatic disease • Prior treatment with MEK inhibitor or docetaxel-containing regimen • Disease progression while on switch maintenance therapy (maintenance using an agent, not in the first-line regimen)
Primary endpoint	ORR	PFS
Measurement of PFS	RECIST version 1.1 (investigator- and BICR-assessed; every 6 weeks for the first 8 assessments then every 12 weeks thereafter).	RECIST version 1.1 (investigator assessed; every 6 weeks; a random sample of scans from 220 evaluable patients BICR assessed).

BICR, blinded independent central review; ECOG, Eastern Cooperative Oncology Group; *KRAS*, Kirsten rat sarcoma viral oncogene homolog; MEK: mitogen activated protein kinase; NSCLC, non-small cell lung cancer; ORR, objective response rate; PFS, progression-free survival; PS, performance status; RECIST, Response Evaluation Criteria in Solid Tumors; WHO, World Health Organization.
Source: Amgen data on file [CodeBreaK 100 CSR] (117); Jänne, van den Heuvel (118); Amgen data on file [0014] (119)

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

Table 42 Baseline characteristics of patients in studies included for the comparative analysis of efficacy and safety

Baseline characteristics [a]	Sotorasib (CodeBreak 100) N = 126	Docetaxel (SELECT-1) N = 256
Age (mean)	62.9	60.9
Gender (% female)	50%	43%
Brain metastases (%)	21%	NR[b]
ECOG (% PS 1 [vs PS 0])	70%	59%
Race (% white)	82%[c]	95%
% KRAS-G12C	100%	42%[d]
Anti-PD-(L)1 in prior line(s)	91%	0%
Number of prior lines (% with 1/2/3 prior lines)	43%/35%/22%	100%/0%/0%
Metastatic disease stage at baseline (% IIIB [vs IV])	97%	96%
Histology (% Non-squamous)	99%	95%
Smoking status (% ever smoker)	93%[e]	92%
Other targetable mutations (EGFR, ALK, BRAF, ROS-1)	3%	NR[f]
PD-L1 protein expression level (<5% [vs. ≥5%])	48%	58%

Key: ECOG, European Co-operative Oncology Group.
Note:
[a] all reported baseline characteristics in SELECT-1 and other key characteristics.
[b], not reported for SELECT-1. Both studies had exclusion criteria for active brain metastases.
[c], 15 percentage points of the 18% remaining correspond to Asian patients.
[d], the rest of the population has KRAS mutations other than G12C.
[e], 2 percentage points of the remaining 7% are missing data.
[f], probably very low due to KRAS mutant.

Comparability of patients across studies

Please consult section 12.1.1 for a comparison of patients across studies.

Comparability of the study populations with Danish patients eligible for treatment

Please consult section 8.2.2.

Appendix D - Efficacy and safety results per study

Definition, validity, and clinical relevance of included outcome measures

Outcome measure	Definition	Validity	Clinical relevance
PFS	Time from the first dose of treatment until disease progression or death from	Pilz, L. R., Manegold, C., & Schmid-Bindert, G. (2012). Statistical	The minimal clinically important difference for PFS is a median of 3 months (7).

Outcome measure	Definition	Validity	Clinical relevance
	any cause according to the RECIST v.1.1 (72).	considerations and endpoints for clinical lung cancer studies: Can progression free survival (PFS) substitute overall survival (OS) as a valid endpoint in clinical trials for advanced non-small-cell lung cancer?.(120)	
OS	Time from the first dose of treatment until death from any cause	Pilz, L. R., Manegold, C., & Schmid-Bindert, G. (2012). Statistical considerations and endpoints for clinical lung cancer studies: Can progression free survival (PFS) substitute overall survival (OS) as a valid endpoint in clinical trials for advanced non-small-cell lung cancer?.(120)	The minimal clinically important difference for OS is a median of 3 months (7).
Treatment discontinuations due to AEs (%)	CodeBreak 100: Time from the first dose of treatment until discontinuation due to AEs according to the CTCAE v.5.0 (73). SELECT-1: Time from the first dose of treatment until discontinuation due to AEs according to the CTCAE v.4.03 (72).	Used in prior DMC submission for NSCLC and for treatment guideline protocol (7).	The minimal clinically important difference for treatment discontinuations due to AEs is 5%-point (7).
AEs grade ≥3 (%)	CodeBreak 100: All AEs after the first dose of study treatment according to the CTCAE v.5.0 (73). SELECT-1: AEs were collected from the time of informed consent until 30 days (±7) after the last dose of the last study treatment according to the CTCAE v.4.03 (72).	Used in prior DMC submission for NSCLC and for treatment guideline protocol (7).	The minimal clinically important difference for patients experiencing one or more grade 3-4 AEs is 5%-point or narrative assessment (7).
PROs and HRQoL	Time to symptom progression and EORTC QLQ-C30 (73).	Groenvold, M., Klee, M. C., Sprangers, M. A., & Aaronson, N. K. (1997). Validation of the EORTC QLQ-C30 quality of life questionnaire through combined qualitative and quantitative assessment	The minimal clinically important difference in QoL described as a meaningful difference using a validated scheme (7).

Outcome measure	Definition	Validity	Clinical relevance
		of patient-observer agreement.(121)	

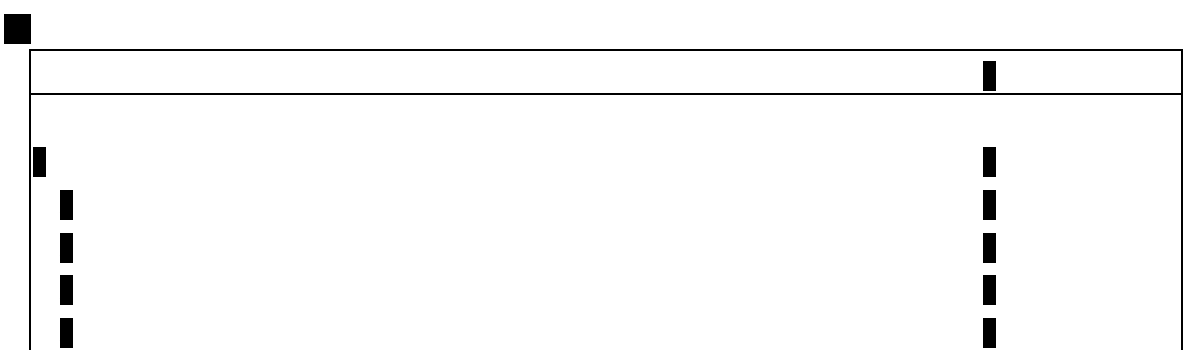
Key: CTCAE v.5.0, Common Terminology Criteria for Adverse Events version 5.0; CTCAE v.4.03, Common Terminology Criteria for Adverse Events version 4.03.

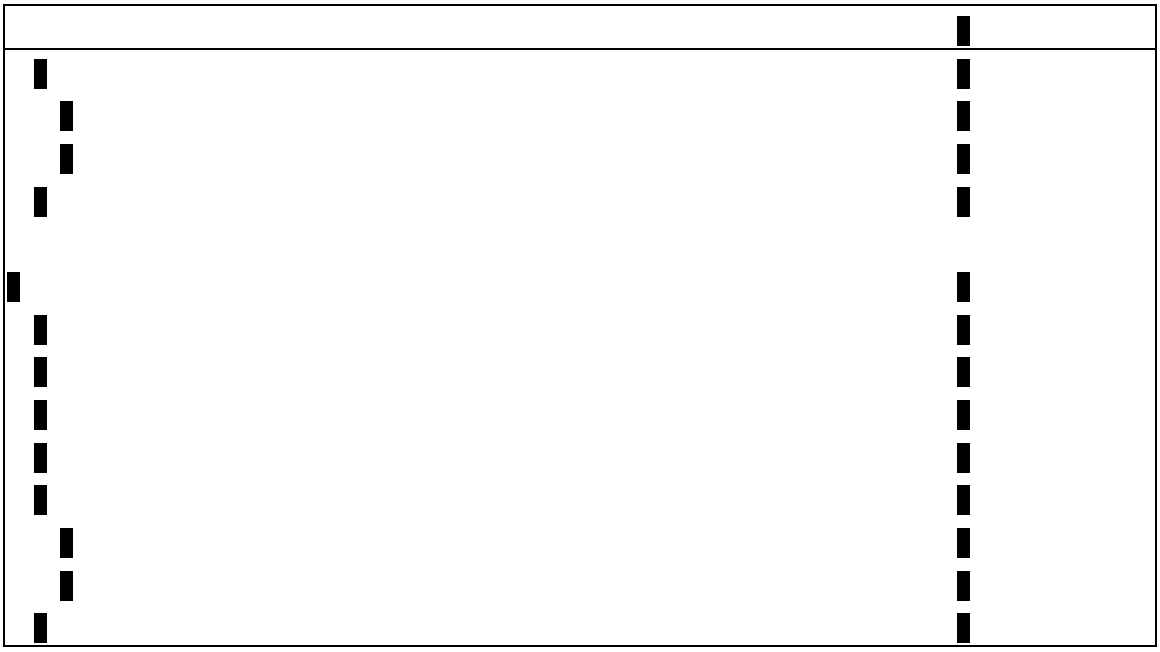
Results per study

Table 43. Results of CodeBreak 100 (NCT03600883) (73)

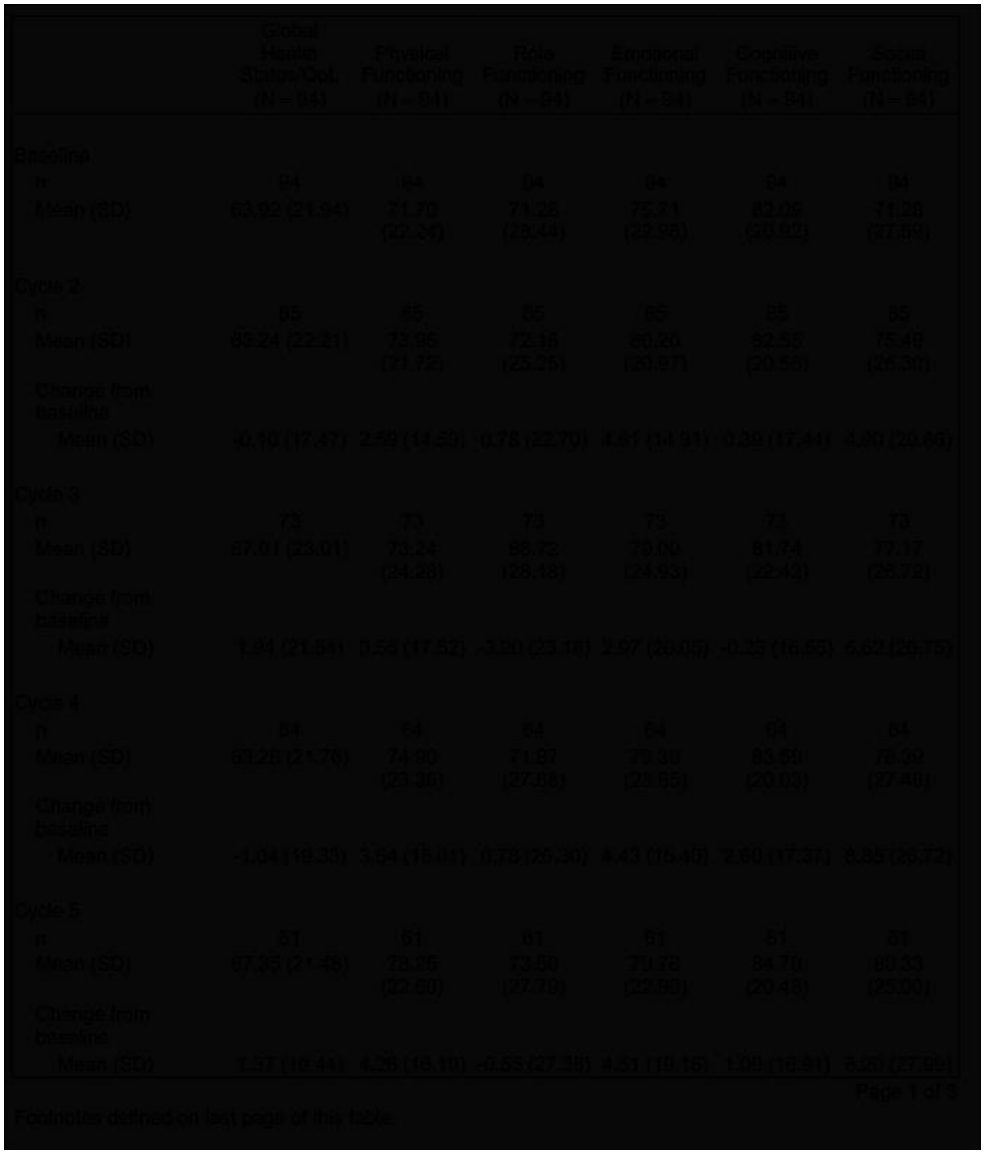
Results of CodeBreak 100 (NCT03600883) (73)											
						Estimated absolute difference in effect	Estimated relative difference in effect		Description of methods used for estimation	References	
Outcome	**Study arm**	**N**	**Result**	**Difference**	**95% CI**	***P* value**	**Difference**	**95% CI**	***P* value**		
Median PFS (CL95%)	Sotorasib	126	6.8 months (5.1-8.2)*	NA	NA	NA	NA	NA	NA	*At the data cut-off in March 2021. The median PFS is based on the Kaplan –Meier estimator.	Skoulidis et al. 2021(73)
Median OS (CL95%)	Sotorasib	126	12.5 months (10.0-NE)*	NA	NA	NA	NA	NA	NA	*At the data cut-off in March 2021. The median OS is based on the Kaplan –Meier estimator using RECIST v.1.1.	Skoulidis et al. 2021(73)

Results of CodeBreak 100 (NCT03600883) (73)											
AEs grade 3+ N (%)	Sotorasib	126	77 (61)*	NA	NA	NA	NA	NA	NA	*At the data cut-off in March 2021	Skoulidis et al. 2021(73)
Serious adverse events N (%)	Sotorasib	126	69 (54.8)*	NA	NA	NA	NA	NA	NA	*At the data cut-off in March 2021	Skoulidis et al. 2021(73)
TRAE (grade 3+)	Sotorasib	126	26(20.6)	NA	NA	NA	NA	NA	NA	*At the data cut-off in March 2021	Skoulidis et al. 2021(73)
Treatment discontinuation due to adverse events N(%)	Sotorasib	126	11 (8.7)*	NA	NA	NA	NA	NA	NA	*At the data cut-off in March 2021	Data on file(75)
Treatment discontinuations due to TRAE N (%)	Sotorasib	126	9 (7.1)*	NA	NA	NA	NA	NA	NA	*At the data cut-off in March 2021	Skoulidis et al. 2021(73)



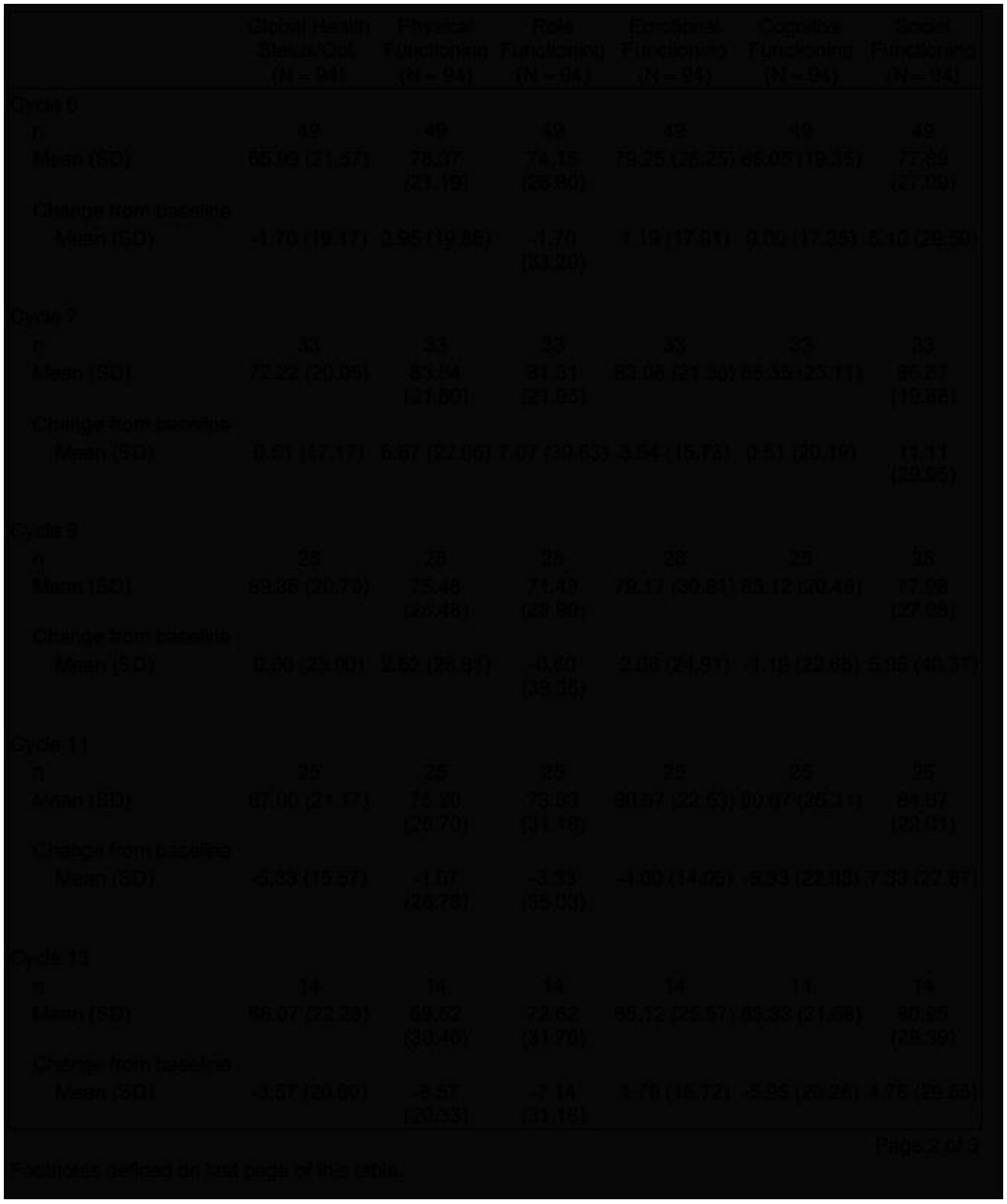


Medicinrådet Dampfærgevej 27-29, 3. th. DK-2100 København Ø +45 70 10 36 00 medicinraadet@medicinraadet.dk www.medicinraadet.dk



	Global Health Status/QoL (N = 84)	Physical Functioning (N = 84)	Role Functioning (N = 84)	Emotional Functioning (N = 84)	Cognitive Functioning (N = 84)	Social Functioning (N = 84)
Baseline						
n	84	84	84	84	84	84
Mean (SD)	63.92 (21.64)	71.75 (22.34)	71.25 (28.44)	75.71 (22.95)	82.06 (20.92)	71.28 (27.89)
Cycle 2						
n	85	85	85	85	85	85
Mean (SD)	63.24 (22.21)	73.05 (21.72)	72.16 (25.25)	80.20 (20.87)	82.35 (20.56)	75.49 (26.37)
Change from baseline						
Mean (SD)	-0.10 (17.47)	2.59 (14.50)	0.78 (22.70)	4.61 (14.91)	0.29 (17.44)	4.20 (20.60)
Cycle 3						
n	73	73	73	73	73	73
Mean (SD)	67.01 (23.01)	73.22 (24.28)	68.72 (28.18)	79.00 (24.93)	81.74 (22.43)	77.17 (25.73)
Change from baseline						
Mean (SD)	1.91 (21.31)	0.56 (17.52)	-3.20 (23.16)	2.97 (20.09)	-0.23 (16.63)	6.82 (20.76)
Cycle 4						
n	84	84	84	84	84	84
Mean (SD)	63.28 (21.76)	74.90 (23.89)	71.67 (27.68)	79.38 (23.85)	83.59 (20.03)	78.39 (27.48)
Change from baseline						
Mean (SD)	-1.04 (19.38)	3.64 (15.81)	0.78 (26.30)	4.43 (15.46)	2.60 (17.37)	8.85 (26.72)
Cycle 5						
n	81	81	81	81	81	81
Mean (SD)	67.35 (21.46)	78.15 (22.00)	73.50 (27.70)	79.78 (23.80)	84.70 (20.43)	80.53 (25.09)
Change from baseline						
Mean (SD)	1.97 (19.41)	4.26 (16.19)	-0.65 (27.38)	4.51 (19.16)	1.09 (16.91)	8.20 (27.66)

Footnotes defined on last page of this table.



	Global Health Status/QoL (N = 94)	Physical Functioning (N = 94)	Role Functioning (N = 94)	Emotional Functioning (N = 94)	Cognitive Functioning (N = 94)	Social Functioning (N = 94)
Cycle 6						
n	49	49	49	49	49	49
Mean (SD)	65.99 (21.97)	78.37 (21.16)	74.15 (25.60)	79.25 (18.25)	68.05 (19.35)	77.89 (27.09)
Change from baseline						
Mean (SD)	-1.70 (19.17)	3.95 (19.86)	-1.70 (33.20)	1.18 (17.01)	0.10 (17.35)	5.10 (28.59)
Cycle 7						
n	33	33	33	33	33	33
Mean (SD)	72.22 (20.06)	85.84 (21.80)	81.31 (21.95)	83.08 (21.30)	65.35 (25.11)	86.87 (19.06)
Change from baseline						
Mean (SD)	0.51 (17.17)	6.67 (22.08)	7.07 (30.63)	3.54 (16.73)	0.51 (20.19)	11.11 (29.95)
Cycle 9						
n	28	28	28	28	28	28
Mean (SD)	69.35 (20.79)	75.48 (26.48)	71.43 (29.90)	78.17 (20.61)	65.12 (20.46)	77.08 (27.08)
Change from baseline						
Mean (SD)	0.00 (23.00)	2.62 (28.81)	-0.60 (38.06)	2.08 (24.91)	-1.19 (22.85)	5.95 (40.37)
Cycle 11						
n	25	25	25	25	25	25
Mean (SD)	67.00 (21.17)	76.20 (28.70)	78.00 (31.16)	80.67 (22.63)	60.67 (26.31)	84.67 (22.01)
Change from baseline						
Mean (SD)	-6.33 (15.57)	-1.07 (26.76)	-3.33 (35.03)	-4.00 (14.05)	-6.33 (22.98)	7.33 (27.87)
Cycle 13						
n	14	14	14	14	14	14
Mean (SD)	66.07 (23.23)	69.52 (30.46)	72.62 (31.70)	85.12 (25.57)	63.33 (21.68)	80.95 (28.39)
Change from baseline						
Mean (SD)	-3.57 (20.66)	-6.67 (30.33)	-7.14 (31.12)	1.79 (16.72)	-6.95 (29.26)	4.76 (25.53)

Page 2 of 3

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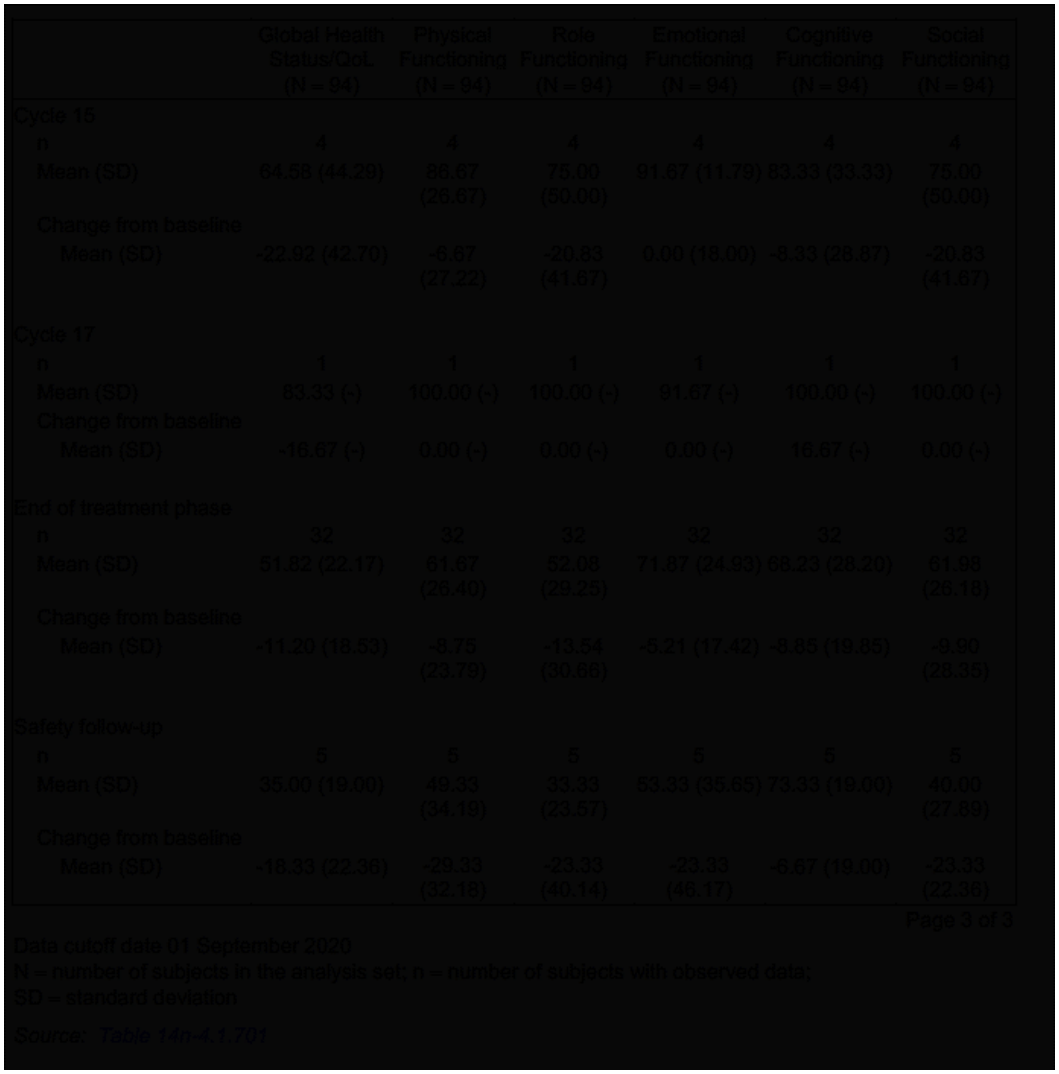

	Global Health Status/QoL (N = 94)	Physical Functioning (N = 94)	Role Functioning (N = 94)	Emotional Functioning (N = 94)	Cognitive Functioning (N = 94)	Social Functioning (N = 94)
Cycle 15						
n	4	4	4	4	4	4
Mean (SD)	64.58 (44.29)	66.67 (26.67)	75.00 (50.00)	91.67 (11.79)	83.33 (33.33)	75.00 (50.00)
Change from baseline						
Mean (SD)	-22.92 (42.70)	-6.67 (27.22)	-20.83 (41.67)	0.00 (18.00)	-8.33 (28.87)	-20.83 (41.67)
Cycle 17						
n	1	1	1	1	1	1
Mean (SD)	83.33 (-)	100.00 (-)	100.00 (-)	91.67 (-)	100.00 (-)	100.00 (-)
Change from baseline						
Mean (SD)	-16.67 (-)	0.00 (-)	0.00 (-)	0.00 (-)	16.67 (-)	0.00 (-)
End of treatment phase						
n	32	32	32	32	32	32
Mean (SD)	61.82 (22.17)	61.67 (26.40)	52.08 (29.25)	71.87 (24.93)	68.23 (28.20)	61.98 (26.18)
Change from baseline						
Mean (SD)	-11.20 (18.53)	-8.75 (23.79)	-13.54 (30.66)	-6.21 (17.42)	-8.85 (19.85)	-9.90 (28.35)
Safety follow-up						
n	5	5	5	5	5	5
Mean (SD)	35.00 (19.00)	49.33 (34.19)	33.33 (23.57)	63.33 (35.65)	73.33 (19.00)	40.00 (27.89)
Change from baseline						
Mean (SD)	-18.33 (22.36)	-29.33 (32.18)	-23.33 (40.14)	-23.33 (46.17)	-6.67 (19.00)	-23.33 (22.36)

Page 3 of 3

Data cutoff date 01 September 2020
N = number of subjects in the analysis set; n = number of subjects with observed data;
SD = standard deviation

Source: Table 14n-4.1.701

Data cut-off date 01 September 2020
N = number of subjects in the analysis set; n = number of subjects with observed data; SD = standard deviation

Table 44. Results of SELECT-1 (NCT01933932) (72)

Results of SELECT-1 (NCT01933932)											
				Estimated absolute difference in effect			Estimated relative difference in effect			Description of methods used for estimation	References
Outcome	**Study arm**	**N**	**Result**	**Difference**	**95% CI**	***P* value**	**Difference**	**95% CI**	***P* value**		
Median PFS (CL95 %)	Selumetinib + Docetaxel	254	3.9 (1.5-5.9) months	1.1 months	NA	NA	HR: 0.93	0.77-1.12	0.44	The median PFS is based on the Kaplan–Meier estimator. The HR is based on a 2-sided 95 % CI.	Jänne et al. 2017. (72)
	Placebo + Docetaxel	256	2.8 (1.4-5.5) months								
Median OS (CL95 %)	Selumetinib + Docetaxel	254	8.7 (3.6-16.8) months	0.9 months	NA	NA	HR: 1.05	0.85-1.30	0.64	Measured at the data cut-off in June 2016. The median OS is based on a stratified log-rank test with factors for World Health Organization Performance Status.	Jänne et al. 2017. (72)
	Placebo + Docetaxel	256	7.9 (3.8-20.1) months								
Treatment discontinuations due to AEs N(%)	Selumetinib + Docetaxel	254	59 (23)	NA	NA	NA	NA	NA	NA	Measured at the data cut-off in June 2016.	Jänne et al. 2017. (72)
	Placebo + Docetaxel	256	37 (14.5%)								
AEs grade ≥3 N(%)	Selumetinib + Docetaxel	254	169 (67)*	NA	NA	NA	NA	NA	NA	Measured at the data cut-off in June 2016.	Jänne et al. 2017. (72)

Results of SELECT-1 (NCT01933932)

	Placebo + Docetaxel	256	115 (45)								
Serious adverse events N(%)	Selumetinib + Docetaxel	254	124 (39)*	NA	NA	NA	NA	NA	NA	Measured at the data cut-off in June 2016.	Jänne et al. 2017. (72)
	Placebo + Docetaxel	256	82 (32)								
EORTC QLQ-C30	Selumetinib + Docetaxel	NA	NA	NA	NA	NA	NA	NA	NA		
EORTC QLQ-C30	Placebo + Docetaxel	NA	NA	NA	NA	NA	NA	NA	NA		

T
0193
3932

ABSI: average symptom burden index.

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

Table 45. Treatment related adverse events

Treatment related adverse events	Sotorasib (CodeBreak-100)* n=126		Docetaxel + placebo (SELECT-1)** n=254	
	Any grade	Grade 3+	Any Grade	Grade 3+
Any TRAE	88 (69.8%)	26 (20.6%)	NR	76 (30.0%)
Diarrhea	40 (31.7)	5 (4.0)	64 (25)	6 (2)
Nausea	24 (19.0)	0	29 (11)	0
Alanine aminotransferase increase	19 (15.1)	8 (6.3)	NA	NA
Aspartate aminotransferase increase	19 (15.1)	7 (5.6)	NA	NA
Fatigue	14 (11.1)	0	43 (17)	4 (2)
Vomiting	10 (7.9)	0	17 (7)	1 (1)
Blood alkaline phosphatase increase	9 (7.1)	1 (0.8)	NA	NA
Maculopapular rash	7 (5.6)	0	NA	NA
Hypokalemia	5 (4.0)	1 (0.8)	NA	NA
Drug-induced liver injury	3 (2.4)	2 (1.6)	NA	NA
γ-Glutamyltransferase increase	3 (2.4)	3 (2.4)	NA	NA
Lymphocyte count decrease	3 (2.4)	1 (0.8)	NA	NA
Dyspnea	2 (1.6)	1 (0.8)	4 (2)	0
Pneumonitis	2 (1.6)	2 (1.6)	NA	NA
Abnormal hepatic function	2 (1.6)	1 (0.8)	NA	NA
Lymphopenia	1 (0.8)	1 (0.8)	NA	NA
Neutropenia	1 (0.8)	1 (0.8)	8 (3)	4 (2)
Hepatotoxic event	1 (0.8)	1 (0.8)	NA	NA
Drug hypersensitivity	1 (0.8)	1 (0.8)	NA	NA
Cellulitis	1 (0.8)	1 (0.8)	NA	NA
Lipase increased	1 (0.8)	1 (0.8)	NA	NA
Increase in liver-function level	1 (0.8)	1 (0.8)	NA	NA

Neutrophil count decrease	1 (0.8)	1 (0.8)	NA	NA
Abnormal aminotransferase level	1 (0.8)	1 (0.8)	NA	NA

*Treatment-related adverse events (TRAEs), Adverse events were graded with the use of the Common Terminology Criteria for Adverse Events version 5.0, Median duration of treatment: 5.5 months (range: 0.2-17.8 months) (73)
**Adverse events causal to treatment reported during randomized treatment patients, Adverse events were graded with the use of the Common Toxicity Criteria for Adverse Events, Median duration of treatment: 2.4 months (range: 0.1-27.4 months) (72)

Table 46 Serious adverse events

Serious adverse event	Sotorasib (CodeBreak-100)* n=126 (%)	Docetaxel + placebo (SELECT-1)** n=254 (%)
Total affected	**69 (54.8)**	**82 (32.3)**
Infections and infestations	16 (12.7)	35 (13.8)
Respiratory, thoracic and mediastinal disorders	19 (15.1)	18 (7.1)
Gastrointestinal disorders	12 (9.5)	15 (5.9)
General disorders	6 (4.8)	14 (5.5)
Blood and lymphatic system disorders	1 (0.8)	8 (3.1)
Metabolism and nutrition disorders	5 (4.0)	5 (2.0)
Cardiac disorders	5 (4.0)	4 (1.6)
Injury, poisoning and procedural complications	5 (4.0)	4 (1.6)
Musculoskeletal and connective tissue disorders	7 (5.6)	4 (1.6)
Immune system disorders	2 (1.6)	3 (1.2)
Nervous system disorders	3 (2.4)	3 (1.2)
Neoplasms benign, malignant and unspec.	5 (4.0)	2 (0.8)
Psychiatric disorders	0 (0)	2 (0.8)
Renal and urinary disorders	0 (0)	1 (0.4)
Vascular disorders	4 (3.2)	1 (0.4)

Footnote: Serious adverse events as reported on https://clinicaltrials.gov/ct2/show/results/NCT01933932 by system organ class compared with corresponding serious adverse events by organ class from Codebreak-100.

Table 47 All-cause adverse events

Treatment related adverse events	Sotorasib (CodeBreak-100)* n=126 (%)		Docetaxel + placebo (SELECT-1)** n=254 (%)	
	Any grade	Grade 3+	Any Grade	Grade 3+
Any AE	**125 (99.2)**	**77 (61.1)**	**235 (92.5)**	**115 (45)**
Diarrhoea	64 (50.8)	7 (5.6)	89 (35.0)	7 (2.8)
Nausea	39 (31.0)	1 (0.8)	62 (24.4)	0 (0)
Fatigue	32 (25.4)	3 (2.4)	79 (31.1)	10 (3.9)
Arthralgia	27 (21.4)	3 (2.4)	20 (7.9)	NA
Aspartate aminotransferase increased	27 (21.4)	9 (7.1)	3 (1.2)	NA
Alanine aminotransferase increased	26 (20.6)	9 (7.1)	5 (2.0)	NA
Constipation	24 (19.0)	1 (0.8)	48 (18.9)	1 (0.4)
Dyspnoea	24 (19.0)	8 (6.3)	44 (17.3)	1 (0.4)
Vomiting	23 (18.3)	1 (0.8)	32 (12.6)	1 (0.4)
Back pain	21 (16.7)	5 (4.0)	31 (12.2)	NA
Cough	19 (15.1)	4 (3.2)	35 (13.8)	0 (0)
Anaemia	18 (14.3)	3 (2.4)	41 (16.1)	11 (4.3)
Oedema peripheral	18 (14.3)	0 (0)	39 (15.4)	0 (0)
Blood alkaline phosphatase increased	17 (13.5)	6 (4.8)	4 (1.6)	NA
Decreased appetite	16 (12.7)	1 (0.8)	60 (23.6)	4 (1.6)
Pleural effusion	13 (10.3)	9 (7.1)	12 (4.7)	NA
Pneumonia	13 (10.3)	9 (7.1)	15 (5.9)	NA
Productive cough	13 (10.3)	0 (0)	10 (3.9)	NA
Stomatitis	1 (0.8)	0 (0)	34 (13.4)	1 (0.4)
Asthenia	8 (6.3)	2 (1.6)	48 (18.9)	7 (2.8)
Pyrexia	12 (9.5)	0 (0)	36 (14.2)	2 (0.8)
Alopecia	2 (1.6)	0 (0)	64 (25.2)	0 (0)

Rash	8 (6.3)	0 (0)	28 (11.0)	1 (0.4)
Headache	11 (8.7)	0 (0)	26 (10.2)	NA
Myalgi	8 (6.3)	0 (0)	37 (14.6)	NA

Footnote: All-cause adverse events in >10% of patients from Codebreak-100 compared with all-cause adverse events from SELECT-1

Table 48. Summary table of TRAE and all cause adverse event data from CodeBreak 100 published 15 March 2021 data cut (75)

Table 14n-6.1.1. Summary of Treatment-emergent Adverse Events (Phase 2 NSCLC in Safety Analysis Set)

	Phase 2 NSCLC 960 mg QD Fasted (N = 126) n (%)
All treatment-emergent adverse events	125 (99.2)
Grade ≥ 2	112 (88.9)
Grade ≥ 3	77 (61.1)
Grade ≥ 4	24 (19.0)
Serious adverse events	69 (54.8)
Leading to discontinuation of AMG 510	11 (8.7)
Serious	7 (5.6)
Non-serious	5 (4.0)
Fatal adverse events	20 (15.9)
Treatment-related treatment-emergent adverse events	88 (69.8)
Grade ≥ 2	50 (39.7)
Grade ≥ 3	26 (20.6)
Grade ≥ 4	1 (0.8)
Serious adverse events	11 (8.7)
Leading to discontinuation of AMG 510	9 (7.1)
Serious	4 (3.2)
Non-serious	5 (4.0)
Fatal adverse events	0 (0.0)

Page 1 of 1

Snapshot date 01APR2021. Phase 2 data cut-off date 15MAR2021.
N = Number of subjects in the analysis set, n = Number of subjects with observed data.

Table 49 All cause adverse events from Codebreak 100 15march 2021 data cut (75)

Table 14n-6.2.1. Treatment-emergent Adverse Events by Preferred Term (Phase 2 NSCLC in Safety Analysis Set)

Preferred Term	Phase 2 NSCLC 960 mg QD Fasted (N = 126) n (%)
Number of subjects reporting treatment-emergent adverse events	125 (99.2)
Diarrhoea	64 (50.8)
Nausea	39 (31.0)
Fatigue	32 (25.4)
Arthralgia	27 (21.4)
Aspartate aminotransferase increased	27 (21.4)
Alanine aminotransferase increased	26 (20.6)
Constipation	24 (19.0)
Dyspnoea	24 (19.0)
Vomiting	23 (18.3)
Back pain	21 (16.7)
Cough	19 (15.1)
Anaemia	18 (14.3)
Oedema peripheral	18 (14.3)
Blood alkaline phosphatase increased	17 (13.5)
Decreased appetite	16 (12.7)
Pleural effusion	13 (10.3)
Pneumonia	13 (10.3)
Productive cough	13 (10.3)
Pruritus	12 (9.5)
Pyrexia	12 (9.5)
Abdominal pain	11 (8.7)
Fall	11 (8.7)
Headache	11 (8.7)
Hypokalaemia	11 (8.7)
Hypertension	10 (7.9)
Rash maculo-papular	10 (7.9)
Hyponatraemia	9 (7.1)
Insomnia	9 (7.1)
Pain	9 (7.1)
Pain in extremity	9 (7.1)
Upper respiratory tract infection	9 (7.1)
Urinary tract infection	9 (7.1)

Page 1 of 11

Snapshot date 01APR2021. Phase 2 data cut-off date 15MAR2021.
N = Number of subjects in the analysis set. n = Number of subjects with observed data.
Coded using MedDRA version 23.1.
Rows are sorted by preferred term in descending order of frequency in the NSCLC column.

Table 50 All cause adverse events from Codebreak 100 15march 2021 data cut (75)

Table 14n-6.2.1. Treatment-emergent Adverse Events by Preferred Term (Phase 2 NSCLC in Safety Analysis Set)

Preferred Term	Phase 2 NSCLC 960 mg QD Fasted (N = 126) n (%)
Weight decreased	9 (7.1)
Abdominal pain upper	8 (6.3)
Anxiety	8 (6.3)
Asthenia	8 (6.3)
Dry skin	8 (6.3)
Hypomagnesaemia	8 (6.3)
Myalgia	8 (6.3)
Non-small cell lung cancer	8 (6.3)
Rash	8 (6.3)
Dehydration	7 (5.6)
Lymphocyte count decreased	7 (5.6)
Oropharyngeal pain	7 (5.6)
Rhinorrhoea	7 (5.6)
Haemorrhoids	6 (4.8)
Neck pain	6 (4.8)
Abdominal distension	5 (4.0)
Chills	5 (4.0)
Dizziness	5 (4.0)
Gamma-glutamyltransferase increased	5 (4.0)
Hypotension	5 (4.0)
Muscle spasms	5 (4.0)
Rhinitis allergic	5 (4.0)
Blood cholesterol increased	4 (3.2)
Blood creatinine increased	4 (3.2)
Chronic obstructive pulmonary disease	4 (3.2)
Depression	4 (3.2)
Drug-induced liver injury	4 (3.2)
Dyspepsia	4 (3.2)
Dysphonia	4 (3.2)
Flatulence	4 (3.2)
Hypoalbuminaemia	4 (3.2)
Hypocalcaemia	4 (3.2)
Nasal congestion	4 (3.2)
Oral candidiasis	4 (3.2)

Page 2 of 11

Snapshot date 01APR2021. Phase 2 data cut-off date 15MAR2021.
N = Number of subjects in the analysis set. n = Number of subjects with observed data.
Coded using MedDRA version 23.1.
Rows are sorted by preferred term in descending order of frequency in the NSCLC column.

Table 51. All cause adverse event data from SELECT-1, published May 9, 2017 (72)

Table 2. Most Frequently Reported Adverse Events (All Causality) Among Patients With Advanced *KRAS*-Mutant Non-Small Cell Lung Cancer Receiving Selumetinib Plus Docetaxel vs Placebo Plus Docetaxel[a]

Preferred Term, Participants With an Event[b]	Selumetinib + Docetaxel, No. (%) (n = 251)		Placebo + Docetaxel, No. (%) (n = 254)	
	All Grades	CTCAE Grade ≥3	All Grades	CTCAE Grade ≥3
Diarrhea	154 (61)	18 (7)	89 (35)	7 (3)
Nausea	94 (38)	3 (1)	62 (24)	1 (1)
Rash	85 (34)	9 (4)	28 (11)	1 (1)
Edema peripheral	76 (30)	6 (2)	39 (15)	0
Fatigue	70 (28)	9 (4)	79 (31)	10 (4)
Asthenia	67 (27)	22 (9)	47 (19)	7 (3)
Vomiting	67 (27)	7 (3)	32 (13)	1 (1)
Stomatitis	65 (26)	9 (4)	34 (13)	1 (1)
Dyspnea	61 (24)	20 (8)	44 (17)	6 (2)
Decreased appetite	56 (22)	5 (2)	60 (24)	4 (2)
Pyrexia	50 (20)	4 (2)	34 (13)	2 (1)
Alopecia	49 (20)	2 (1)	64 (25)	0
Anemia	49 (20)	12 (5)	41 (16)	11 (4)
Constipation	41 (16)	0	48 (19)	1 (1)
Cough	37 (15)	0	35 (14)	0
Dermatitis acneiform	30 (12)	4 (2)	2 (1)	0
Dry skin	30 (12)	0	14 (6)	0
Neutropenia	26 (10)	18 (7)	15 (6)	10 (4)
Abdominal pain	25 (10)	3 (1)	21 (8)	1 (1)

Abbreviation: CTCAE, Common Toxicity Criteria for Adverse Events (score range: 1 [mild] to 5 [death]).

[a] Population: safety analysis set.

[b] All-causality adverse events reported during randomized treatment in 10% or more of patients in either treatment group, by frequency in the selumetinib + docetaxel group.

Table 52 Treatment related adverse events from SELECT-1

eTable 1. Most Frequently Reported Adverse Events Causally Related to selumetinib/placebo

Preferred term, No. (%) participants with an event	Selumetinib + docetaxel n=251		Placebo + docetaxel n=254	
	All grades	CTCAE grade ≥3	All grades	CTCAE grade ≥3
Diarrhea	125 (50)	16 (6)	64 (25)	6 (2)
Rash	79 (32)	8 (3)	23 (9)	1 (1)
Nausea	53 (21)	3 (1)	29 (11)	0
Fatigue	47 (19)	4 (2)	43 (17)	4 (2)
Stomatitis	46 (18)	7 (3)	20 (8)	0
Edema peripheral	43 (17)	3 (1)	13 (5)	0
Vomiting	41 (16)	6 (2)	17 (7)	1 (1)
Asthenia	33 (13)	12 (5)	24 (9)	2 (1)
Decreased appetite	32 (13)	3 (1)	28 (11)	2 (1)
Dermatitis acneiform	29 (12)	4 (2)	1 (1)	0
Dry skin	24 (10)	0	12 (5)	0
Neutropenia	18 (7)	14 (6)	8 (3)	4 (2)
Anemia	17 (7)	2 (1)	8 (3)	0
Dyspnea	13 (5)	4 (2)	4 (2)	0
Face edema	16 (6)	0	3 (1)	0

Population: safety analysis set, data cut-off 7 June 2016
Adverse events causally related to selumetinib/placebo reported during randomized treatment in ≥5% of patients in either treatment group, by frequency in selumetinib + docetaxel group.
CTCAE, Common Toxicity Criteria for Adverse events; No., number of participants

Appendix F - Comparative analysis of efficacy and safety

[redacted]

Table 53 Naive comparison of safety data grade 3+ and discontinuation due to AE's comparing sotorasib to docetaxel

Outcome	Studies included in the analysis	Absolute difference in effect			Relative difference in effect			Method used for quantitative synthesis	Result used in the health economic analysis?
		Difference	CI	*P* value	Difference	CI	*P* value		
Grade 3+ adverse events	CodeBreak 100 & SELECT-1	16% (61%-45%)	NA	NA	35.5% ((61%-45%))/45%)	NA	NA	Naïve comparison	*no*
Discontinuation Due to AE's	CodeBreak 100 & SELECT-1	-5.8% (8.7%-14.5%)	NA	NA	40% ((14.5%-8,7%)/14.5%)	NA	NA	Naïve comparison	*no*

Appendix G - Extrapolation

Please consult section 8.3 for information on extrapolations of time-to-event data.

[redacted]

[redacted] *generated using muhaz package for ITT population (N =126)

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[redacted]

*generated using muhaz package for ITT population (N =123)

Appendix H - Literature search for HRQoL data

Not applicable, no literature search for HRQoL data has been conducted.

Appendix I - Mapping of HRQoL data

Not applicable, no mapping of HRQoL data has been conducted.

Appendix J - Probabilistic sensitivity analyses

Please find all data/assumptions that form the basis for the probabilistic sensitivity analysis in Table 54. All values are varied in the 'Model parameters'-sheet within the CEA model.

Table 54. List of model parameters and parameter values included in the base-case and sensitivity analysis

[redacted]	[redacted]	[redacted]	[redacted] x	[redacted] x	[redacted]	[redacted]
[redacted]						
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
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Appendix K - MAIC

12.1.1 Data sources and feasibility assessment for indirect comparisons

12.1.1.1 Data sources

The exact method to provide comparative effectiveness data for sotorasib versus the primary and secondary comparator is determined by the availability of data for the comparators in the population of interest.

Outcomes data for patients specifically with *KRAS G12C-mutated* NSCLC are limited. The systematic literature reviews described in Appendix A sought to identify clinical trials of therapies conducted in patients with *KRAS*-mutant NSCLC, and identified only one RCT (SELECT-1) that provided sufficient PFS and OS data for docetaxel monotherapy (the primary comparator) in a population of patients with *KRAS*-mutated NSCLC (including *G12C* and non-*G12C* mutations) (127).

Several published observational studies in Western (European, Australian and US) populations show that survival in patients with *KRAS G12C*-mutated NSCLC is similarly poor as that in patients with other *KRAS* mutations or wild type disease who are not eligible for existing targeted therapies (72, 128, 129). The SELECT-1 trial itself showed that survival outcomes were highly consistent for those with *KRAS G12C-mutated* and those with other *KRAS*-mutated NSCLC (129). On this basis, the PFS and OS data for docetaxel from the SELECT-1 trial in patients with *KRAS*-mutant NSCLC (including *G12C* and non-*G12C* mutations) is considered to be sufficiently reflective of PFS and OS in patients with *KRAS G12C*-mutated NSCLC who receive placebo plus docetaxel. The SELECT-1 trial was therefore considered to be a candidate to provide comparator data for the primary comparison of sotorasib vs. placebo plus docetaxel. This approach was agreed as reasonable by the five UK clinical experts attending an Amgen advisory board meeting in February 2021 for the NICE submission (130).

12.1.1.2 Compatibility of data sources

Having determined the most appropriate candidate data sources and their ability to reflect the populations and comparators of interest it was necessary to further determine the compatibility of these and the sotorasib CodeBreak 100 trial to determine the feasibility of conducting the indirect treatment comparisons. As the comparison is of sotorasib vs. placebo plus docetaxel, for which the primary comparator data source is the SELECT-1 trial, the assessment of compatibility below relates to the compatibility of CodeBreak 100 vs. SELECT-1.

Study designs and eligibility criteria of CodeBreak 100 and SELECT-1

An overview of the study designs and eligibility criteria of CodeBreak 100 and SELECT-1 is provided in Table 55.

Table 55. Overview of study designs of CodeBreak 100 and SELECT-1

Study characteristics	Sotorasib (CodeBreak 100) (87)	Placebo plus docetaxel (SELECT-1) (72)
Blinding	Open label	Double-blinded
Inclusion criteria	Male or female patients (≥ 18 years) Histologically confirmed locally advanced or metastatic NSCLC *KRAS p.G12C* mutation identified through molecular testing ECOG Performance Status 0 – 1	Male or female patients (≥ 18 years) Histologically confirmed locally advanced or metastatic NSCLC KRAS-mutation identified through molecular testing WHO Performance Status 0 – 1

	≥ 1 prior line of systemic anticancer therapy	1 prior line of systemic anticancer therapy
Key exclusion criteria	Active brain metastases Anti-tumor therapy including chemotherapy, antibody therapy, molecular targeted therapy, retinoid therapy within 28 days of study day 1	Active brain metastases Received >1 prior anti-cancer drug regimen for advanced or metastatic NSCLC Prior treatment with a MEK inhibitor or any docetaxel-containing regimen (prior treatment with paclitaxel is acceptable)
Primary endpoint	Centrally-assessed ORR	Investigator-assessed PFS
Key secondary endpoints	Centrally-assessed PFS; Investigator-assessed PFS; OS	OS

Key: ECOG, Eastern cooperative oncology group; KRAS, MEK, mitogen activated protein kinase; NSCLC, non-small cell lung cancer; ORR, objective response rate; OS, overall survival; PFS, progression-free survival; VEGFR, vascular endothelial growth factor receptor; WHO, World Health Organization

CodeBreak 100 and SELECT-1 were both multicentre studies that recruited patients with confirmed locally advanced or metastatic NSCLC (Stage IIIB – IV) who had failed prior therapy. CodeBreak 100 specifically enrolled patients with *KRAS G12C* mutations, whereas SELECT-1 enrolled patients with KRAS mutations at codon 12, 13 or 61 (131). CodeBreak 100 enrolled patients with 1 to 3 prior therapies, whereas SELECT-1 included patients with 1 prior therapy. Both studies excluded subjects with active brain metastases although both permitted inclusion of stable brain metastases.

The two studies reported PFS and OS as primary or secondary endpoints. PFS was assessed by investigators in SELECT-1, by both independent central review and by investigator in CodeBreak 100.

Patient profiles in CodeBreak 100 and SELECT-1

A comparison of patient profiles in the CodeBreak 100 and SELECT-1 trials is presented in Table 56. The distribution of patients between the two trials is similar in terms of age, disease stage and histology, and the majority of patients had ECOG/WHO performance status of 1.

Key characteristics for which there are differences between the trials arise from the different time points at which the trials were conducted. In addition to differences in KRAS mutation status, CodeBreak 100 included patients taking 1-3 prior therapies and a high proportion of patients had prior use of PD(L)-1 inhibitors, reflecting the current treatment pathway for patients with *KRAS G12C* -mutated NSCLC in Denmark. In contrast, the SELECT-1 trial were conducted before the evidence base supported front-line use of immunotherapy, included patients taking 1 prior therapy only and no PD(L)-1 inhibitors.

Table 56. Comparison of baseline characteristics in CodeBreak 100 and SELECT-1

Baseline characteristics [a]	**Sotorasib (CodeBreak 100) n=126(87)**	**Placebo plus docetaxel (SELECT-1) (n=256) (130)**
Age	62.9 (mean)	60.9 (mean)

Gender (% female)	50%	43%
Brain metastases (%)	21%	NR[c]
Performance status (ECOG or WHO; % PS 1 [vs PS 0])	70%	59%
Race (% white)	82%[d]	95%
% *KRAS G12C*-mutated	100%	42%[b]
Anti-PD-(L)1 in prior line(s)	91%	0%
Number of prior lines (% with 1/2/3 prior lines)	43%/35%/22%	100%/0%/0%
Metastatic disease at baseline	96%	96%
Histology (% Non-squamous)	99%	95%
Smoking status (% ever smoker)	93%[e]	92%
Other targetable mutations (EGFR, ALK, BRAF, ROS-1)	3%	NR[f]
PD-L1 expression at baseline (<5% [vs ≥5%])	48%	58%

Key: ECOG, European Co-operative Oncology Group; NR, not reported
Note:
[a] all reported baseline characteristics in SELECT-1 and other key characteristics
[b] the rest of the population has KRAS mutations other than G12C
[c] not reported for SELECT-1. All studies had exclusion criteria for active brain metastases
[d] 15 percentage points of the 18% remaining correspond to Asian patients
[e] 2 percentage points of the remaining 7% are missing data
[f] probably very low due to KRAS mutant

12.1.1.3 Conclusions on the feasibility of undertaking indirect comparisons

Despite some differences between CodeBreak 100 and SELECT-1, UK clinical experts considered these were the best and most relevant sources of data available with which to make indirect comparisons for sotorasib in patients with *KRAS G12C-mutated* NSCLC in the NICE submission. The data are considered adequate to reflect PFS and OS outcomes with sotorasib and placebo plus docetaxel following prior therapy in this population of patients.

A propensity score weighted analysis approach such as MAIC requires the matching of prognostic patient characteristics to generate robust comparative treatment effect estimates. Due to missing data or other differences between the trials it would not be possible to match across all trials for *KRAS G12C* mutation status, brain metastases, prior lines of therapy or prior use of PD-L1 inhibitors. Given that PFS and OS outcomes are similar in the absence of targeted therapies, irrespective of *KRAS* status, the inability to match by specific KRAS status is unlikely to lead to biased estimates. Patients with brain metastases were excluded from SELECT-1 trial whereas CodeBreak 100 permitted enrolment of non-active brain metastases; however, as brain metastases are an important prognostic characteristic, the inclusion of patients with brain metastases in the CodeBreak 100 trial but not in the SELECT-1 trial may lead to conservative estimates of relative treatment effects for sotorasib. Although CodeBreak 100 included patients with 1-3 prior therapies, to match only patients with 1 prior therapy, as per SELECT-1 would effectively reduce the available CodeBreak 100 trial population by 57%, which would have significant implications for the precision of any relative treatment effect estimates. The inability to robustly match for number of prior lines of therapy or prior use of immunotherapy is therefore a potential limitation that arises due to limited comparator trial data specifically in KRAS-mutant NSCLC. However, PFS and OS outcomes are likely to be worse for patients with each successive line of therapy. Given that CodeBreak 100 included 57% of patients with 2 or more prior lines of therapy, a comparison of PFS and OS data from the whole of the CodeBreak 100 NSCLC population against PFS and OS data from patients in SELECT-1, who had received only one prior line of therapy, is likely to be conservative.

On balance, in the context of this rare disease with limited available comparator trial data, an indirect comparison using these data sources is feasible and appropriate. The patient population in SELECT-1 appears to be closely aligned with the CodeBreak 100 trial population. On this basis, any formal indirect comparison using propensity score weighting approaches, which requires matching of patient characteristics, a robust comparison is likely to be achieved using CodeBreak 100 and SELECT-1. The primary comparison will be as following:

- **Primary comparison of sotorasib vs. docetaxel monotherapy**:
    - Primary analysis - formal MAIC for CodeBreak 100 vs. SELECT-1

12.1.2 Estimation of weights for MAIC

12.1.2.1 Estimation of weights

To make an adjusted comparison between sotorasib and docetaxel, individual sotorasib-treated patients will be assigned statistical weights that adjust for their over- or underrepresentation relative to the average prognostic factors and treatment effect modifiers observed in the SELECT-1 trial. The following weighting and average baseline characteristics will be balanced for the sotorasib-treated patients and the docetaxel-treated patients.

Weights will be derived using an MAIC, a form of propensity score weighting (132). The propensity score logistic regression model estimates the odds of being enrolled into the CodeBreak 100 trial or the SELECT-1 trial. For this, a method of moments will be used to allow a propensity score logistic regression model to be estimated without patient-level data for the comparative evidence sources. The model will be estimated on the basis of individual patient data available for the sotorasib-treated patients and the published summary data available for the SELECT-1 trial. Following estimation of the weights, it is necessary to explore their distribution. Re-scaled weights will be explored via the use of histograms to determine whether specific patient(s) or groups of patients (based on covariate values) will be over- or underrepresented in the analysis. The use of scaled weights aids interpretation; a scaled weight of > 1 means that an individual carries more weight in the re-weighted sample than in the original sample, and a scaled weight of < 1 means that an individual carries less weight.

12.1.2.2 Calculation of rescaled weights

The rescaled weights were calculated using the following formula:

$$Rescaled\ weight_i = \frac{weight_i}{\sum_{i=1}^{n} weight_i} \times N$$

The robustness of the analyses will be also considered by approximating the effective sample size (ESS). For a weighted estimate, the ESS is the number of independent non-weighted individuals that would be required to give an estimate with the same precision as the weighted sample estimate. A small ESS, relative to the original sample size, is an indication that the weights are highly variable due to a lack of population overlap, and that the estimate may be unstable.

12.1.2.3 Calculation of effective sample size

The following formula was used to calculate the ESS:

$$ESS = \frac{\left(\sum_{i=1}^{n} weight_i\right)^2}{\sum_{i=1}^{n} weight_i^2}$$

12.1.2.4 Statistical analysis for incorporating weights

After the matching procedure was conducted and the weights were derived, PFS or OS outcomes were compared between balanced treatment groups using analyses that incorporate the derived weights. In particular, the comparator pseudo-patient-level data (or extracted response data) was combined with the weighted CodeBreak

100 data (each patient in the comparator data was assigned a weight of 1) and an HR (or OR) was estimated from a weighted Cox proportional hazards model (or a weighted logistic regression model) with a treatment covariate.

To account for the fact that weights were estimated rather than fixed and known, uncertainty in the estimation of weights was included in the calculation of uncertainty around relative treatment effects. Likewise, robust standard errors were generated using the weighted Cox models.

The HR and corresponding 95% CI for the different MAIC models are presented in section 7.2.1.4. The base-case model for use in the cost-effectiveness analyses includes the following covariates: ECOG, disease stage and smoking status. The rationale is that this model includes all variables identified as at least somewhat important in the physician insights report, with the exception of PD-L1 expression and number of prior lines of therapy. These two variables are excluded on the basis that they lead to a significant reduction in the effective sample size.

Further rationale for excluding the PD-L1 protein expression is that PD-L1 expression was indicated to be a strong predictive factor for treatments with anti-PD-(L)1 only, as detailed in the physician's insight report (76). Moreover, physicians mentioned three expression groups relevant to treatment decisions (<1%, 1-49%, >= 50%). In SELECT-1, however, aggregate data were presented for the expression groups <5% and ≥5% only; therefore, it was not possible to perform the matching based on the categories identified as relevant by the physicians.

12.1.3 Alternative scenarios for use in MAIC

Scenarios involving the alternative MAIC approaches are presented in this section. MAIC SET 2 (Section 12.1.3.1) is the scenario where all available covariates were use.

12.1.3.1 MAIC SET 2 – using all available covariates

A comparison of the unadjusted and adjusted HR for SET 2 is presented in the tabel below The MAIC adjustment improved the HR's for all endpoints. The results for SET 2 are better than Model 1 but these are more uncertain as these are based on smaller ESS. As such, SET 1 was chosen as base case.

Sot, Sotorasib, Doc, Docetaxel, CI, Confidence interval, ESS, Effective sample size, HR, Hazard ratio, PFS, Progression-free survival, OS, Overall survival.. N and ESS are for patients in CodeBreaK 100 arm only. a: Investigator, b: Central Review

Figure 13 Distribution of statistical weights of MAIC for SET 2

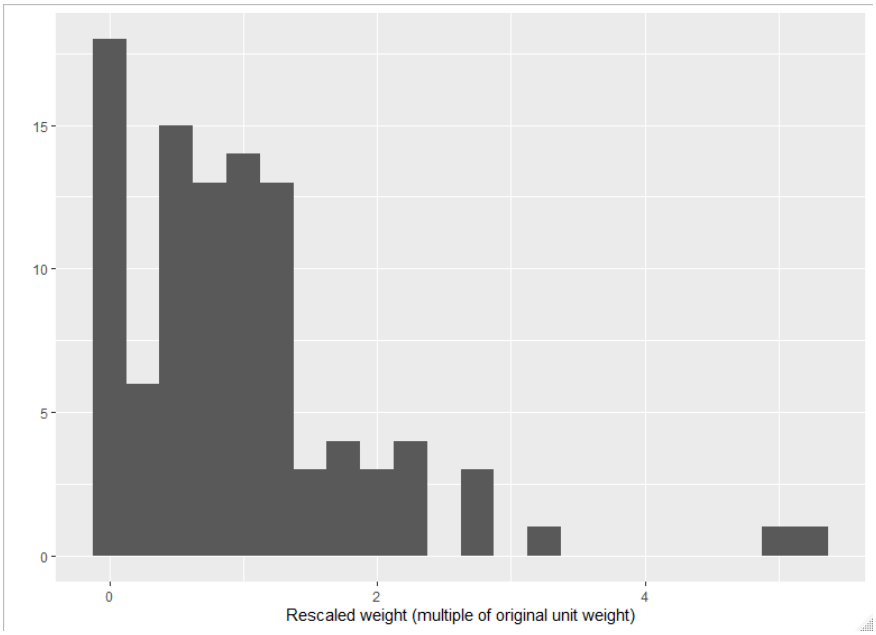


Table 57 Baseline characteristics for SET 2 can be seen in the table below below

	As reported For docetaxel N = 256	**Pre-matching** For sotorasib N = 98	**Post-matching** For sotorasib N = 98
Covariates	**SELECT-1**	**CodeBreaK 100**	**CodeBreaK 100**
ECOG (% PS 1 [vs PS 0])	[redacted]	[redacted]	[redacted]
Age (mean)	[redacted]	[redacted]	[redacted]
Metastatic at baseline (%)	[redacted]	[redacted]	[redacted]
Smoking status (% ever smoker)	[redacted]	[redacted]	[redacted]
PD-L1 expression level (<5% vs. ≥5%)	[redacted]	[redacted]	[redacted]
Gender (% female)	[redacted]	[redacted]	[redacted]
Histology (% Non-squamous)	[redacted]	[redacted]	[redacted]

Race (% white)	95	81	95

12.1.3.1.1 Overall survival

Parametric model fitting was carried out using MAIC SET 2 using all available covariates adjusted OS KM data, in accordance with the algorithm proposed by NICE DSU TSD 14. Six parametric distributions were used including exponential, Weibull, Gompertz, generalized gamma, log-normal and log-logistic. Goodness-of-fit statistics are reported for independent fitted and jointly fitted (unrestricted and restricted) models in Table 58.

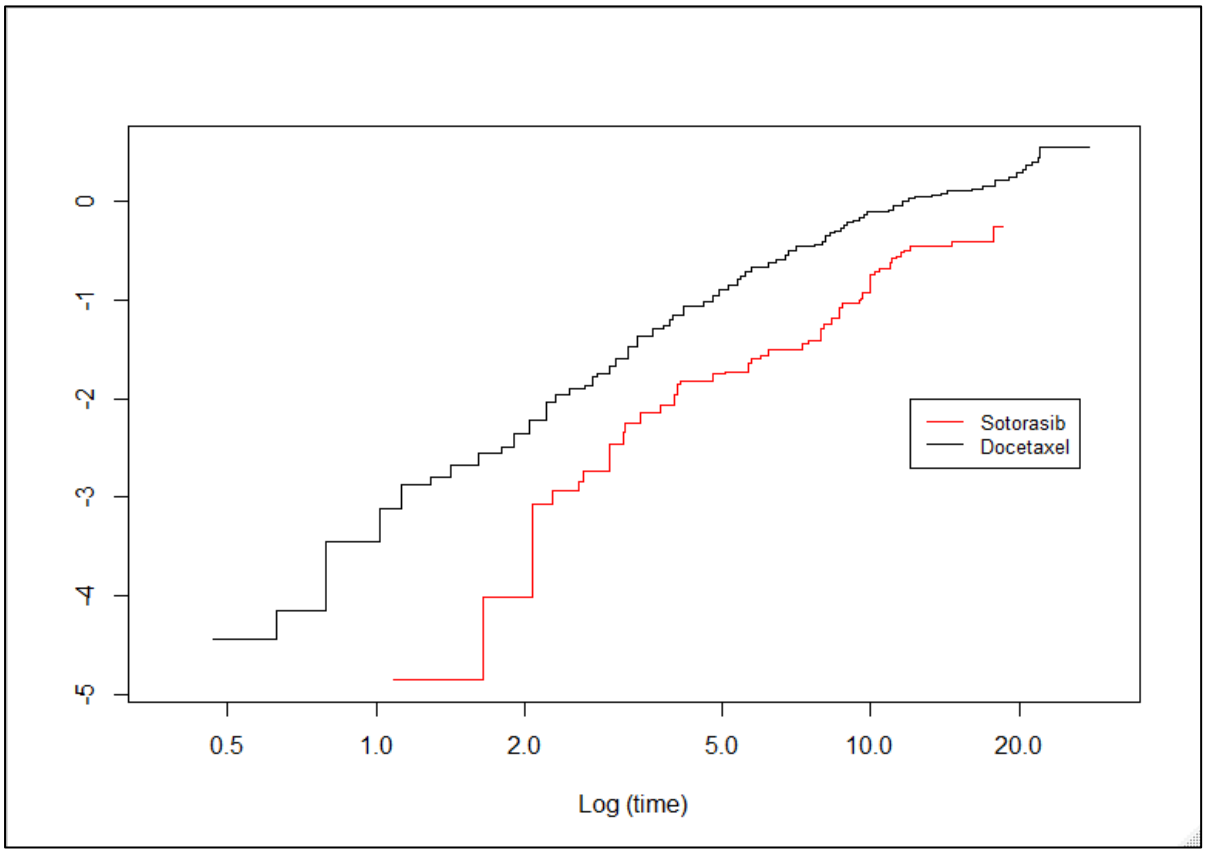
Table 58. OS Goodness-of-fit Statistics for Fitted Models Using MAIC SET 2

Model	Independent fit – sotorasib		Independent fit - docetaxel		Joint fit (unrestricted)		Joint fit (restricted)	
	AIC	BIC	AIC	BIC	AIC	BIC	AIC	BIC
Exponential	256.6	259.2	1209.7	1213.2	1466.3	1474.0	1466.3	1474.0
Gompertz	258.1	263.3	1211.4	1218.5	1465.5	1485.0	1466.2	1479.9
Weibull	256.1	261.2	1209.6	1216.7	1465.7	1481.2	1464.7	1476.3
Generalized Gamma	254.7	262.5	1194.6	1205.2	1449.3	1472.5	1445.6	1461.1
Loglogistic	254.5	259.7	1196.3	1203.4	1450.8	1466.3	1448.9	1460.5
Lognormal	253.2	258.4	1192.8	1199.9	1446.1	1461.5	1444.1	1455.7

Key: AIC, Akaike information criterion; BIC, Bayesian information criterion.
Note: Underlined values indicate the best statistically fitting parametric distribution.

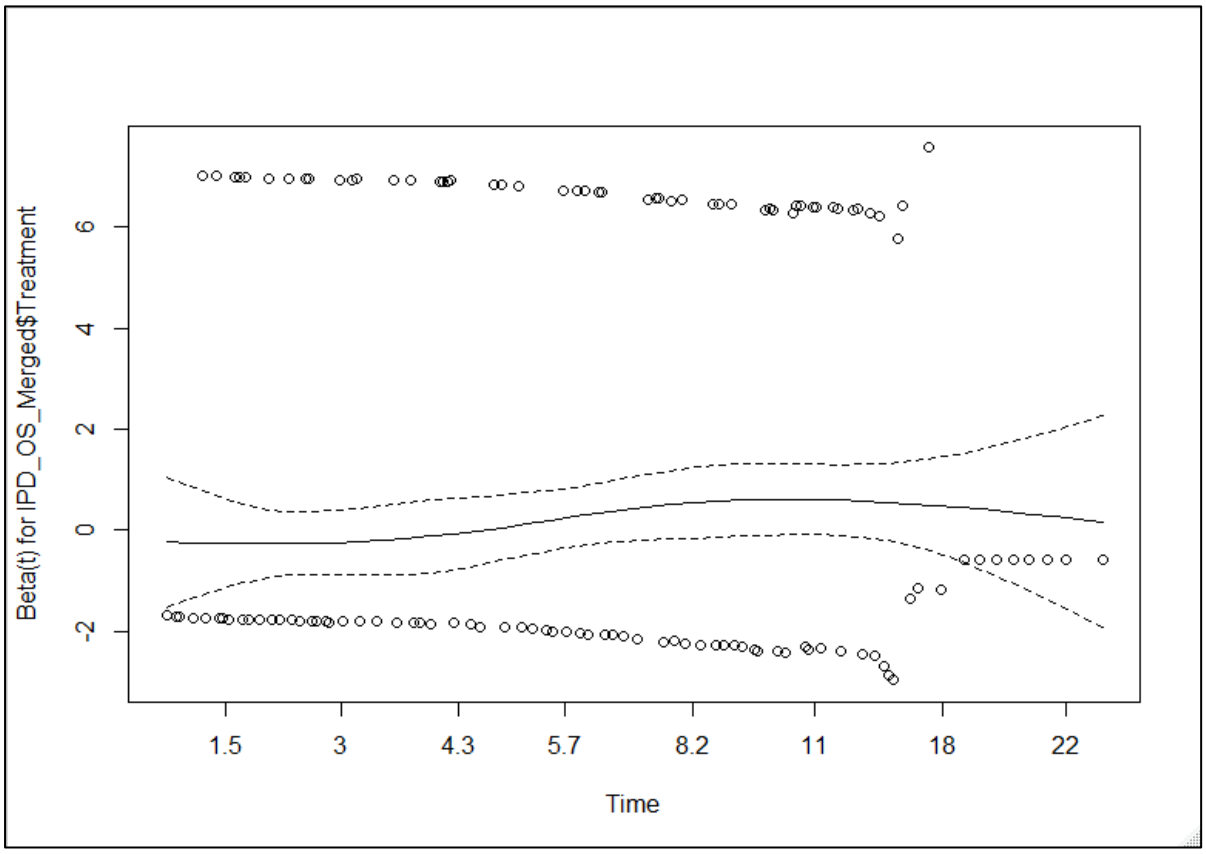
The proportional hazards assumption between the two datasets was assessed using the log-cumulative hazards plot (Figure 14) and the corresponding Schoenfeld residuals plot (Figure 15). The QQ plot is also presented (Figure 16).

Figure 14. Log-Cumulative Hazards Plot for OS Using MAIC SET 2



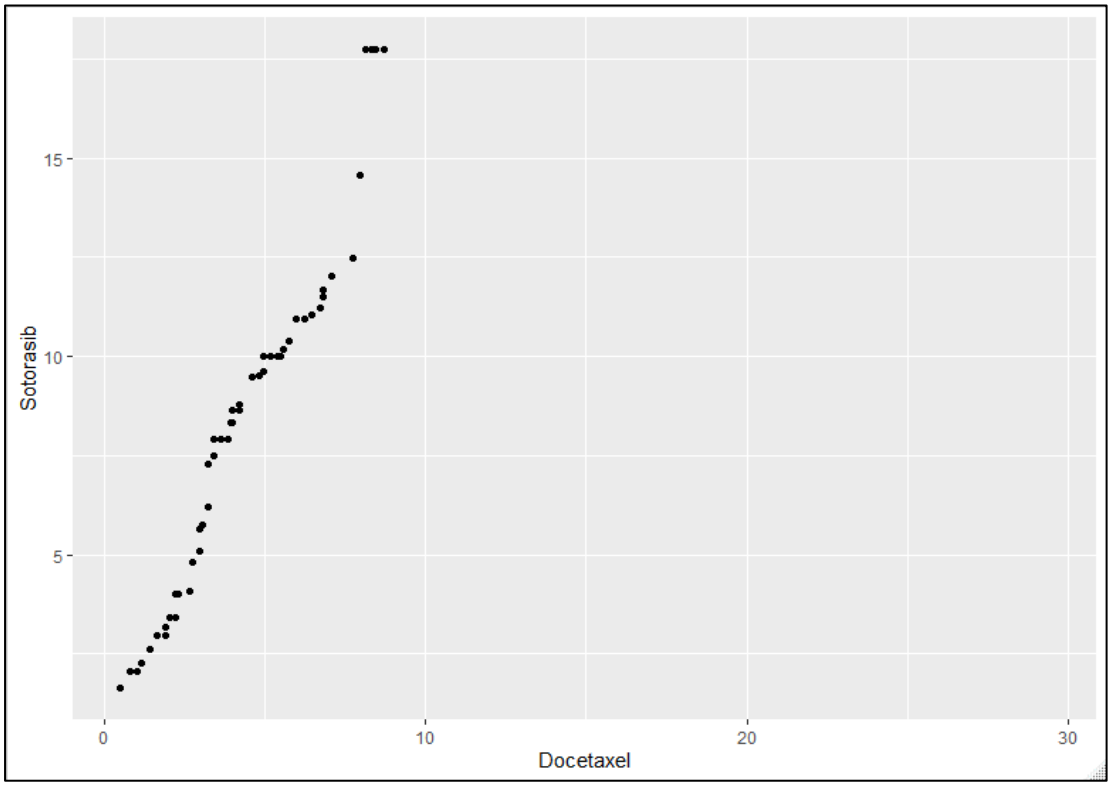
Key: MAIC, matching-adjusted indirect comparison; OS, overall survival.

Figure 15. Schoenfeld Residuals Plot for OS Using MAIC SET 2



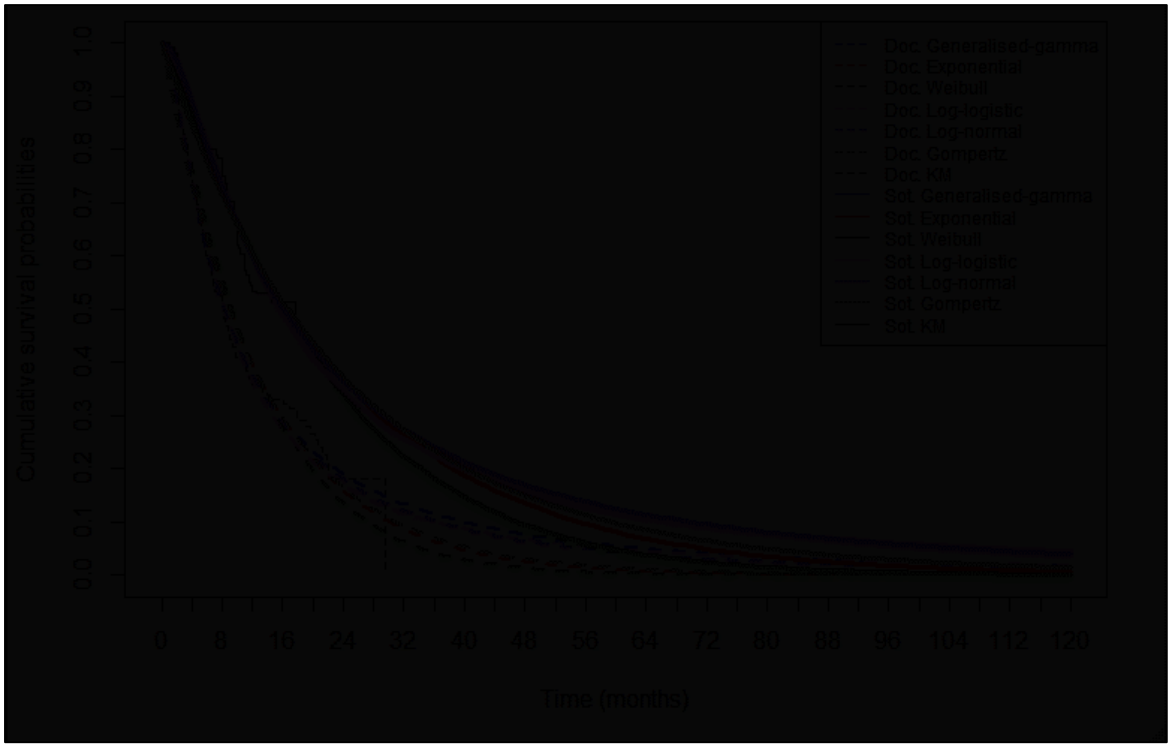
Key: MAIC, matching-adjusted indirect comparison; OS, overall survival.

Figure 16. QQ Plot for OS for MAIC SET 2



Key: MAIC, matching-adjusted indirect comparison; OS, overall survival.

A plot of adjusted OS KM data and the standard six parametric functions jointly fitted with restricted model presented in **Error! Reference source not found.**.



Key: Doc, docetaxel; KM, Kaplan-Meier; MAIC, matching-adjusted indirect comparison; OS, overall survival; Sot, sotorasib.

12.1.3.1.2 Progression-free survival

Parametric model fitting was carried out using MAIC SET 2 using all available covariates adjusted PFS KM data, in accordance with the algorithm proposed by NICE DSU TSD 14. Six parametric distributions were used including exponential, Weibull, Gompertz, generalized gamma, log-normal and log-logistic. Goodness-of-fit statistics are reported for independent fitted and jointly fitted (unrestricted and restricted) models in Table 59.

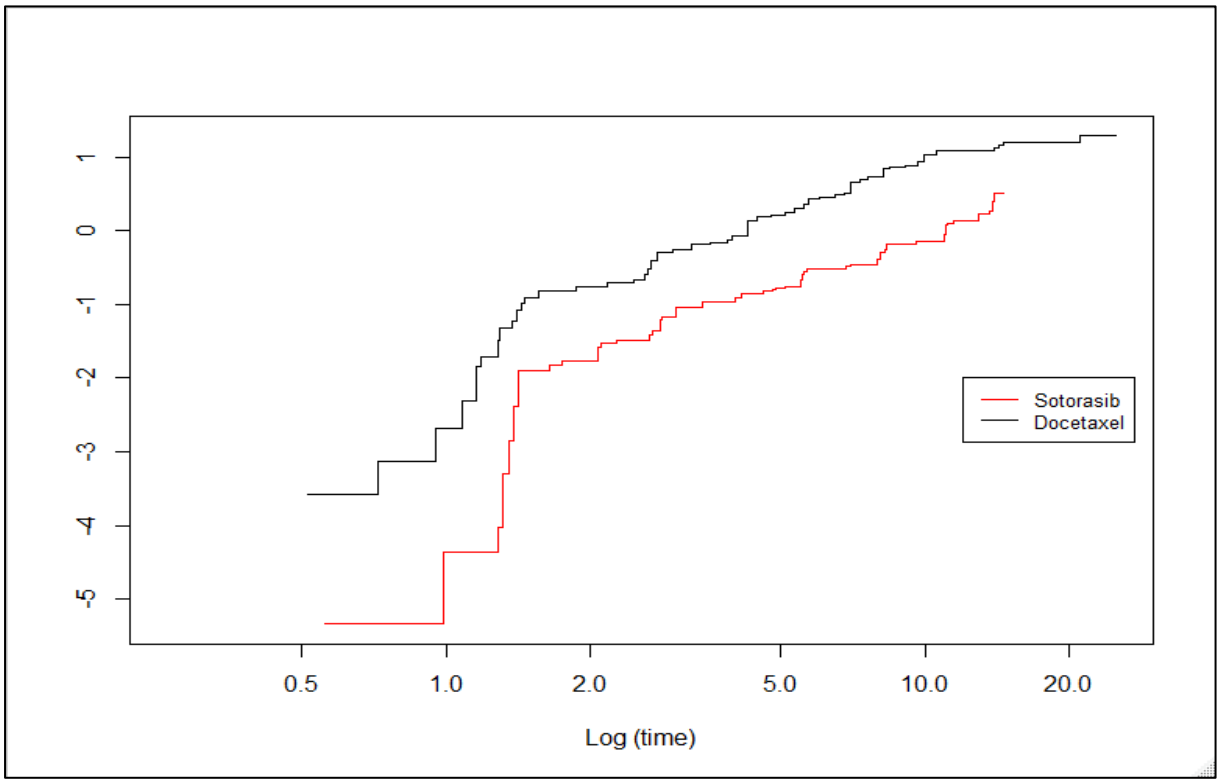
Table 59. PFS Goodness-of-fit Statistics for Fitted Models Using MAIC SET 2

Model	Independent fit – sotorasib		Independent fit - docetaxel		Joint fit (unrestricted)		Joint fit (restricted)	
	AIC	BIC	AIC	BIC	AIC	BIC	AIC	BIC
Exponential	325.9	328.5	1166.5	1170.0	1492.4	1500.2	1492.4	1500.2
Gompertz	326.5	331.7	1166.9	1174.0	1489.4	1508.9	1491.9	1505.5
Weibull	325.5	330.7	1160.6	1167.7	1486.1	1501.6	1484.3	1495.9
Generalized Gamma	324.7	332.4	1099.5	1110.1	1424.2	1447.4	1426.1	1441.6
Loglogistic	325.6	330.8	1113.5	1120.6	1439.1	1454.6	1440.2	1451.8
Lognormal	322.8	328.0	1105.7	1112.8	1431.5	1446.9	1429.5	1441.1

Key: AIC, Akaike information criterion; BIC, Bayesian information criterion.
Note: Underlined values indicate the best statistically fitting parametric distribution.

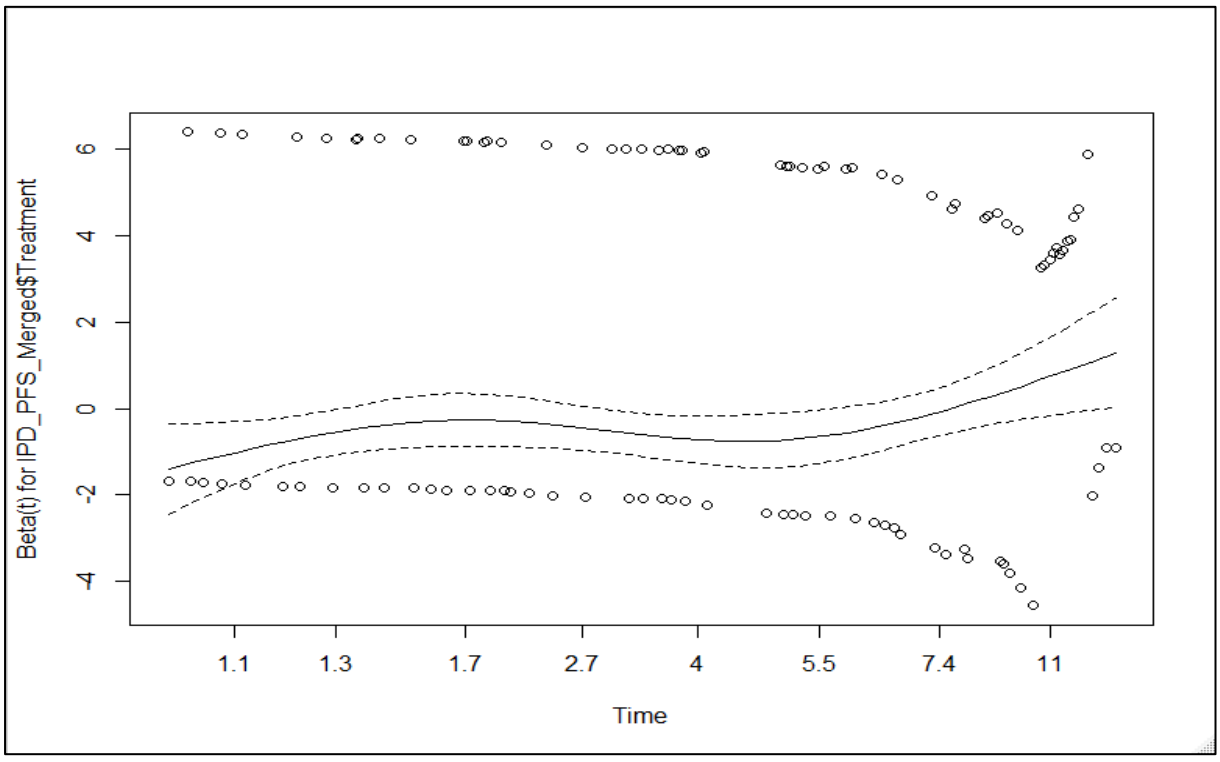
The proportional hazards assumption between the two datasets was assessed using the log-cumulative hazards plot (Figure 17) and the corresponding Schoenfeld residuals plot (Figure 18). The QQ plot is also presented (Figure 19).

Figure 17. Log-Cumulative Hazards Plot for PFS Using MAIC SET 2



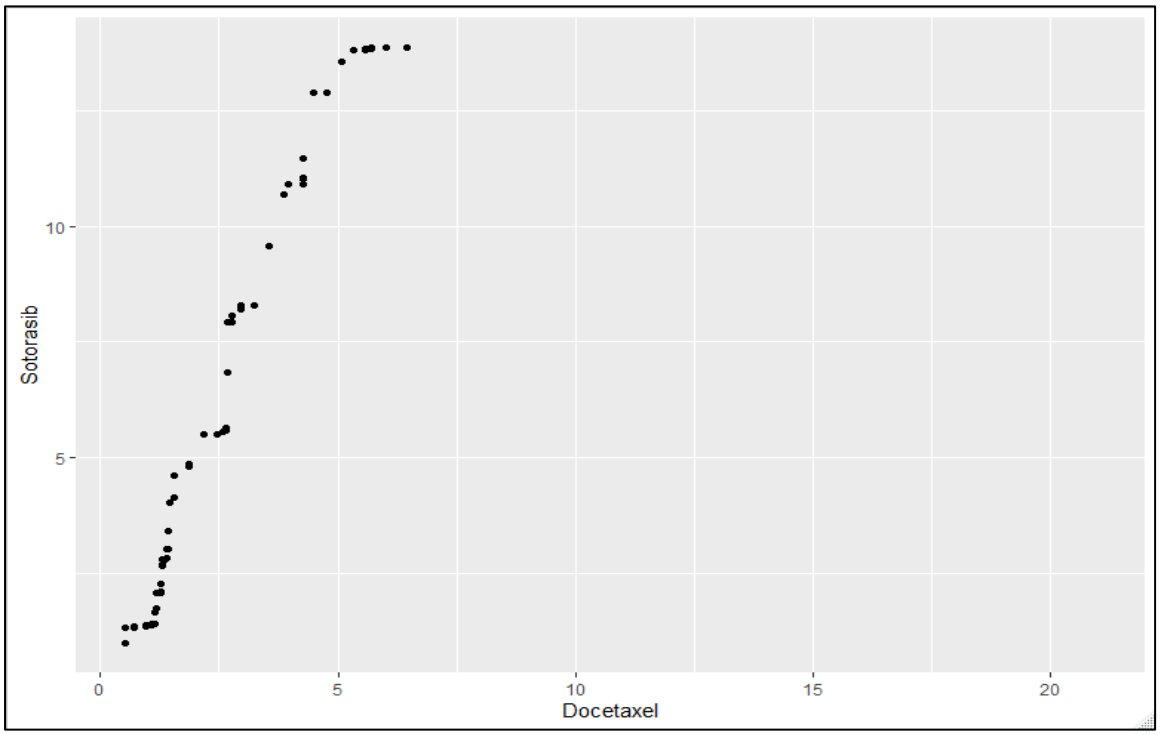
Key: MAIC, matching-adjusted indirect comparison; PFS, progression-free survival.

Figure 18. Schoenfeld Residuals Plot for PFS Using MAIC SET 2



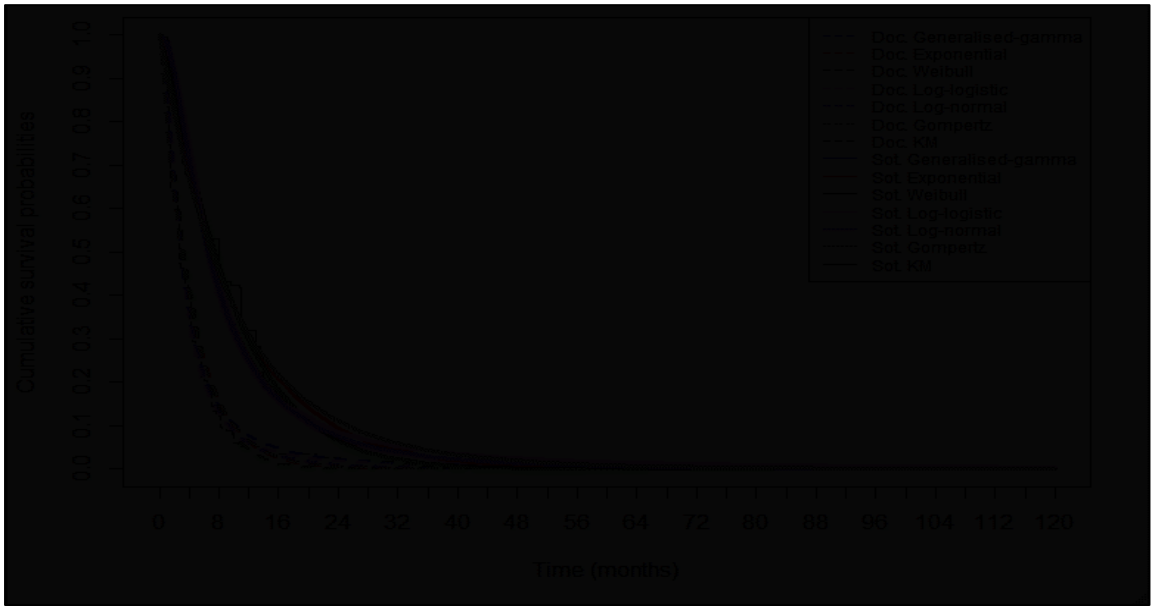
Key: MAIC, matching-adjusted indirect comparison; PFS, progression-free survival.

Figure 19. QQ Plot for PFS for MAIC SET 2



Key: MAIC, matching-adjusted indirect comparison; PFS, progression-free survival.

A plot of adjusted PFS KM data and the standard six parametric functions jointly fitted with restricted model presented in **Error! Reference source not found.**.



Key: Doc, docetaxel; KM, Kaplan–Meier; MAIC, matching-adjusted indirect comparison; PFS, progression-free survival; Sot, sotorasib.

12.1.4 Strengths and weaknesses of the MAIC analysis

Although unanchored MAICs are expected to be associated with higher uncertainty and higher risk of bias compared to anchored MAICs, the bias was expected to be minimal given the similarity of the populations in CodeBreak 100 and SELECT-1. The following section outlines the key strengths and limitations of the MAIC analysis.

- Both CodeBreak 100 and SELECT-1 had similar inclusion/exclusion criteria and had similar criteria for measuring PFS (both using RECIST 1.1 every 6 weeks), which lowers the risk of bias for this comparison. Key differences were the type of KRAS mutation (any for SELECT-1, G12C only for CodeBreak 100), and the type and number of prior lines of therapy (only one prior treatment with platinum-based chemotherapy for SELECT-1, between 1 and 3 prior lines of treatment for CodeBreak including an anti-PD-(L)1 AND/OR a platinum-based chemotherapy.
- Current evidence and expert opinion suggest there is no difference in prognostic between KRAS G12C and other KRAS mutations, which limits the risk of bias (133-135)
- CodeBreak 100 subsects were more heavily pre-treated than SELECT-1 subjects. This is a conservative limitation for the comparative effectiveness as a more heavily pre-treated population is generally associated with poorer clinical outcomes.
- Most patients in CodeBreak 100 had received an anti-PD-(L)1 regimen in prior lines whereas no patient received it in SELECT-1. There is limited evidence that the use of anti-PD-1 therapies in prior lines can enhance the tumor response on subsequent chemotherapy (including docetaxel). However, so far, no significant difference has been found in terms of PFS or OS.
- One limitation is that it was not possible to adjust on all key characteristics due to either a lack of overlap (KRAS G12C, anti-PD-1 in prior line, number of prior lines) or lack of data (% with controlled brain metastases, presence of other targetable mutations).
- The presence of other targetable mutations is very low in CodeBreak 100 (3%) and expected to be very low as well in SELECT-1 as the presence of other targetable mutations is very rare in KRAS mutated patients.
- The proportion of patients with controlled brain metastases (both trials excluded patients with active brain metastases) was not reported in SELECT-1 and was 21% in CodeBreak 100 pre-matching (18% post matching). The analysis is potentially conservative for the comparative efficacy of sotorasib vs. docetaxel in this regard, as the presence of brain metastases is a negative prognostic factor, whereas in other previously treated NSCLC RCTs, the proportion of patients with controlled brain metastases was consistently lower than in CodeBreak 100, suggesting there were potentially fewer patients with brain metastases in the SELECT-1 trial.

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Appendix L - Flatiron

12.2 Flatiron propensity weighting score analysis

The section presented details of the propensity weighting score analysis conducted between CodeBreak 100 and the Flatiron dataset.

This supplementary analysis was undertaken to explore an alternative data source and method of estimating relative treatment effects for sotorasib vs docetaxel monotherapy (using the basket of standard of care chemotherapy regimens in the Amgen Flatiron real-world evidence cohort as a proxy for docetaxel monotherapy

However, the most common regimen amongst the basket of chemotherapy regimens in the Flatiron dataset was platinum-based chemotherapy (see table below). This analysis therefore also provides a pragmatic reflection of the likely relative treatment effects of sotorasib versus platinum-based chemotherapy.

Table 60 Summary of chemotherapy treatment mix in the flatiron cohort

	Unweighted cohort		ATT-weighted cohort	
Regimen	**n**	**% of cohort**	**n**	**% of cohort**
KRAS mutant population				
	(N = 206)		**(N = 120.57)**	
Platinum-based chemotherapy	64	31.07%	27.78	23.04%
Chemotherapy monotherapy (excluding docetaxel)	61	29.61%	32.48	26.94%
Docetaxel plus ramucirumab	45	21.84%	41.24	34.20%
Docetaxel monotherapy	21	10.19%	12.16	10.09%
Other chemotherapy-based regimens	15	7.28%	6.91	5.73%
KRAS p.G12C mutated population				
	(N = 85)		**(N = 133.11)**	
Platinum-based chemotherapy	25	29.41%	23.83	17.90%
Chemotherapy monotherapy (excluding docetaxel)	24	28.24%	30.42	22.85%
Docetaxel plus ramucirumab	18	21.18%	64.17	48.21%
Docetaxel monotherapy	11	12.94%	8.56	6.43%
Other chemotherapy-based regimens	7	8.24%	6.13	4.61%

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12.2.1 Populations of the propensity score analysis

12.2.1.1 Index date

The index date for subjects in CodeBreak 100 refers to the date at which the first dose of sotorasib was administered. Patients from the Flatiron real-world cohort may have received more than one LOT. Therefore, the index date for these patients refers to the start date of the selected LOT. In particular, for the Flatiron cohort the index date was selected as follows:

- If a patient received ≥ 2 but ≤ 4 lines of therapy on/before 31 March 2020, the last LOT that met the inclusion criteria was selected.
- If a patient received more than four lines on/before 31 March 2020, the 4th line was selected. If the 4th line contained (a) a clinical study drug or (b) an anti PD-(L)1 regimen in patients with no prior history of anti PD-(L)1 exposure in prior lines, the immediate prior LOT not containing a clinical study drug/anti PD-(L)1 drug and which meets the inclusion/exclusion criteria was selected.

If no line met the inclusion/exclusion criteria, the patient was not included in the analyses.

12.2.1.2 Analysis sets

Two analysis sets were considered: for the main analysis the KRAS Mutant Analysis Set, which for the FLATIRON cohort allowed subjects with any KRAS Mutation, and for exploratory analysis and to check for consistency the G12C-only Analysis Set.

Data from the Flatiron cohort were filtered to match the key primary inclusion criteria from the CodeBreak 100 phase 2 NSCLC portion.

All NSCLC subjects enrolled in the CodeBreak 100 Phase II trial and received at least one dose of sotorasib were included in the analysis. The CodeBreak 100 key eligibility criteria include:

- Subjects diagnosed with KRAS G12C mutant advanced NSCLC.
- Age 18 years or older.
- Subjects must have progressed after receiving anti PD-1 or anti PD-L1 immunotherapy (unless contraindicated) AND/OR platinum-based combination chemotherapy. Subjects must have received no more than three prior lines of therapy
- Baseline ECOG performance status <=1.

Inclusion criteria of the Flatiron cohort were:

- Diagnosed with advanced NSCLC between 01 January 2011 and the index date.
- Patient's entry date is any time before or up to 21 days after the index date.
- Age 18 years or older at index date.
- Started the selected LOT on/before 31 March 2020 (to allow for sufficient opportunity of a minimum of 6 months of follow-up).
- Structured electronic health record activity in the first 90 days on/after advanced diagnosis date.
- Patients previously treated with at least one regimen before index date, containing at least one of the following agents, either alone or in combination: anti-PD-1, anti-PD-L1 or platinum-based chemotherapy.
- The selected LOT does not contain a clinical study drug.
- The selected LOT does not contain an anti-PD(L)1 drug, unless the subject has already had prior exposure to anti PD-(L)1 drugs in the previous lines
- Baseline ECOG <= 1.

Finally, subjects were removed from the comparator arm if their treatment was not chemotherapy based. In particular, active treatments with anti PD-1 and other non-chemotherapy-based treatments were excluded.

The KRAS Mutant Analysis Set was defined with the same criteria as the G12C-only Analysis set but including all patients from the FIH-FMI CGDB identified as having any KRAS mutation from an FMI test any time on/before or up to 21 days after the index date, which did not affect subjects in the CodeBreak 100 cohort. Patients with a KRAS mutation from the Flatiron cohort were included.

A propensity score weighting approach was used for this analysis, as the limited sample size of the two studies prohibits the use of propensity score matching. The average treatment effect of the treated (ATT) weight was used to balance the covariates of the chemotherapy-treated (Flatiron) population to fit the characteristics of the sotorasib-treated population in CodeBreaK100.

12.2.2 Propensity score analysis expert elicitation

The output of clinical expert elicitation to determine the important prognostic factors for NSCLC are presented (Table 61).

Table 61. Output of Clinical Expert Elicitation for Covariates Related to Prognosis

Covariate	Include (Y/N)	Justification
Baseline ECOG (0 or 1)	Yes	ECOG was considered as the most important baseline characteristics for the prognosis of NSCLC patients
Presence of brain metastases (Y; N)	Yes	Brain metastases was considered the second most important prognostic factor
Metastatic at baseline (Y; N)	No	In both populations, the proportion of patients not metastatic at baseline were low; there was no need to adjust on metastasis at baseline specifically. After adjustment with propensity score weighting, the populations remained balanced
PD-L1 protein expression (<1%, 1-49%, >=50%)	No	PD-L1 expression was mentioned as important for patients anti PD-(L)1 naïve who are considered for treatment with anti PD-(L)1 based regimen. These patients were not in the scope of the analysis. Moreover, the proportion of patients with missing PD-L1 expression was relatively high in both populations
Presence of at least one of the following mutations/alterations: EGFR, ALK, BRAF, ROS-1 (Y; N)	No	The presence of these co-mutations in KRAS mutant patients are very rare and this was observed in both populations. Given the dataset, there was no need to adjust this variable.
Age (18–64 yrs, 65–74 yrs, 75+ yrs)	Yes	The population in Flatiron was relatively older than in CodeBreak 100. In addition to age group, continuous age was also tested in the model
Smoking status	No	% of smokers was very high and balanced before adjustment
BMI	No	Distribution of BMI was very similar across populations
Presence of liver metastases (Y; N)	No	% of patients with liver metastases was overall balanced in the two populations and liver metastasis was a less important factor than brain metastases
Presence of bone metastases (Y; N)	No	Same considerations as for liver metastases
Number of metastatic sites (0, 1, 2, 3 or more)	No	There are potential differences in how the number of metastatic sites in CodeBreak 100 and Flatiron are counted. The number of sites was not included in the model but balance after matching was examined
Time from prior line initiation to the index date (<=3 months, between 3 and 6 months, more than 6 months)	Considered in some models	Inclusion of this variable was explored in some scenarios
Type of prior therapies	Yes	There is imbalance in the % of patients with prior PD-1 therapy in CodeBreak vs. Flatiron, this was corrected for
Laboratory values (Albumin, LDH, ALT/ AST, (eGFR))	No	High proportion of missing values + not seen as very important by clinical experts

Key: BMI, body mass index; ECOG, European Co-operative Oncology Group; LDH, lactic acid dehydrogenase; NSCLC, non-small cell lung cancer.

12.2.3 Flatiron patient disposition

The disposition of patients in the Flatiron KRAS-G12C cohort, Other KRAS cohort and the Triple WT cohort are presented (**Error! Reference source not found.**).

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12.2.4 Propensity score analysis baseline characteristics

This section presents the comparison of baseline characteristics of CodeBreak 100 and Flatiron KRAS mutant (**Error! Reference source not found.** and Figure 20) and KRAS-G12C (**Error! Reference source not found.** and Figure 21).

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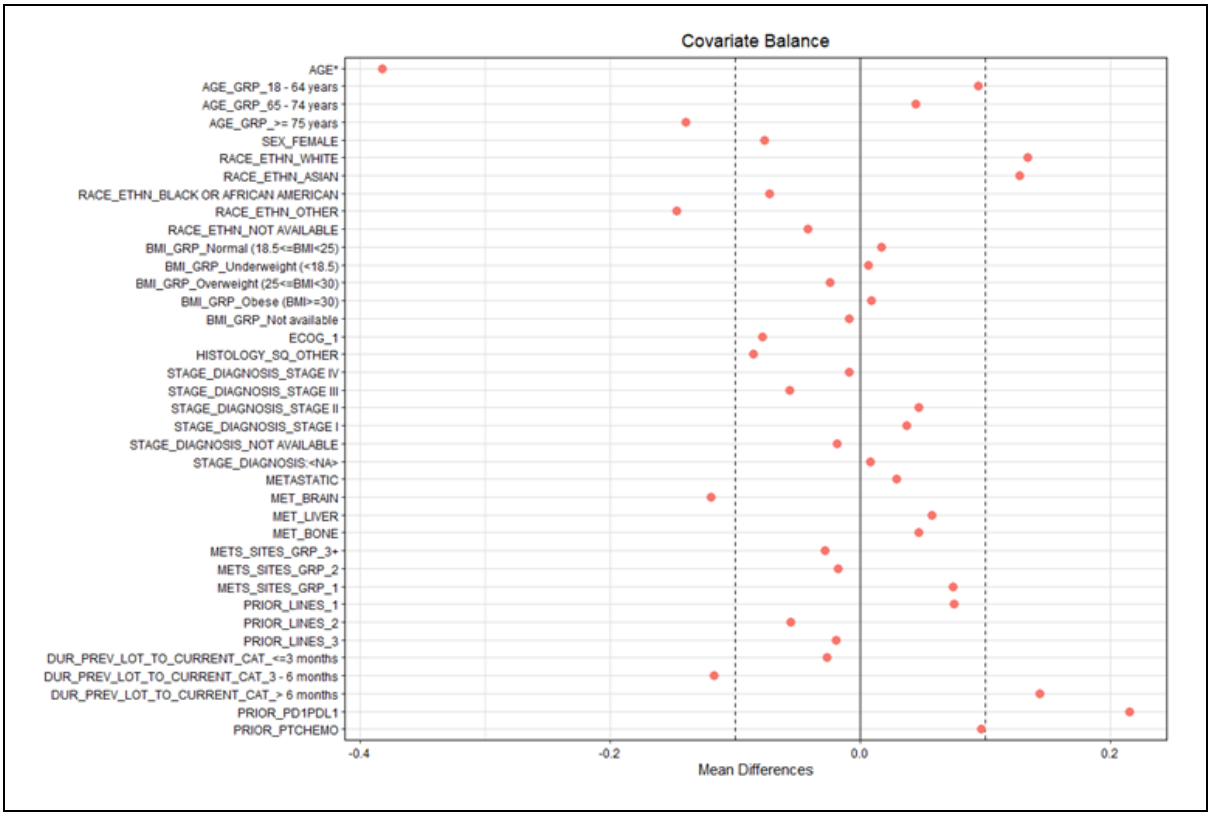
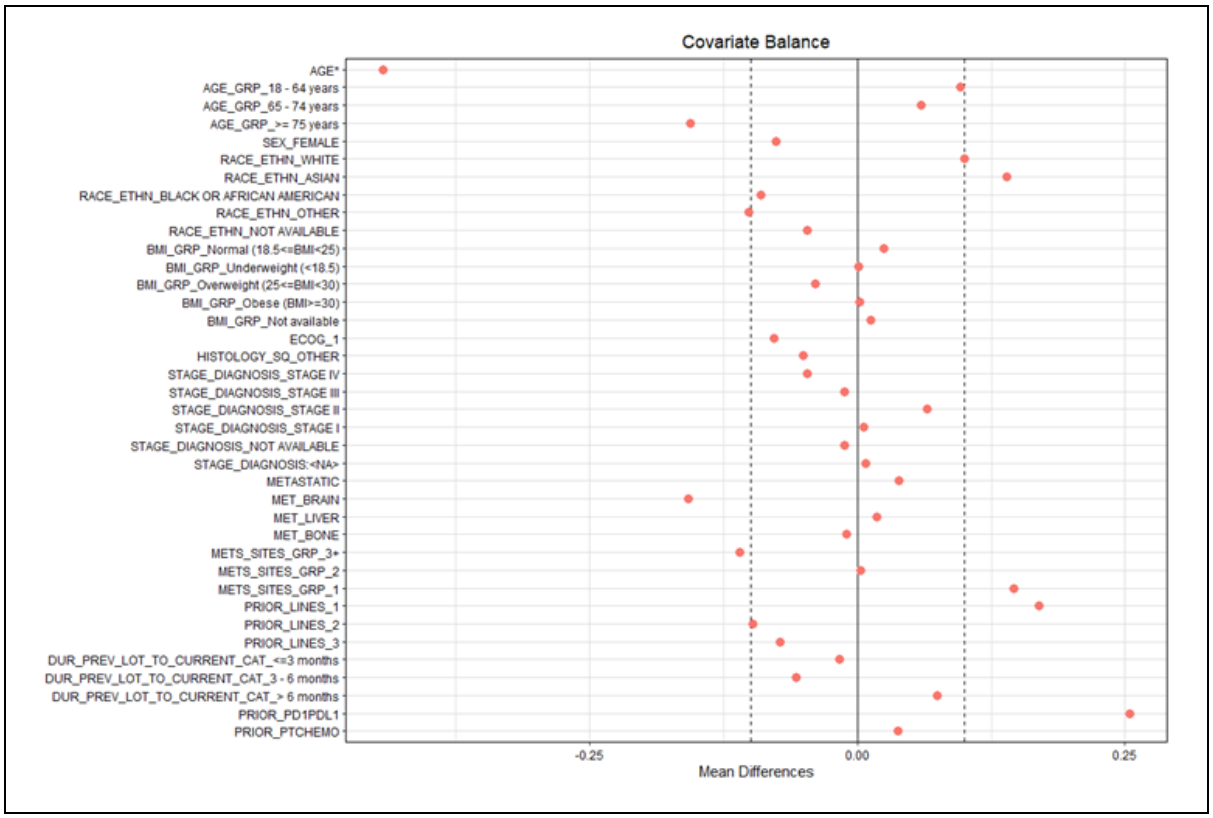
Figure 20. Baseline Characteristics for CodeBreak 100 and Flatiron KRAS mutant



Key: BMI, body mass index; DUR, duration; ECOG, European Co-operative Oncology Group; ETHN, ethnicity; GRP, group; MET, metastatic; PREV, previous

Note: Balance was assessed by mean differences for binary/categorical outcomes and by standardized mean differences for continuous variables, with a difference of > 10% considered imbalanced

Figure 21. Baseline Characteristics for CodeBreak 100 and Flatiron KRAS-G12C



Key: BMI, body mass index; DUR, duration; ECOG, European Co-operative Oncology Group; ETHN, ethnicity; GRP, group; MET, metastatic; PREV, previous

Note: Balance was assessed by mean differences for binary/categorical outcomes and by standardized mean differences for continuous variables, with a difference of > 10% considered imbalanced

12.2.5 Propensity score analysis methods

12.2.5.1 Variables

Overall survival

OS was defined as time from index date to death from any cause. Subjects who did not die were censored on the last date the subject was known to be alive. If the date last known to be alive is after the data cut-off date, the subject was censored at the cut-off date. For the Flatiron cohort, patients who subsequently began a clinical study drug were censored at the start date of the LOT containing the clinical study drug. Month-year granularity for death date was imputed using the 15th of the month. Patients with only year-level of granularity for death date were excluded from the survival analysis.

Progression-free survival in CodeBreak 100

In CodeBreak 100, PFS was defined as time from start of treatment to disease progression or death from any cause (whichever occurred first). Disease progression was assessed using RECIST 1.1, with radiographic scans performed every six weeks (for eight assessments, and then every 12 weeks afterwards). For this analysis, investigator-rated disease progression was applied. It contained fewer missing values than the corresponding rating of the blinded independent central review committee. Avoidance of missing values was judged important, as the analyses informed a partitioned survival model and the populations of OS and PFS should be consistent.

In addition, investigator-rated disease progression was likely to be more comparable to real-world PFS from Flatiron, where no blinded review is possible.

Subjects without an event were censored on their last evaluable assessment. Subjects who started subsequent anti-cancer therapy and had no events or had an event after starting subsequent anti-cancer therapy were censored on the last evaluable assessment before or at the start of subsequent anti-cancer therapy.

Progression-free survival in Flatiron

In the Flatiron cohort, real-world PFS (rwPFS) was defined as time from index date to disease progression or death from any cause (whichever comes first). Disease progression was identified from clinic notes from visits at which a patient was evaluated for progression by the treating clinician. Patients without evidence of progression or death were censored on the last clinical note date, which refers to the date the patient was last evaluated for rwPFS by their treating physician. Patients who had a subsequent LOT were censored on the earlier of last clinical note date or day before subsequent LOT, if they had no evidence of progression or death, or had evidence of progression after subsequent LOT but no death.

If the patient's last clinic note date was on/before the start date of the selected LOT, OS data were used for imputation. This imputation overestimated the PFS for the comparator arm, and thus was considered conservative. However, the imputation assured the consistency between the OS and the PFS population.

Covariates

Candidate covariates for inclusion in the propensity score model were based on a list of the most important covariates for confounding in patients with advanced NSCLC. This list was generated based on a review of the literature and extensive documented discussions with experienced NSCLC physicians (76).

The following covariates were indicated as being very important to assess the prognosis of patients with advanced NSCLC by a majority of medical oncologists interviewed (at least 4 of the 6 medical oncologists interviewed):

- Baseline ECOG (0 or 1)
- Presence of brain metastases (Y; N)
- Metastatic at baseline (Y; N)
- PD-L1 protein expression (<1%, 1-49%, >=50%) (it was mentioned as being relevant only for patients receiving an anti PD-(L)1 therapy in the LOT of interest)
- Presence of at least one of the following mutations/alterations: EGFR, ALK, BRAF, ROS-1 with known significance (Y; N)

The following additional covariates were identified as being at least somewhat important for assessing the prognosis of patients with advanced NSCLC by a majority of medical oncologists:

- Age (18–64 yrs, 65–74 yrs, 75+ yrs)
- Smoking status (history of smoking vs. no history of smoking)
- BMI
- Presence of liver metastases (Y; N)
- Presence of bone metastases (Y; N)
- Number of sites of metastasis (0, 1, 2, 3 or more)
- Number of prior lines of therapies (1, 2, 3)
- Type of therapies administered in prior lines
    - Prior PD-1 or PD-L1 immunotherapy (Y; N)
    - Prior platinum-based chemotherapy (Y; N)

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- Time from prior line initiation to the index date (<3 months, between 3 and 6 months, more than 6 months)
- Albumin at baseline
- Liver function (ALT, AST) at baseline
- Renal function (eGFR) at baseline

Serum lactic acid dehydrogenase was also identified as being at least somewhat important for assessing the prognosis of patients with advanced NSCLC; however, there were no subjects with observed values for this covariate in the Phase II portion of CodeBreak 100, therefore serum lactic acid dehydrogenase was excluded from all analyses.

12.2.5.2 Analysis methods

This was a propensity score analysis of adult (≥18 years) patients with advanced NSCLC from two different studies: a clinical trial of subjects receiving sotorasib and a real-world dataset of patients receiving chemotherapy-based standard of care. The propensity score in this context was the propensity of being treated with sotorasib

12.2.5.3 Populations

Index date

The index date for subjects in CodeBreak 100 refers to the date at which the first dose of sotorasib was administered. Patients from the Flatiron real-world cohort may have received more than one line of therapy. Therefore, the index date for these patients refers to the start date of the selected LOT. In particular, for the Flatiron cohort the index date was selected as follows:

- If a patient received ≥ 2 but ≤ 4 lines of therapy on/before 31 March 2020, the last LOT that met the inclusion criteria was selected.
- If a patient received more than four lines on/before 31 March 2020, the 4th line was selected. If the 4th line contained (a) a clinical study drug or (b) an anti PD-(L)1 regimen in patients with no prior history of anti PD-(L)1 exposure in prior lines, the immediate prior LOT not containing a clinical study drug/anti PD-(L)1 drug and which meets the inclusion/exclusion criteria was selected.

If no line met the inclusion/exclusion criteria, the patient was not included in the analyses.

Analysis sets

Two analysis sets were considered: for the main analysis, the KRAS Mutant Analysis Set, which for the FLATIRON cohort allowed subjects with any KRAS Mutation, and for exploratory analysis and to check for consistency the G12C-only Analysis Set.

Data from the Flatiron cohort were filtered to match the key primary inclusion criteria from the CodeBreak 100 Phase II NSCLC portion.

All NSCLC subjects enrolled in the CodeBreak 100 Phase II trial and who received at least one dose of sotorasib were included in the analysis. The CodeBreak 100 key eligibility criteria include:

- Subjects diagnosed with KRAS G12C mutant advanced NSCLC.
- Age 18 years or older.
- Subjects must have progressed after receiving anti PD-1 or anti PD-L1 immunotherapy (unless contraindicated) AND/OR platinum-based combination chemotherapy. Subjects must have received no more than three prior LOTs

- Baseline ECOG performance status <=1.

Inclusion criteria of the Flatiron cohort were:

- Diagnosed with advanced NSCLC between 01 January 2011 and the index date.
- Patient's entry date is any time before or up to 21 days after the index date.
- Age 18 years or older at index date.
- Started the selected LOT on/before 31 March 2020 (to allow for sufficient opportunity of a minimum of 6 months of follow-up).
- Structured electronic health record activity in the first 90 days on/after advanced diagnosis date.
- Patients previously treated with at least one regimen before index date, containing at least one of the following agents, either alone or in combination: anti-PD-1, anti-PD-L1 or platinum-based chemotherapy.
- The selected LOT does not contain a clinical study drug.
- The selected LOT does not contain an anti-PD(L)1 drug, unless the subject has already had prior exposure to anti PD-(L)1 drugs in the previous lines
- Baseline ECOG <= 1.

Finally, subjects were removed from the comparator arm if their treatment was not chemotherapy based. In particular, active treatments with anti PD-1 and other non-chemotherapy-based treatments were excluded.

The KRAS Mutant Analysis Set was defined with the same criteria as the G12C-only Analysis set but including all patients from the FIH-FMI CGDB identified as having any KRAS mutation from an FMI test any time on/before or up to 21 days after the index date, which did not affect subjects in the CodeBreak 100 cohort. Patients with a KRAS mutation from the Flatiron cohort were included.

12.2.5.4 Statistical methods

The steps to carry out the statistical analysis were as follows:

1. Develop the propensity score model by selecting variables considered relevant for discriminating between those who were and were not treated with sotorasib. The final model was used for generating each patient's propensity score.
2. Evaluate the balance between treatment groups with respect to their propensity score by comparing before and post weighting via box-plots.
3. If a balance is adequately achieved, conduct the clinical outcome analysis using the resulting weights.

Propensity score model development

Candidate covariates were entered into a logistic regression model with sotorasib treatment as the binary response. Covariates identified as being very important were fixed in the propensity score model, regardless of their statistical significance. The exception to this was PD-L1 protein expression, which had a high proportion of missing data. A stepwise variable selection algorithm was run on the covariates identified as being somewhat important, whereby the AIC (to be minimized) was used as the criterion of adding or removing covariates to or from the model. The covariate eGFR was excluded from the model selection due to the high proportion of missing data.

Balance diagnostics

Upon deriving propensity scores for each patient, balance between the two treatment groups with respect to their propensity scores was assessed before and post weighting via box-plots. With respect to individual covariates considered for the propensity score model, two methods were employed to ascertain the balance

between the data sources before and after propensity score adjustments. The method involved the calculation of standardized differences between the sotorasib treated and untreated groups. For a continuous variable, the standardized differences were calculated as:

$$d = \frac{(\overline{X_1} - \overline{X_2})}{\sqrt{\frac{s_1^2 + s_2^2}{2}}}$$

where $\bar{X}_1$ and $\bar{X}_2$ denote the sample mean of the covariate in sotorasib treated and untreated subjects, respectively, whereas s_1 and s_2 denote the sample variance of the covariate in the sotorasib treated and untreated subjects, respectively. For a dichotomous variable, the standardized differences were calculated as:

$$d = \frac{(\hat{P}_1 - \hat{P}_2)}{\sqrt{\frac{[\hat{P}_1(1-\hat{P}_1) + \hat{P}_2(1-\hat{P}_2)]}{2}}}$$

where $\hat{P}_1$ and $\hat{P}_2$ denote the sample prevalence of the variable in treated and control subjects, respectively. When assessing the after-effects of the PS adjustment, the sample means, sample variances, and sample prevalences in the formulae above were replaced by their weighted equivalents.

Propensity score adjustment method

The propensity score weighting approach was used for this analysis as the limited sample size of the two studies prohibits the use of PS matching.

The ATT weight, which balances the covariates of the control population to fit the characteristics of the treated population, was applied (136, 137). It works by giving all sotorasib treated subjects from the CodeBreak 100 study equal weighting of one and control patients larger weights for higher propensity scores:

$$w_i = Z_i + \frac{e_i(1 - Z_i)}{(1 - e_i)}$$

where the subscript i denotes the i^{th} subject, Z is assigned a value of 1 for treated (sotorasib) subjects and 0 for untreated subjects, e represents the propensity score and w represents the weight, which is the reciprocal of the probability of receiving the treatment that was actually received.

Scatter plots of each subject's propensity score vs. the ATT weights were produced so that the distribution and impact of the weights could be visually ascertained.

Effective sample size

Though propensity score weighting methods are useful in reducing the effects of confounding, they also lead to a reduction in the effective sample size (ESS). The effective sample size is an estimate of the number of independent unweighted subjects that would be required to attain the same level of precision as the weighted sample, and can be calculated as follows:

$$\text{ESS} = \frac{\left(\sum_{i=1}^{N} w_i\right)^2}{\left(\sum_{i=1}^{N} {w_i}^2\right)}.$$

A small ESS is likely to negatively impact the precision of the estimate. The ESS was calculated for each analysis set for the sotorasib treated and untreated subjects separately. For the ATT weights, all sotorasib treated

subjects from the CodeBreak 100 Study are assigned an equal weighting of one; therefore, for this group the ESS will be equal to the number of subjects.

Missing values

A propensity score analysis can only be performed when all the variables are observed, including the outcome. Covariates PD-L1 protein expression and eGFR were excluded from the propensity score model development due to high levels of missing data, particularly within the historical comparator arm. Other covariates, including smoking history, BMI, albumin, ALT and AST, had only a small proportion of missing data (n=7), and so subjects with missing values for these variables were excluded from the analysis, resulting in a reduction in sotorasib cohort size to 119. A summary of missing data is presented (Table 62).

Table 62. Summary of Missing Data

	Comparator cohort	**Sotorasib cohort**
'*KRAS mutant*' analysis – N	**225**	**126**
PD-L1 protein expression – n (%)	222 (98.7)	26 (20.6)
eGFR (mL/min/1.73m^2) – n (%)	85 (37.8)	1 (0.8)
ALT (U/L) – n (%)	12 (5.3)	1 (0.8)
Albumin (g/L) – n (%)	11 (4.9)	1 (0.8)
AST (U/L) – n (%)	11 (4.9)	1 (0.8)
BMI (kg/m^2) – n (%)	7 (3.1)	3 (2.4)
Smoking history – n (%)	0 (0.0)	3 (2.4)
'*p.G12C-only*' analysis – N	**92**	**126**
PD-L1 protein expression – n (%)	89 (96.7)	26 (20.6)
eGFR (mL/min/1.73m^2) – n (%)	29 (31.5)	1 (0.8)
ALT (U/L) – n (%)	5 (5.4)	1 (0.8)
Albumin (g/L) – n (%)	5 (5.4)	1 (0.8)
AST (U/L) – n (%)	5 (5.4)	1 (0.8)
BMI (kg/m^2) – n (%)	2 (2.2)	3 (2.4)
Smoking history – n (%)	0 (0.0)	3 (2.4)

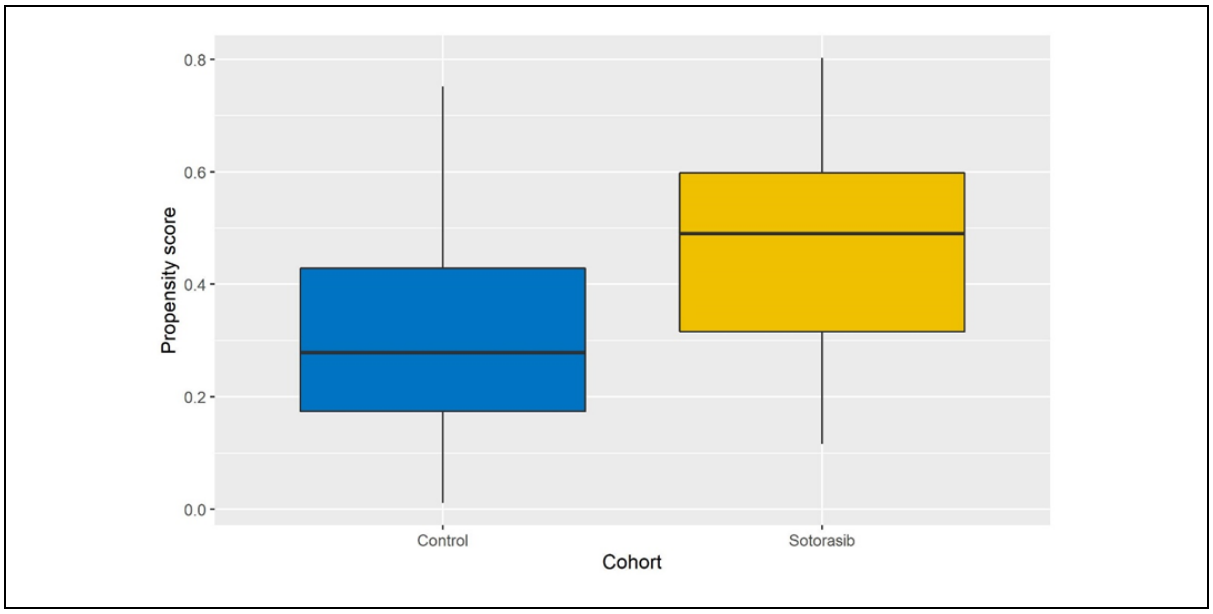
Key: ALT, alanine aminotransferase; AST, aspartate aminotransferase; BMI, body mass index; eGFR, estimated glomerular filtration rate; N, Number of subjects in the analysis set, n, Number of subjects with missing data for the corresponding covariate; PD-LI, Programmed death ligand-1

Note: Percentages are calculated with respect to the total number of subjects in the corresponding analysis set.

12.2.6 Efficacy results

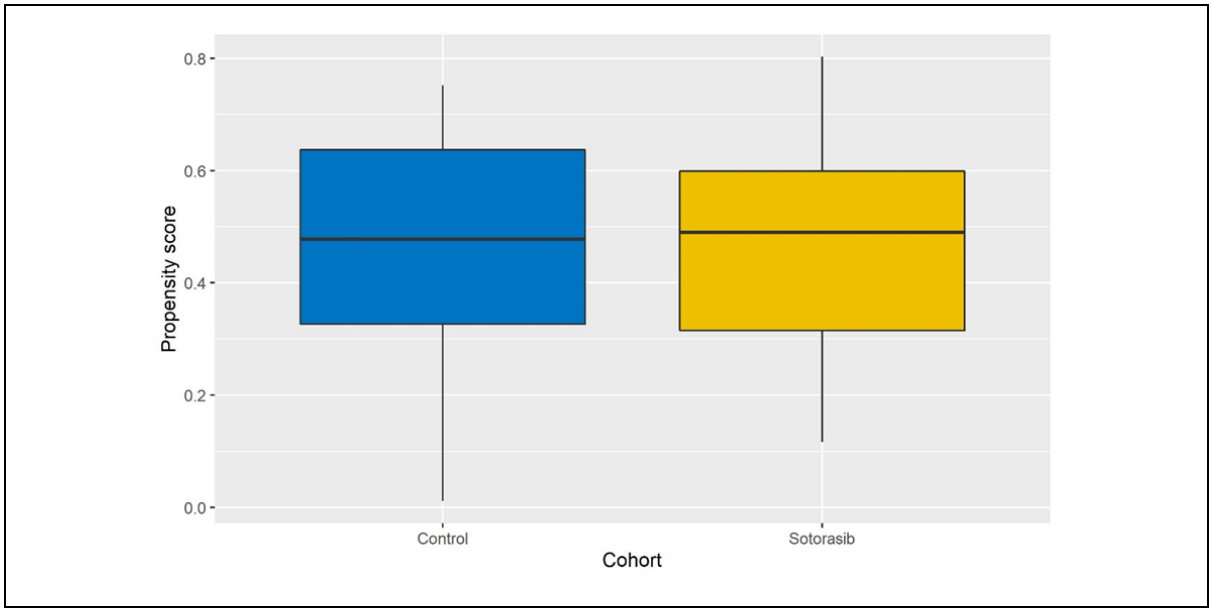
Figure 22 shows the boxplots in the KRAS Mutant Analysis Set before weighting. The distribution between both treatment arms differs substantially. After ATT weighting (Figure 23), the distribution of the propensity scores between both arms is reasonably balanced.

Figure 22. Distribution of the Propensity Score in the KRAS mutant Analysis Set Before Weighting



Key: None

Figure 23. Distribution of the Propensity Score in the KRAS mutant Analysis Set After ATT Weighting



Key: ATT, Average treatment effect of the treated

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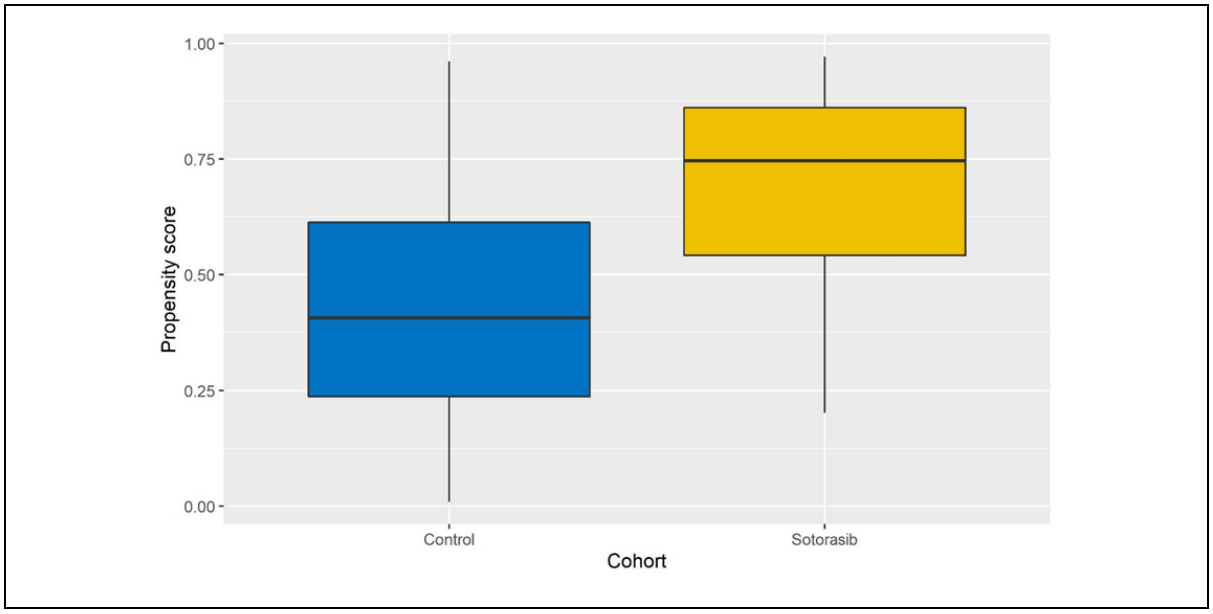
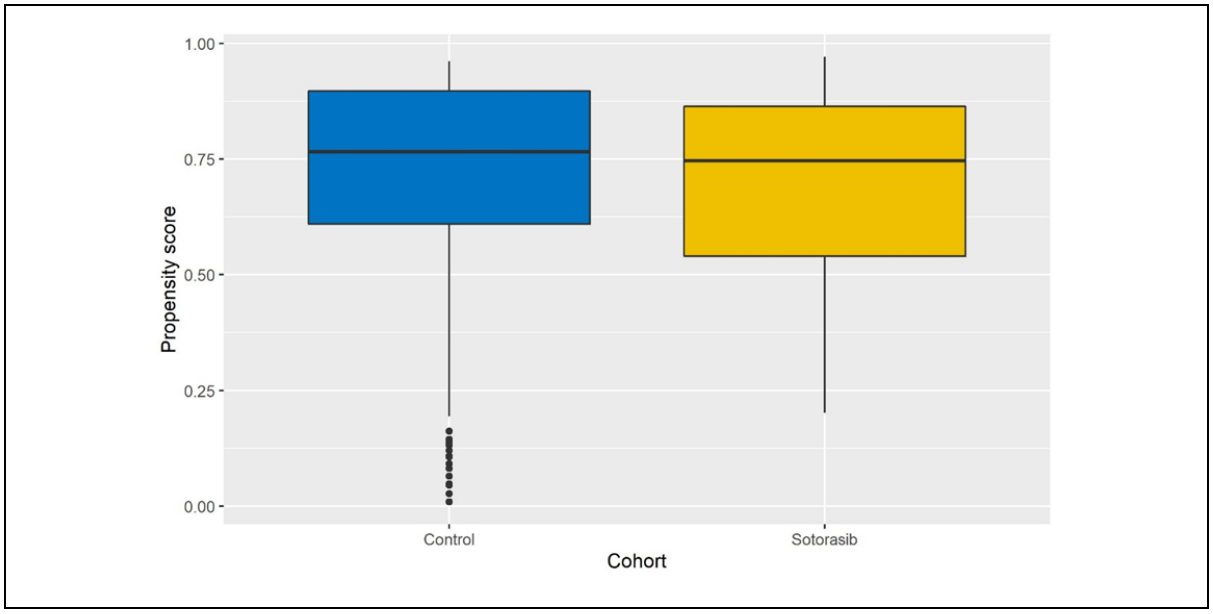
When the Flatiron cohort is restricted to G12C subjects, the balance after propensity score weighting is less good (Figure 24 and Figure 25). After ATT weighting, a noticeable difference in the lower quartile was observed. Furthermore, there is a series of subjects classified as 'outliers' which appear to occur systematically. The balance that can be achieved for the G12C-only comparator cohort is therefore less accurate and may result in uncertainty and bias.

Figure 24. Distribution of the Propensity Score in the G12C-only Analysis Set Before Weighting



Key: None

Figure 25. Distribution of the Propensity Score in the G12C-only Analysis Set After ATT Weighting

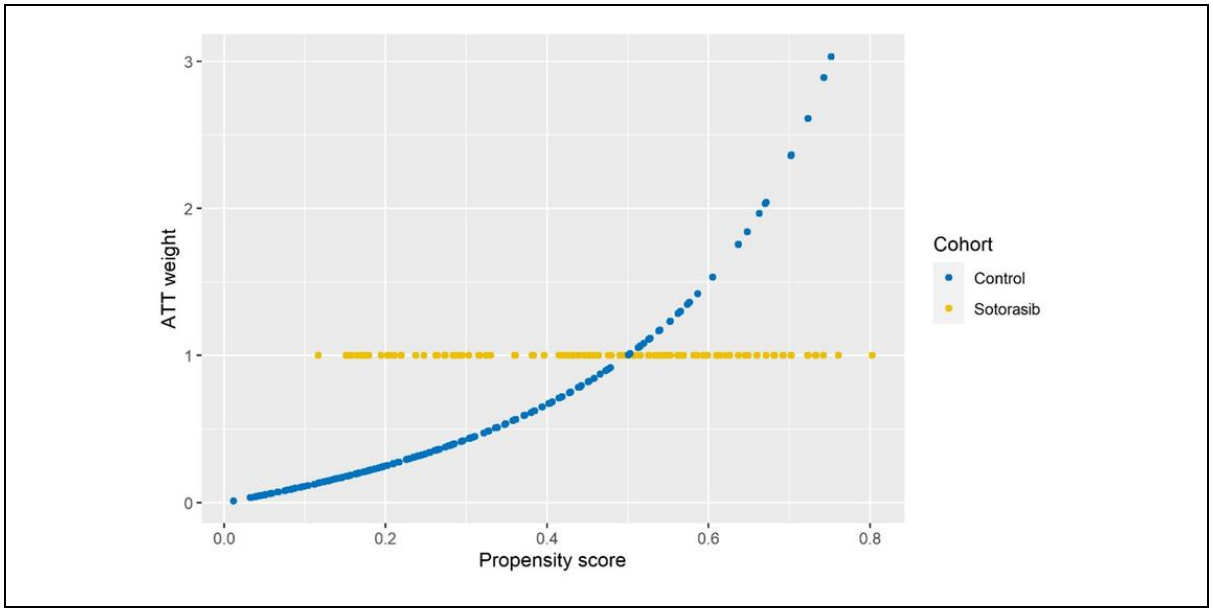


Key: ATT, Average treatment effect of the treated

The ATT weights for the KRAS Mutant Analysis set are shown in Figure 26. The corresponding sensitivity analysis for the G12C only comparator cohort is shown in Figure 27. For the KRAS mutant comparator cohort, no outliers

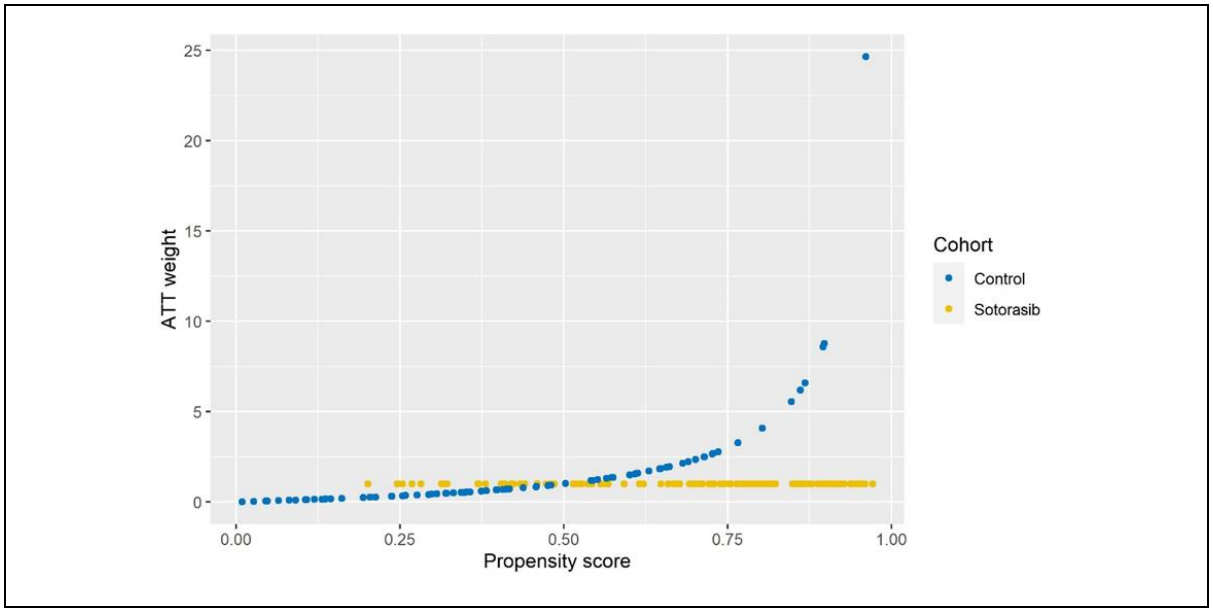
or subjects with a very high weight are observed. Conversely, for the G12C only cohort, one subject has an ATT weight of 25, whereas all other subjects have an ATT weight below 10, and the majority of subjects are below 5.

Figure 26. ATT Weights in the KRAS Mutant Analysis Set



Key: ATT, Average treatment effect of the treated

Figure 27. ATT Weights in the G12C-only Analysis Set



Key: ATT, Average treatment effect of the treated

The balance between treatment groups with respect to the baseline covariates after ATT adjustment is summarized in Figure 28. After ATT adjustment, 10 of the 19 covariates have absolute standardized differences >0.1; however, only one of these, smoking history, has a p-value < 0.05. Though this result implies a statistically significant imbalance between the two treatment groups, the difference in the proportion of patients with a

history of smoking is limited (99.5% for in the historical control vs. 95.8% for sotorasib); therefore, this is unlikely to be clinically significant.

12.2.7 Effective sample size

The effective sample size for the Flatiron control with KRAS mutation (any type) reduced from 206 (unadjusted) to 104.8 when adjusted (Table 63). The effective sample size for the Flatiron control with KRAS G-12C mutation reduced from 85 (unadjusted) to 17.8 when adjusted.

Table 63. Effective sample size

	Control	Sotorasib
KRAS mutant		
Unadjusted	206	119
Adjusted (ATT)	104.8	119
G12C		
Unadjusted	85	119
Adjusted (ATT)	17.8	119

Key: ATT, Average treatment effect of the treated

12.2.8 Propensity score analysis results

This section presents the model outcomes for the balance of all covariates for CodeBreak 100, Flatiron KRAS G12C and KRAS mutation. The results for KRAS G12C and KRAS mutant respectively are presented for Model 1 (Figure 28 and Figure 29), Model 2 (Figure 30 and Figure 31) and Model 3 (Figure 32 and Figure 33).

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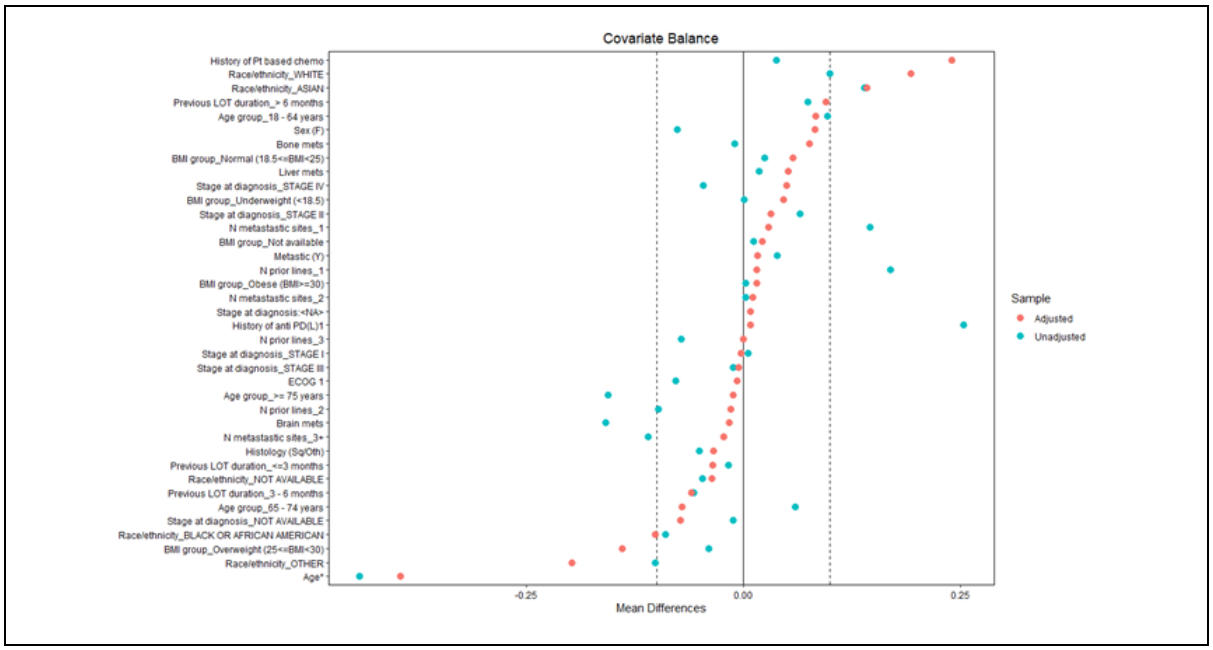
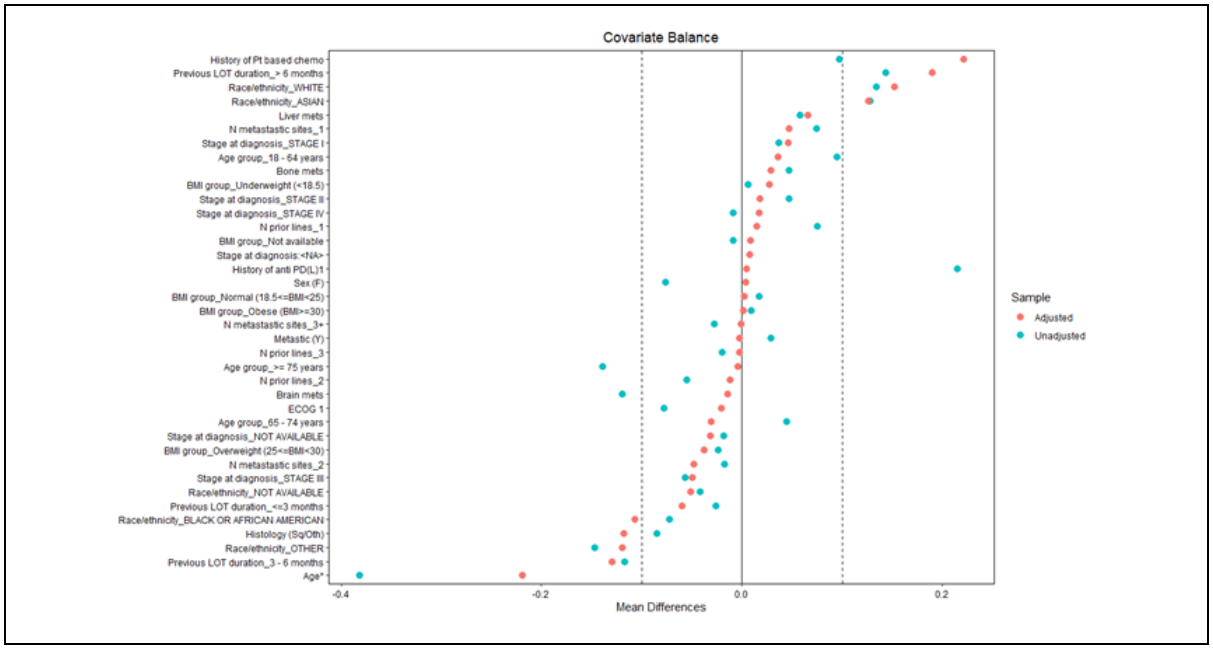
Figure 28. Propensity Score Model 1. Balance of All Covariates. Flatiron KRAS G12C



Key: BMI, body mass index; DUR, duration; ECOG, European Co-operative Oncology Group; ETHN, ethnicity; GRP, group; MET, metastatic; PREV, previous

Note: Balance was assessed by mean differences for binary/categorical outcomes and by standardized mean differences for continuous variables, with a difference of > 10% considered imbalanced

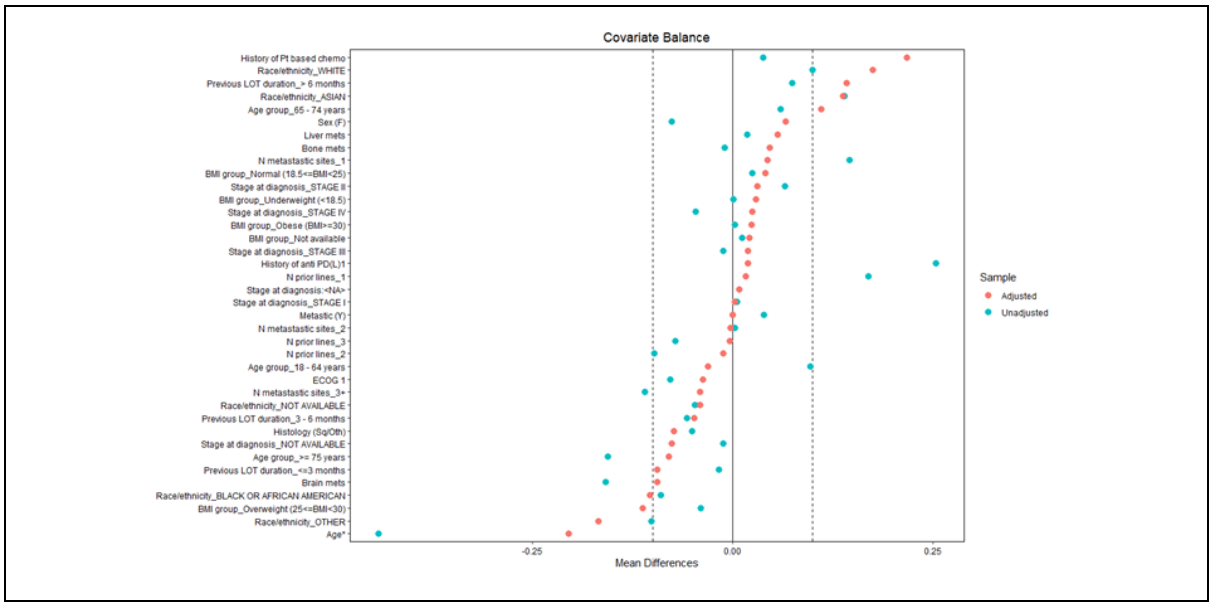
Figure 29. Propensity Score Model 1. Balance of All Covariates. Flatiron KRAS Mutant



Key: BMI, body mass index; DUR, duration; ECOG, European Co-operative Oncology Group; ETHN, ethnicity; GRP, group; MET, metastatic; PREV, previous

Note: Balance was assessed by mean differences for binary/categorical outcomes and by standardized mean differences for continuous variables, with a difference of > 10% considered imbalanced

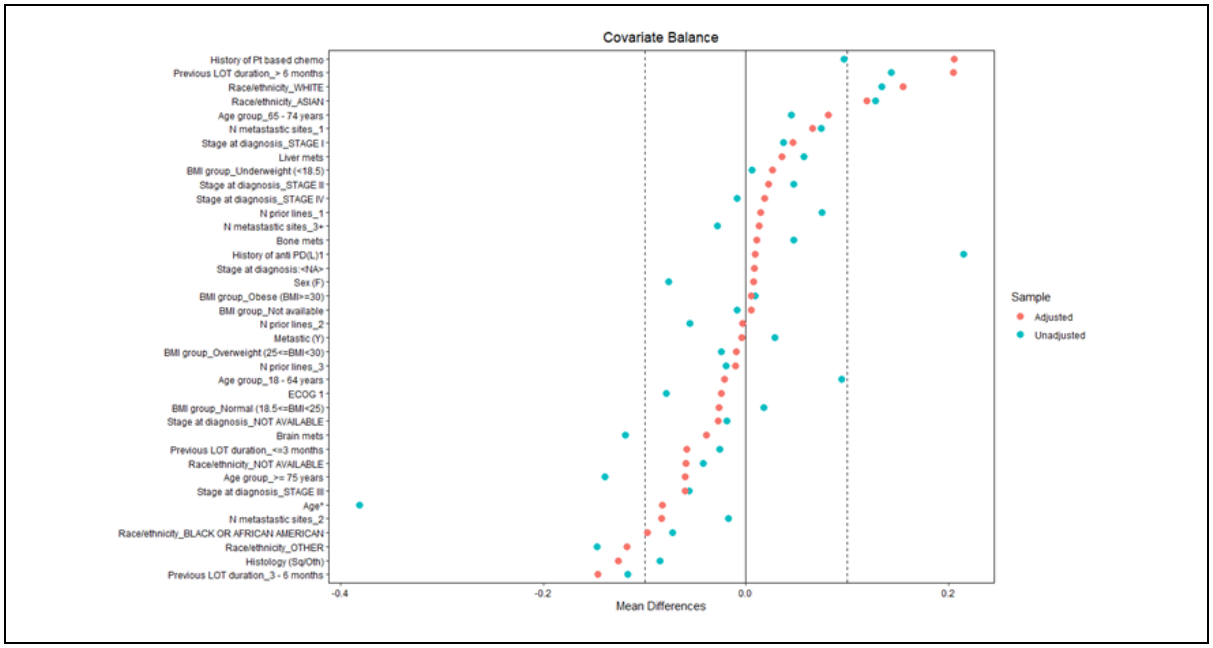
Figure 30. Propensity Score Model 2. Balance of All Covariates. Flatiron KRAS G12C



Key: BMI, body mass index; DUR, duration; ECOG, European Co-operative Oncology Group; ETHN, ethnicity; GRP, group; MET, metastatic; PREV, previous

Note: Balance was assessed by mean differences for binary/categorical outcomes and by standardized mean differences for continuous variables, with a difference of > 10% considered imbalanced

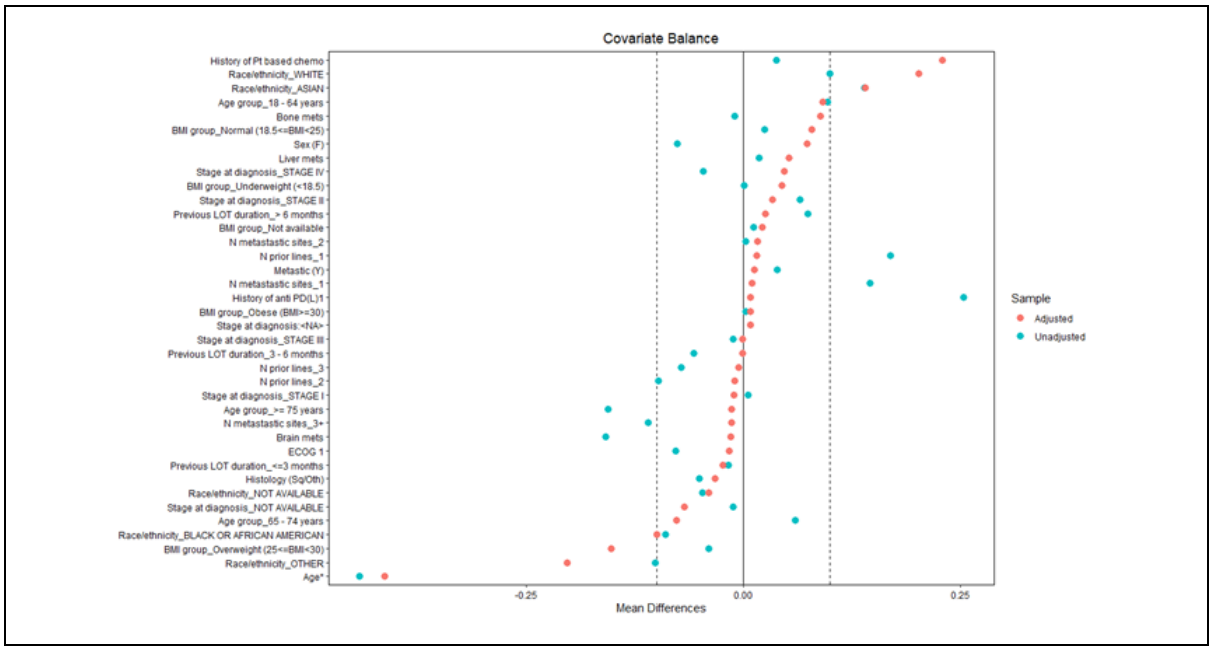
Figure 31. Propensity Score Model 2. Balance of All Covariates. Flatiron KRAS Mutant



Key: BMI, body mass index; DUR, duration; ECOG, European Co-operative Oncology Group; ETHN, ethnicity; GRP, group; MET, metastatic; PREV, previous

Note: Balance was assessed by mean differences for binary/categorical outcomes and by standardized mean differences for continuous variables, with a difference of > 10% considered imbalanced

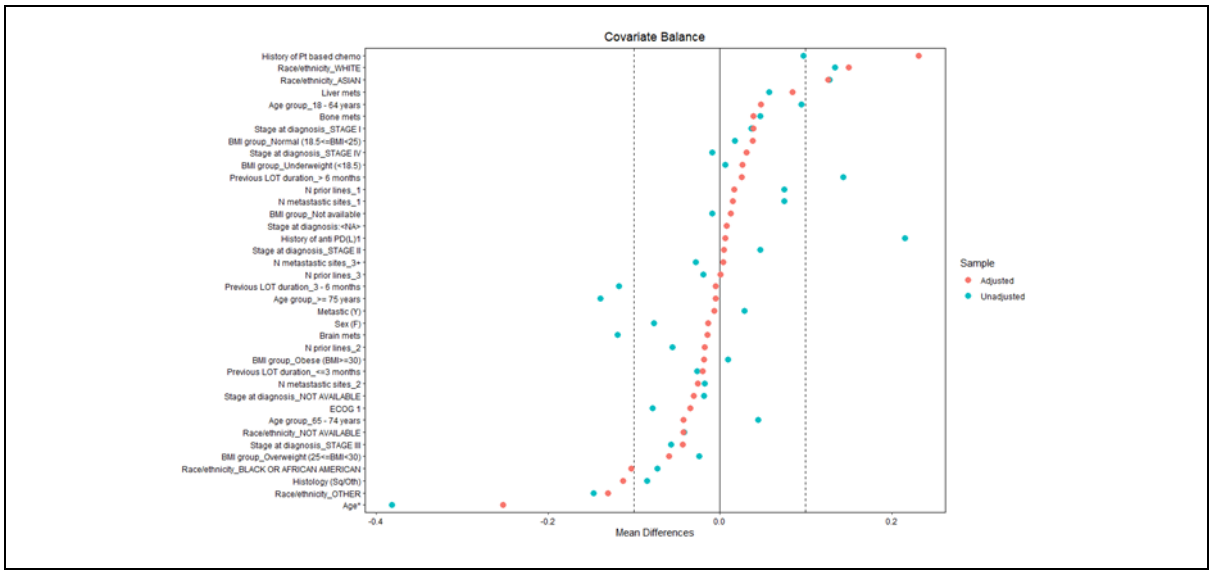
Figure 32. Propensity Score Model 3. Balance of All Covariates. Flatiron KRAS G12C



Key: BMI, body mass index; DUR, duration; ECOG, European Co-operative Oncology Group; ETHN, ethnicity; GRP, group; MET, metastatic; PREV, previous

Note: Balance was assessed by mean differences for binary/categorical outcomes and by standardized mean differences for continuous variables, with a difference of > 10% considered imbalanced

Figure 33. Propensity Score Model 3. Balance of All Covariates. Flatiron KRAS Mutant



Key: BMI, body mass index; DUR, duration; ECOG, European Co-operative Oncology Group; ETHN, ethnicity; GRP, group; MET, metastatic; PREV, previous

Note: Balance was assessed by mean differences for binary/categorical outcomes and by standardized mean differences for continuous variables, with a difference of > 10% considered imbalanced

12.3 Chemotherapy-based standard of care using Flatiron

The objective of this analysis was to compare OS and PFS in patients with advanced NSCLC with *KRAS G12C* mutation from the Phase II portion of the CodeBreak 100 study to the Flatiron chemotherapy-treated real-world cohort. The rationale of this analysis was to address some of the key limitations of the MAIC analysis: (i) as patients from the SELECT-1 trial were naive to anti PD-(L)1 treatment, which does not represent current clinical and reimbursement landscapes (ii) to address potential bias in the unanchored MAIC adjustment.

12.3.1 Flatiron database

The FIH-FMI CGDB database (Amgen data on file 2020d) is a real-world data base which links the Flatiron Health electronic health record to the comprehensive genomic profiling database from Foundation Medicine and contains over 25,000 cancer patients treated in over 275 community oncology centres in the US from January 2011 onwards (Singal et al. 2019). The database identified NSCLC patients with a positive test for *KRAS G12C* mutation and recorded their treatment patterns and clinical outcomes.

Although some patients (<20%) in the Phase II trial have not received an anti-PD-(L)1-based treatment in any previous line, it is expected that at the time of sotorasib launch, most patients eligible to receive sotorasib will have been treated with a prior anti PD-(L)1 therapy in the majority of countries. To reflect current and future practice, PD-1 therapy is not included and the treatment basket in the matched historical cohort included patients treated with chemotherapy only.

The inclusion of the database was done to address the key limitations of the MAIC using the outcomes observed in real world practice and to help demonstrate the robustness of the analysis using an alternative approach.

12.3.2 Propensity score weighting analysis overview

The propensity score weighting analysis (PWSA) was conducted to qualitatively compare the benefit of sotorasib vs. chemotherapy-based standard of care treatments. The approach attempted to mimic the effect of randomization by creating a balance between the sotorasib treated and the chemotherapy-treated real-world patients with respect to important available baseline covariates that determine both the propensity for a patient to be treated (with the treatment under evaluation) and a patient's prognosis. To mimic the treatment effect compared to a hypothetical comparator arm in the CodeBreak 100 trial, the ATT was calculated, assigning weights to the subjects in the comparator arm (Flatiron propensity weighting score analysis).

The advantage of utilizing a propensity score analysis is to create a balance across multiple observed factors that are thought to affect prognosis between the sotorasib -treated subjects in the Phase II portion of CodeBreak 100 and a historical comparator arm comprised of patients from the FIH-FMI CGDB. Such a balance, if adequately achieved, would limit bias and thus reinforce the validity of a statistical comparison of the clinical outcomes of sotorasib treated subjects vs. patients treated with chemotherapy-based standard of care.

Due to sample size restrictions, and based on clinical expertise, the comparator cohort captured 206 patients with any KRAS mutation; including 85 patients with *KRAS G12C* . The rationale for restricting this analysis to chemotherapy-based treatment was to achieve a comparison most relevant for future reimbursement situations. In particular, PD-(L)1 therapy was disregarded from the comparator arm, as it is normally used in 1L in current clinical practice (clinical advisory board (11 February 2011) conducted by Amgen (138).

For validity assessment, a Cox regression model was also run where the comparator cohort was restricted to KRAS G12C patients only. The intention of this analysis was to demonstrate the consistency of the results with the KRAS-mutant cohort and to demonstrate the implications on stochastic uncertainty. Due to the small

effective sample size of 17.8 patients in the comparator arm, the KRAS-p.G12C cohort was not suitable for parametric curve fitting.

Similar to the MAIC analyses, data with DCO 15 March 2021 from the CodeBreak 100 trial were used. The Flatiron database covered the period from 01 January 2011 to 30 September 2020. To allow for a minimum follow up of 6 months, patients were included in the analysis if their index date (start date of selected line of therapy) was on or before 31 March 2020,

12.3.2.1 Propensity score weighting analysis results

For the main 'KRAS mutant' analysis, in addition to the 'very important' covariates that were included in the propensity score model by default (baseline ECOG score, presence of brain metastases, metastatic status at baseline, and presence of other gene alterations (EGFR, ALK, BRAF, or ROS-1)), the following 'somewhat important' covariates were included in the model based on the variable selection procedure: age, number of prior lines of therapy, treatment with prior PD-1 or PD-L1 immunotherapy, treatment with prior platinum-based chemotherapy, and albumin at baseline. For the exploratory 'p.G12C-only' analysis, the propensity score model included the same covariates as the 'KRAS mutant' analysis, plus BMI at baseline, and presence of liver metastases at baseline.

Baseline covariates included in the propensity score model before and after ATT adjustment are summarized in Table 64 and Table 65 for the main 'KRAS mutant' analysis and exploratory 'p.G12C-only' analysis, respectively. These outcomes show that, after weighting, covariates included in the propensity score model were well balanced between cohorts for the 'KRAS mutant' analysis, with no standardized differences exceeding the range of -0.1 to 0.1. However, in the 'p.G12C-only' analysis, 3 of the 11 covariates included in the propensity score model exhibited standardized differences <-0.1 or >0.1 (for at least one level in the case of categorical variables). Full lists of baseline characteristics and standardized differences (before and after ATT adjustment) are shown in **Error! Reference source not found.** and **Error! Reference source not found.**.

Table 64. Covariates Included in the Propensity Score Model Before and After ATT Adjustment – 'KRAS mutant' Analysis

	Before Adjustment		After ATT Adjustment
Baseline characteristic	**Control**	**Sotorasib**	**Control**
ECOG: 1	74.27%	70.59%	70.46%
Brain metastasis: Yes	28.16%	21.01%	20.89%
Metastatic: Yes	92.72%	97.48%	97.88%
Presence of EGFR/ALK/BRAF/ROS-1 mutation	8.25%	3.36%	3.43%
Age (categories)			
18 to 64 years	43.20%	52.10%	50.82%
65 to 74 years	33.98%	39.50%	41.02%
≥ 75 years	22.82%	8.40%	8.15%
Number of prior lines of therapy			

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1	36.41%	44.54%	47.27%
2	40.29%	31.93%	30.45%
3	23.30%	23.53%	22.28%
Prior PD-(L)1 immunotherapy: Yes	73.30%	90.76%	90.64%
Prior platinum-based chemotherapy: Yes	84.47%	89.08%	89.39%
Albumin (g/L)	37.26	38.00	38.00

Key: AST, aspartate transaminase; BMI, body mass index; ECOG, Eastern Cooperative Oncology Group, eGFR, estimated glomerular filtration rate; PD-1, programmed cell death protein 1; PD-L1, programmed death-ligand 1

Note: Values correspond to sample means for continuous variables (albumin) and proportions for categorical variables

Table 65. Covariates Included in the Propensity Score Model Before and After ATT Adjustment – 'p.G12C-only' Analysis

	Before Adjustment		After ATT Adjustment
Baseline characteristic	**Control**	**Sotorasib**	**Control**
ECOG: 1	70.59%	70.59%	72.27%
Brain metastasis: Yes	30.59%	21.01%	21.75%
Metastatic: Yes	90.59%	97.48%	98.06%
Presence of EGFR/ALK/BRAF/ROS-1 mutation	8.24%	3.36%	2.14%
Age (categories)			
18 to 64 years	41.18%	52.10%	41.22%
65 to 74 years	35.29%	39.50%	51.17%
≥ 75 years	23.53%	8.40%	7.61%
BMI (kg/m2)	26.25	25.29	24.98
Number of prior lines of therapy			
1	34.12%	44.54%	55.25%
2	40.00%	31.93%	25.51%
3	25.88%	23.53%	19.24%
Liver metastasis: Yes	14.12%	21.01%	34.98%
Prior PD-(L)1 immunotherapy: Yes	65.88%	90.76%	91.08%
Prior platinum-based chemotherapy: Yes	87.06%	89.08%	90.18%
Albumin (g/L)	37.57	38.00	37.68

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Key: AST, aspartate transaminase; BMI, body mass index; ECOG, Eastern Cooperative Oncology Group, eGFR, estimated glomerular filtration rate; PD-1, programmed cell death protein 1; PD-L1, programmed death-ligand 1

Note: Values correspond to sample means for continuous variables (BMI and albumin) and proportions for categorical variables

12.3.2.1.1 Treatment regimens in the comparator cohort

The number and proportion of patients in the control cohort receiving each category of chemotherapy-based treatment, before and after ATT-weighting, is shown inTable 66. Overall, ATT-weighting decreased the proportion of patients receiving platinum-based chemotherapy (from 31.07% to 23.04% in the main 'KRAS mutant' analysis), and increased the proportion treated with docetaxel in combination with ramucirumab (from 21.84% to 34.20% in the 'KRAS mutant' analysis). Around 10% of the comparator cohort were taking docetaxel monotherapy. The pragmatic assumption that the outcomes with this mix of chemotherapy regimens sufficiently reflect outcomes with docetaxel monotherapy is likely to be conservative and underestimate the relative effectiveness of sotorasib vs docetaxel monotherapy.

Table 66 Summary of chemotherapy treatment mix in the cohort

Regimen	Unweighted cohort		ATT-weighted cohort	
	n	% of cohort	n	% of cohort
KRAS mutant population				
	(N = 206)		**(N = 120.57)**	
Platinum-based chemotherapy	64	31.07%	27.78	23.04%
Chemotherapy monotherapy (excluding docetaxel)	61	29.61%	32.48	26.94%
Docetaxel plus ramucirumab	45	21.84%	41.24	34.20%
Docetaxel monotherapy	21	10.19%	12.16	10.09%
Other chemotherapy-based regimens	15	7.28%	6.91	5.73%
KRAS p.G12C mutated population				
	(N = 85)		**(N = 133.11)**	
Platinum-based chemotherapy	25	29.41%	23.83	17.90%
Chemotherapy monotherapy (excluding docetaxel)	24	28.24%	30.42	22.85%
Docetaxel plus ramucirumab	18	21.18%	64.17	48.21%
Docetaxel monotherapy	11	12.94%	8.56	6.43%
Other chemotherapy-based regimens	7	8.24%	6.13	4.61%

12.3.2.2 Results

The effective sample size of the comparator arm was 104.8 for the KRAS mutant cohort and 17.8 for the p.G12C only cohort. The OS HR (95% CI) based on the Cox model for the was estimated at [redacted] for the KRAS mutant population (**Error! Reference source not found.**), and [redacted]) for the p.G12C only cohort. Correspondingly, the PFS HR (95% CI) based on the Cox model was estimated at [redacted] for the KRAS mutant cohort and [redacted] for the p.G12C only cohort.

[redacted]

	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]		

12.3.2.3 Overall survival

Parametric model fitting was carried out to the OS KM data for KRAS mutant chemotherapy patients in line with the methods detailed in NICE DSU TSD 14 (88). Standard parametric distributions were fitted to the unadjusted KM data with independent fitting and joint fitting (unrestricted and restricted models) approaches using the statistical software R (ver. 4.0.3) and the corresponding '*flexsurv*' package. The parametric distributions modelled included the exponential, Weibull, Gompertz, generalized gamma, log-normal and log-logistic distribution.

The vast majority of goodness-of-fit statistics were pointing to the log-normal distribution (Table 67). Solely the independent fit of the Flatiron cohort, based on the BIC, not based on the AIC was pointing to the exponential distribution which has one parameter less. Considering all goodness-of-fit statistics jointly, the log-normal distribution was deemed most appropriately. There was no sufficient evidence which would justify selecting distribution functions which would differ across the treatment arms. For a given log-normal distribution both the AIC and the BIC were pointing to the restricted model. (Table 67).

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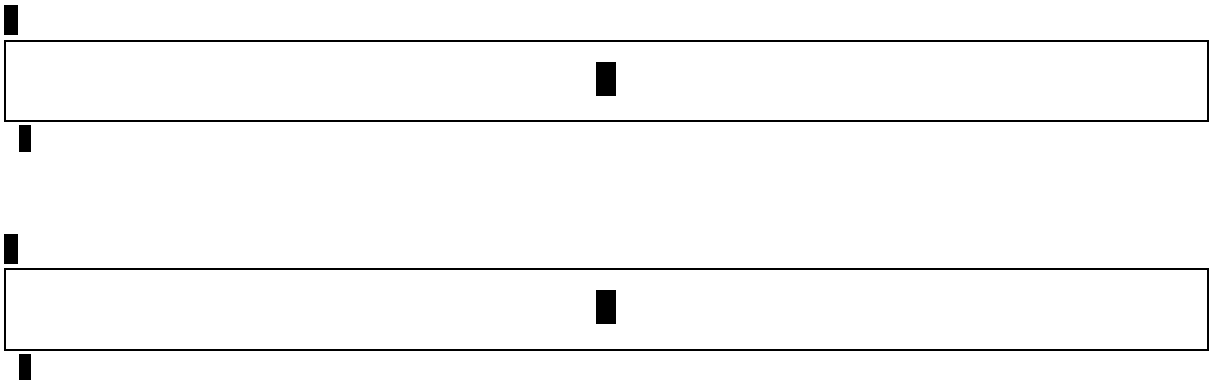
Table 67. Goodness-of-fit Statistics for Jointly-Fitted OS Models for KRAS-mutant Patients (ATT Weighting)

Model	Independent fit – sotorasib		Independent fit - chemo		Joint fit (unrestricted)		Joint fit (restricted)	
	AIC	BIC	AIC	BIC	AIC	BIC	AIC	BIC
Exponential	479.1	481.9	605.1	608.4	1084.2	1091.7	1084.2	1091.7
Gompertz	481.0	486.5	605.7	612.4	1086.7	1101.8	1085.5	1096.8
Weibull	478.5	484.0	606.6	613.2	1085.0	1100.2	1086.1	1097.4
Generalized Gamma	472.2	480.1	604.1	614.1	1076.4	1099.1	1075.8	1090.9
Loglogistic	474.9	480.5	604.6	611.3	1079.5	1094.7	1078.9	1090.3
Lognormal	472.0	477.54	602.4	609.0	1074.4	1089.5	1073.9	1085.2

Key: AIC, Akaike information criterion; BIC, Bayesian information criterion

Note: Underlined values indicate the best statistically fitting parametric distribution

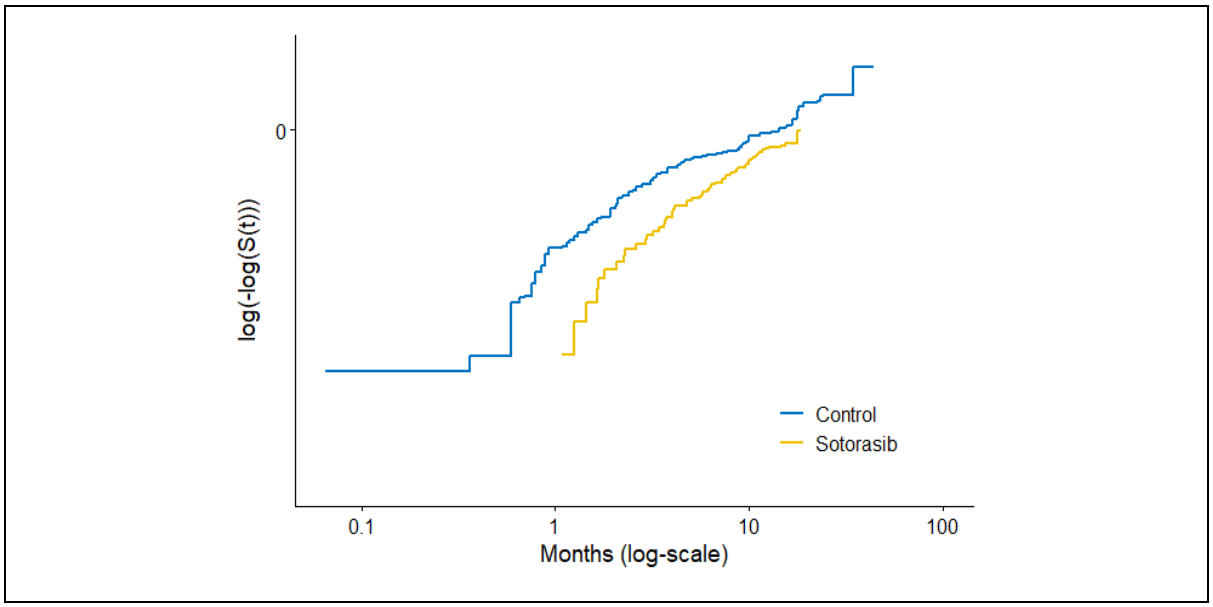
The visual fit of the ATT population KM data to the log-normal distribution extrapolations is shown in **Error! Reference source not found.** for restricted models and **Error! Reference source not found.** for unrestricted models.



Although a higher number of parameters is expected to result in an improved visual fit (unrestricted models require more parameters than restricted models), there is no evidence that the long-term projection would differ between both groups. Therefore, consistently with the goodness-of-fit statistics, the restricted log-normal distribution was selected in the base-case.

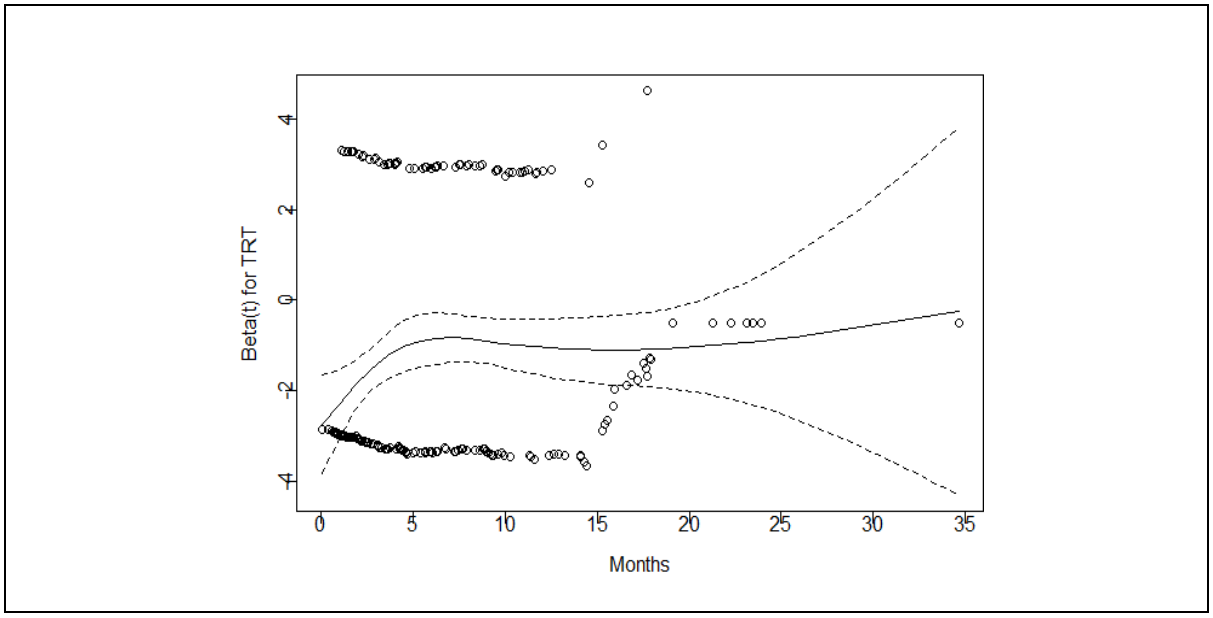
The proportional hazards assumption was evaluated for OS using the log-cumulative hazards plot (Figure 34) and the Schoenfeld residuals plot (Figure 35). These plots indicated the proportional hazards assumption was not valid. Accelerated failure time for OS was assessed using a QQ plot (Figure 36). The plot indicated some deviation either side from the fitted line but was inconclusive as to whether the assumption of accelerated failure time holds.

Figure 34. OS Log-Cumulative Hazards Plot for Sotorasib and Control



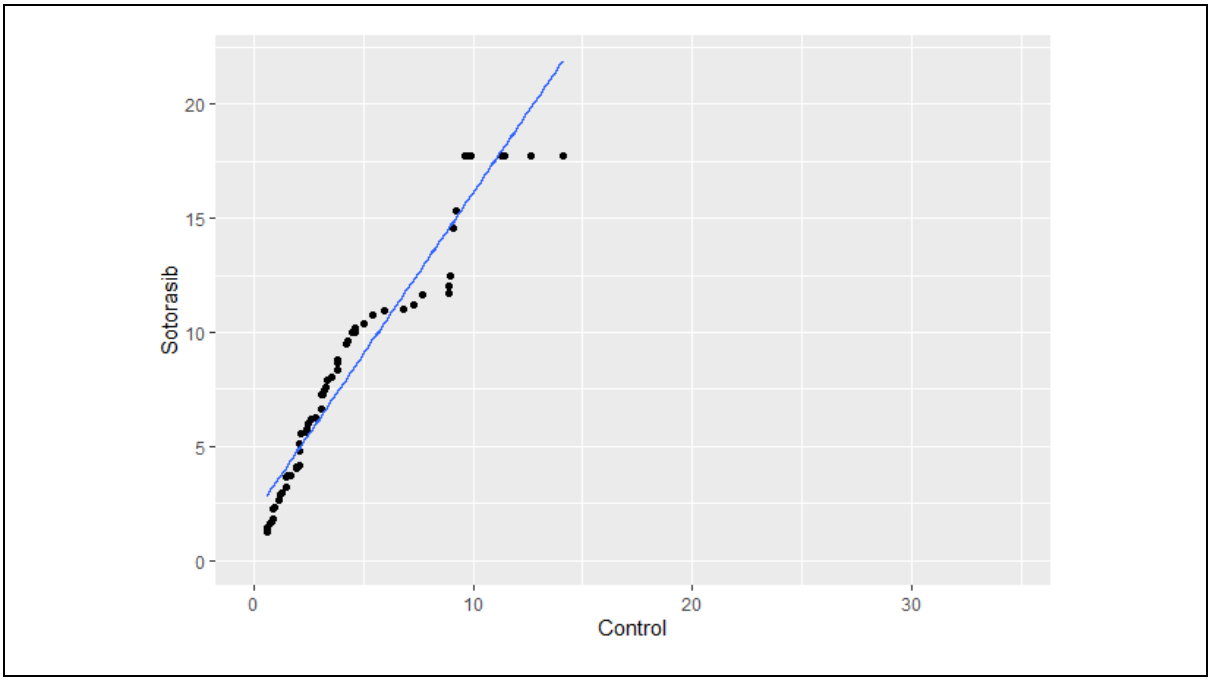
Key: OS, overall survival.

Figure 35. OS Schoenfeld Residuals Plot for Sotorasib and Control



Key: OS, overall survival.

Figure 36. OS QQ Plot for Sotorasib and Control



Key: OS, overall survival.

In summary, and to be consistent with the approaches taken in the primary analyses, the jointly fitted (restricted model) extrapolation using the log-normal distribution was used to model OS for the Flatiron dataset.

12.3.2.4 Progression-free survival

Parametric model fitting was carried out to the PFS KM data for KRAS mutant chemotherapy patients in line with the methods detailed in NICE DSU TSD 14 (88) Standard parametric distributions were fitted to the unadjusted KM data with independent fitting and joint fitting (unrestricted and restricted model) approach using the statistical software R (ver. 4.0.3) and the '*flexsurv*' package. The parametric distributions modelled included exponential, Weibull, Gompertz, generalized gamma, log-normal and log-logistic.

All of goodness-of-fit statistics (AIC and BIC for all fitted models) were pointing to the log-normal distribution (Table 68). Furthermore, both AIC and BIC were lower for the restricted model, which based on goodness-of-fit therefore is the most appropriate.

Table 68. Goodness-of-fit Statistics for Jointly Fitted PFS Models for KRAS Mutant ATT

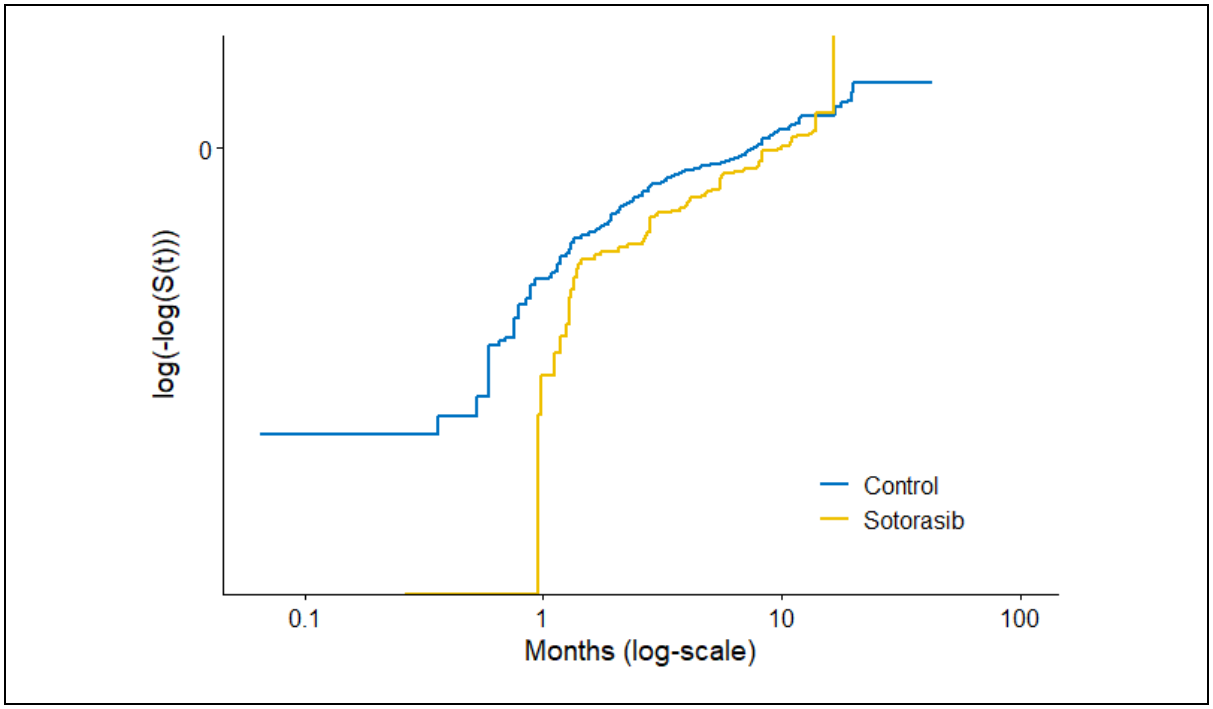
Distribution	Independent fit – sotorasib		Independent fit - chemo		Joint fit (unrestricted)		Joint fit (restricted)	
	AIC	BIC	AIC	BIC	AIC	BIC	AIC	BIC
Exponential	564.5	567.3	601.5	604.8	1166.0	1173.6	1166.0	1173.6
Gompertz	562.8	568.4	603.0	609.7	1165.8	1180.9	1167.7	1179.0
Weibull	559.5	565.1	603.4	610.1	1162.9	1178.0	1164.5	1175.8
Generalized Gamma	556.7	565.1	597.7	607.6	1154.4	1177.1	1152.3	1167.5
Loglogistic	558.8	564.4	598.8	605.4	1157.6	1172.7	1156.8	1168.1
Lognormal	554.7	560.3	595.9	602.5	1150.6	1165.7	1150.4	1161.8

Key: ATT, average treatment effect of the treated; AIC, Akaike information criterion; BIC, Bayesian information criterion; PFS, progression-free survival
Note: Underlined values indicate the best statistically fitting parametric distribution

The visual fit of the ATT population KM data to the log-normal distribution extrapolations is shown in **Error! Reference source not found.** and **Error! Reference source not found.** for restricted and unrestricted models respectively, and indicates a close visual fit of the extrapolation to the KM data.

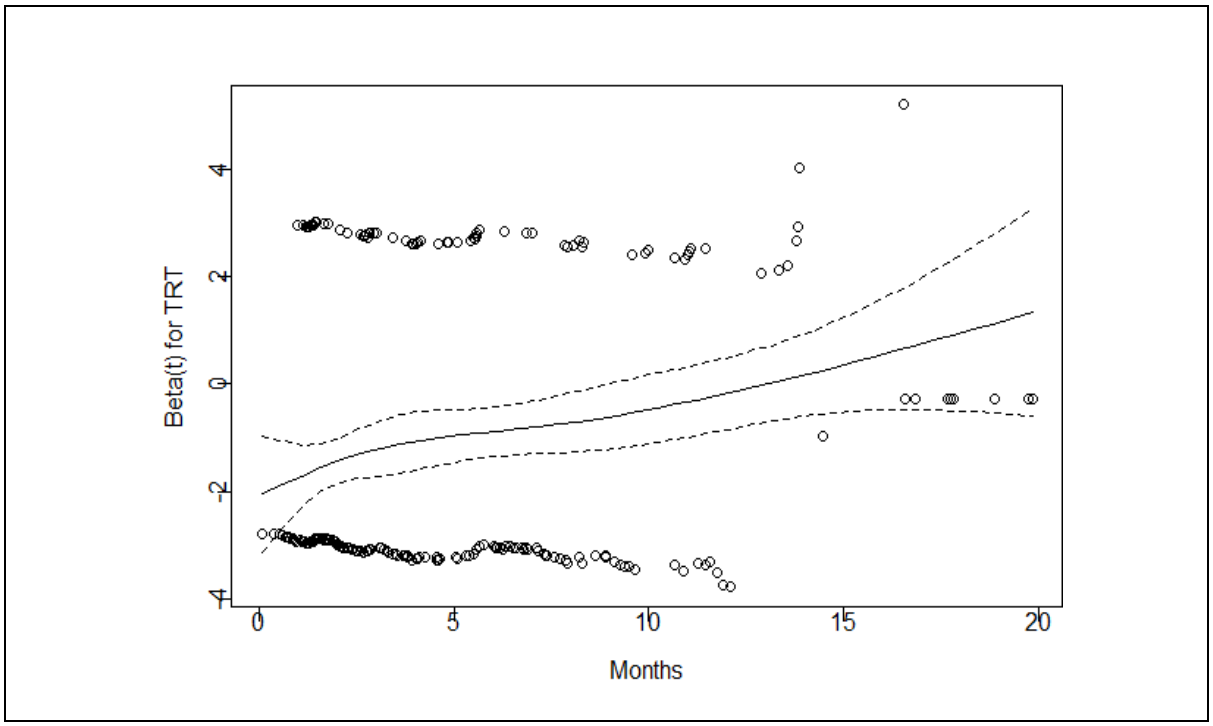
The proportional hazards assumption was evaluated for PFS using the log cumulative hazards plot (Figure 37) and the Schoenfeld residuals plot (Figure 38). These plots indicated the proportional hazards assumption was not valid. Accelerated time failure for OS was assessed using a QQ plot (Figure 39). The plot indicated some deviation either side of the fitted line, but was inconclusive as to whether the assumption of accelerated failure time holds.

Figure 37. PFS Log-Cumulative Hazards Plot for Sotorasib and Control



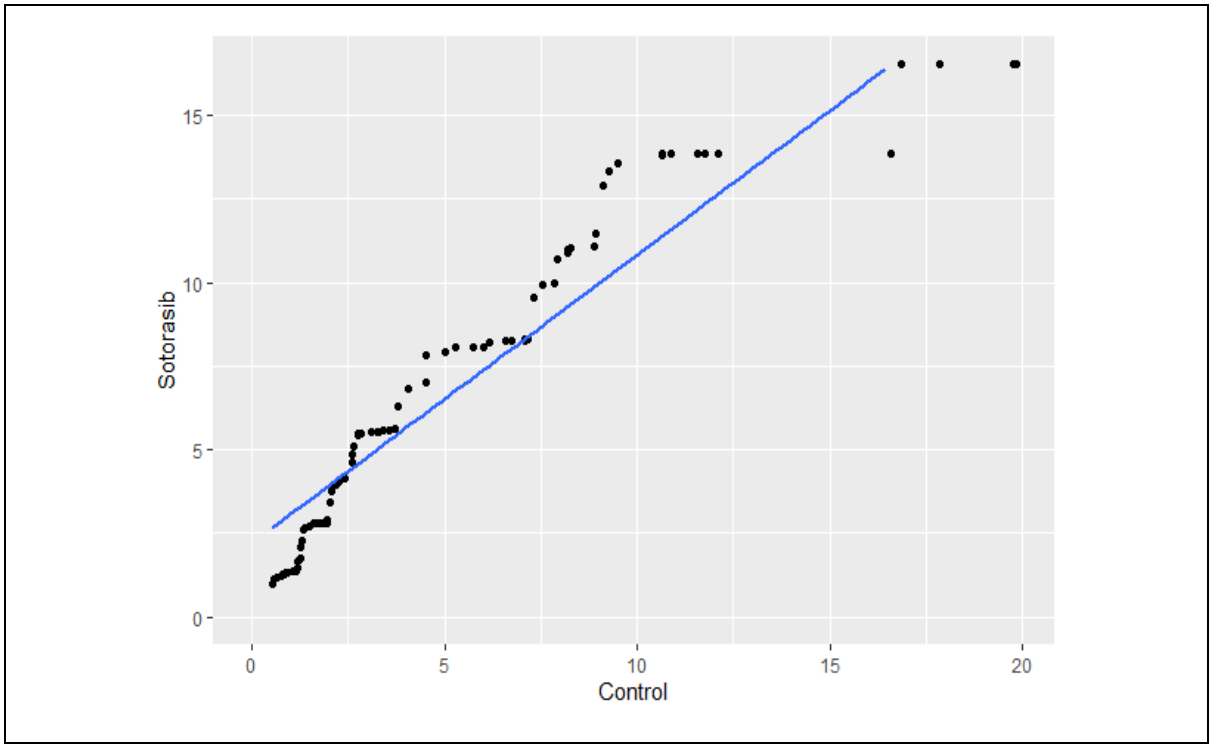
Key: PFS, progression-free survival.

Figure 38. PFS Schoenfeld Residuals Plot for Sotorasib and Control



Key: PFS, progression-free survival.

Figure 39. PFS QQ Plot for Sotorasib and Control



Key: PFS, progression-free survival.

In summary, the jointly fitted restricted extrapolation using the log-normal distribution was selected for PFS in the base-case, which was consistent with the approach used in OS and in the main comparator.

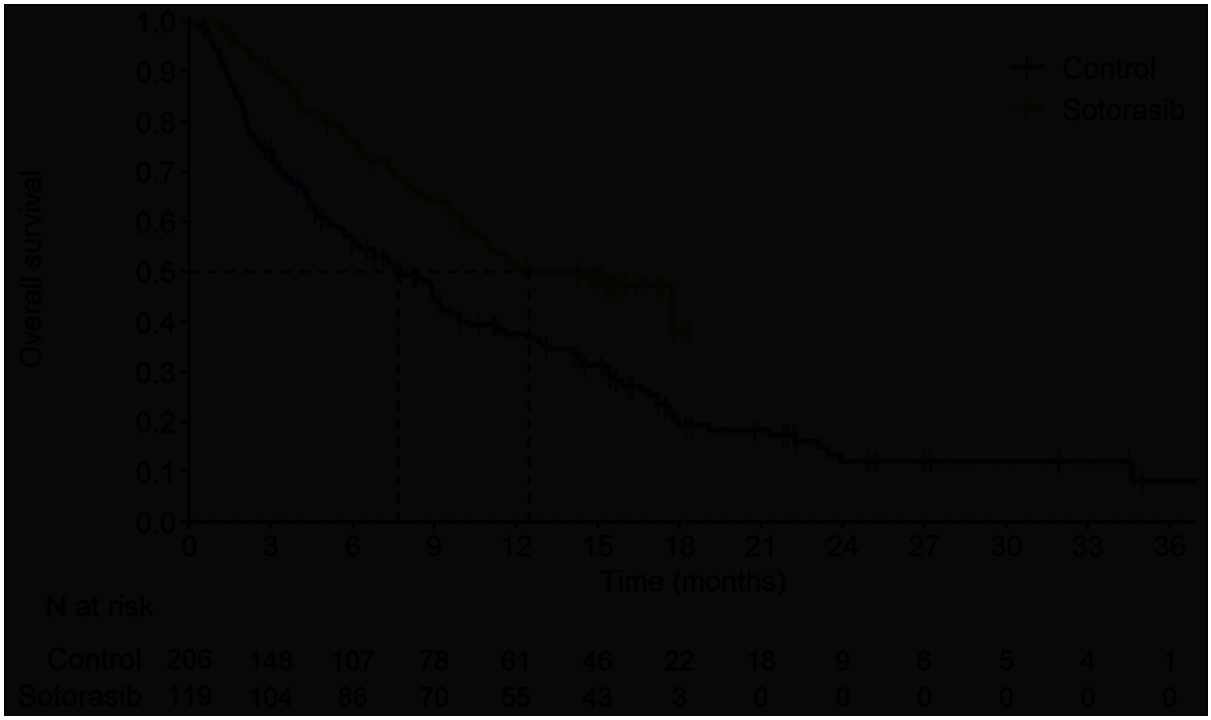
12.3.2.4.1 Results of the Propensity score weighting analysis using CodeBreaK100 and Amgen Flatiron Health real-world evidence study

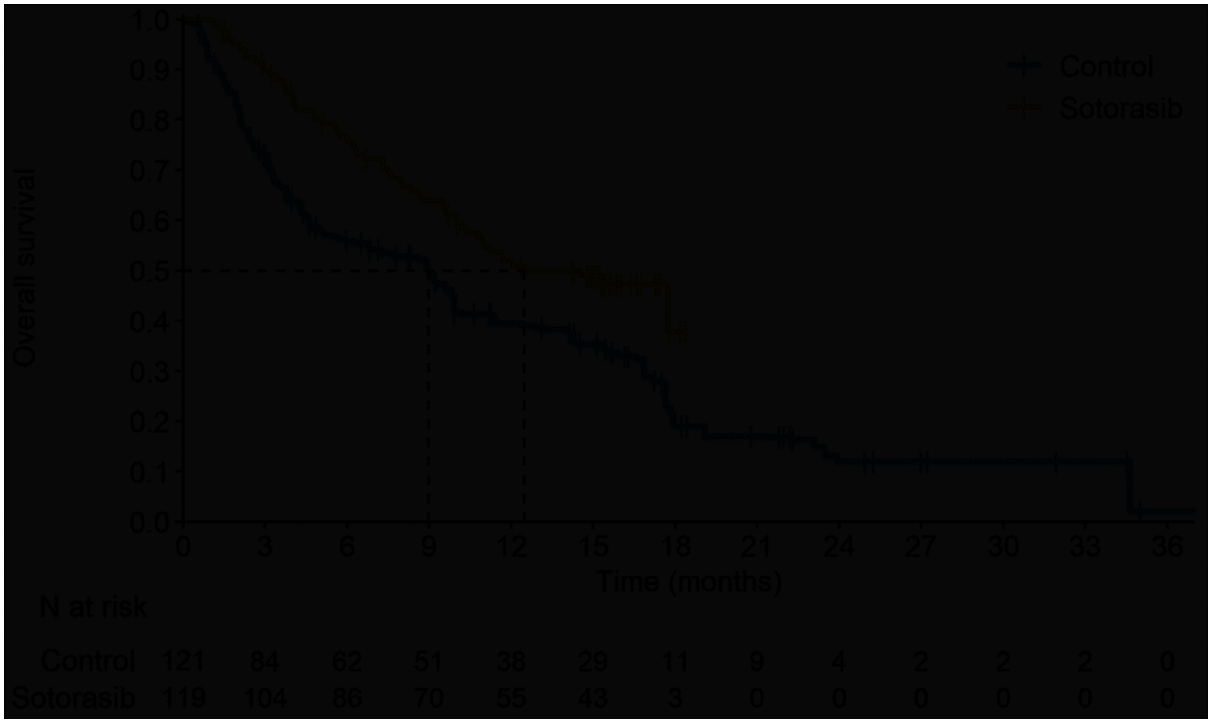
This supplementary analysis was undertaken to explore an alternative data source and method of estimating relative treatment effects for sotorasib vs docetaxel monotherapy (using the basket of standard of care chemotherapy regimens in the Amgen Flatiron real-world evidence cohort as a proxy for docetaxel monotherapy).

OS outcomes for the main '*KRAS* mutant' analysis are shown as Kaplan-Meier curves before and after ATT weighting in **Error! Reference source not found.** and **Error! Reference source not found.**, respectively. In both cases, outcomes show an OS advantage for the sotorasib cohort compared with the control cohort.

The OS hazard ratio based on the Cox proportional hazards model for sotorasib versus the control cohort was estimated at [redacted]) prior to adjustment, [redacted] after ATT adjustment, indicating that sotorasib produces a statistically significant reduction in the rate of death versus chemotherapy-based treatment.

[redacted]



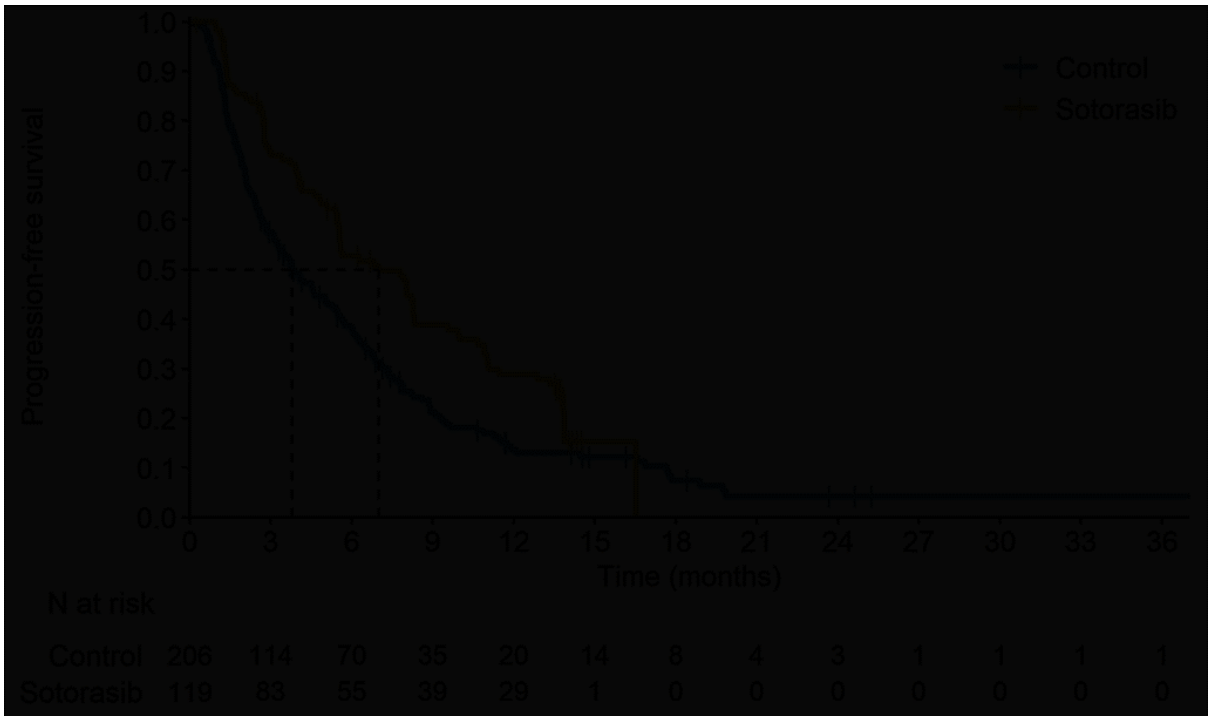


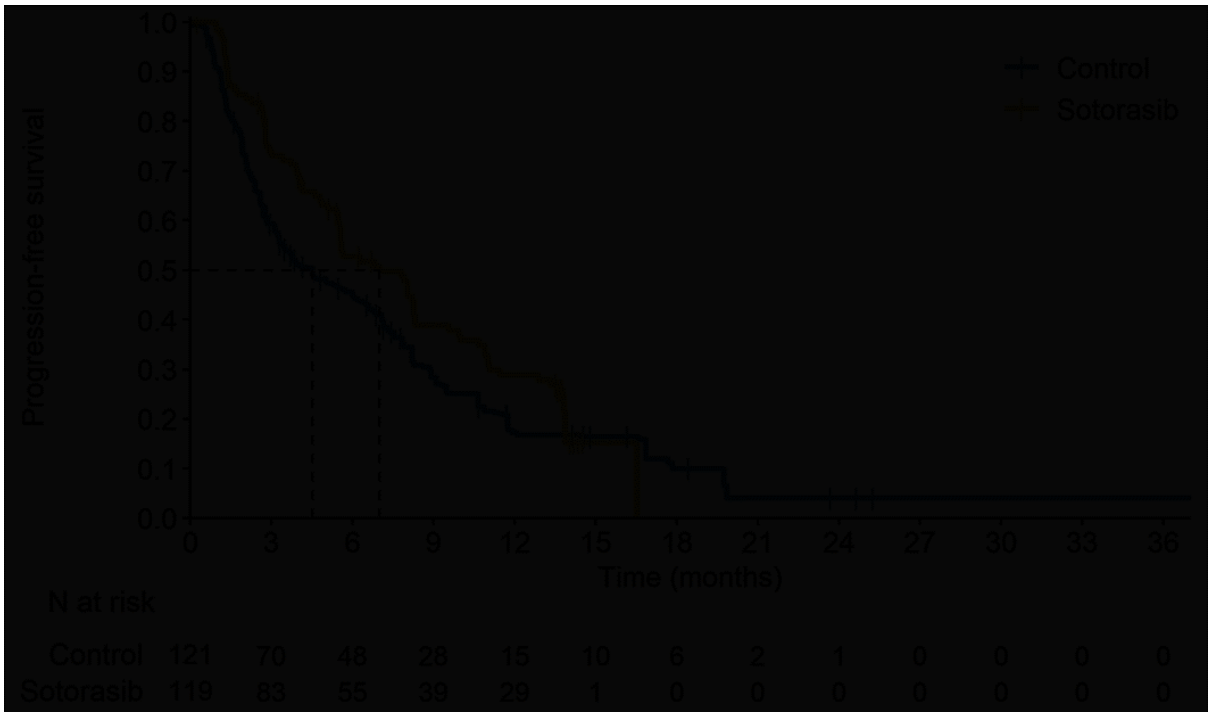
Key: ATT, Average treatment effect on the treated
Note: In the ATT-weighted analysis, the N at risk corresponds to the sum of weights in each arm

12.3.2.5 Progression-free survival

PFS outcomes for the '*KRAS* mutant' analysis are shown as Kaplan-Meier curves before and after ATT weighting in **Error! Reference source not found.** and **Error! Reference source not found.** respectively. In both cases, outcomes show that PFS is higher for the sotorasib cohort versus the control cohort.

The PFS hazard ratio for sotorasib versus the control cohort based on the Cox proportional hazards model was estimated at [redacted] prior to adjustment, and [redacted]) after ATT adjustment, indicating that sotorasib produces an improvement in PFS (although this effect is not statistically significant after ATT weighting).





Key: ATT, Average treatment effect on the treated
Note: In the ATT-weighted analysis, the N at risk corresponds to the sum of weights in each arm

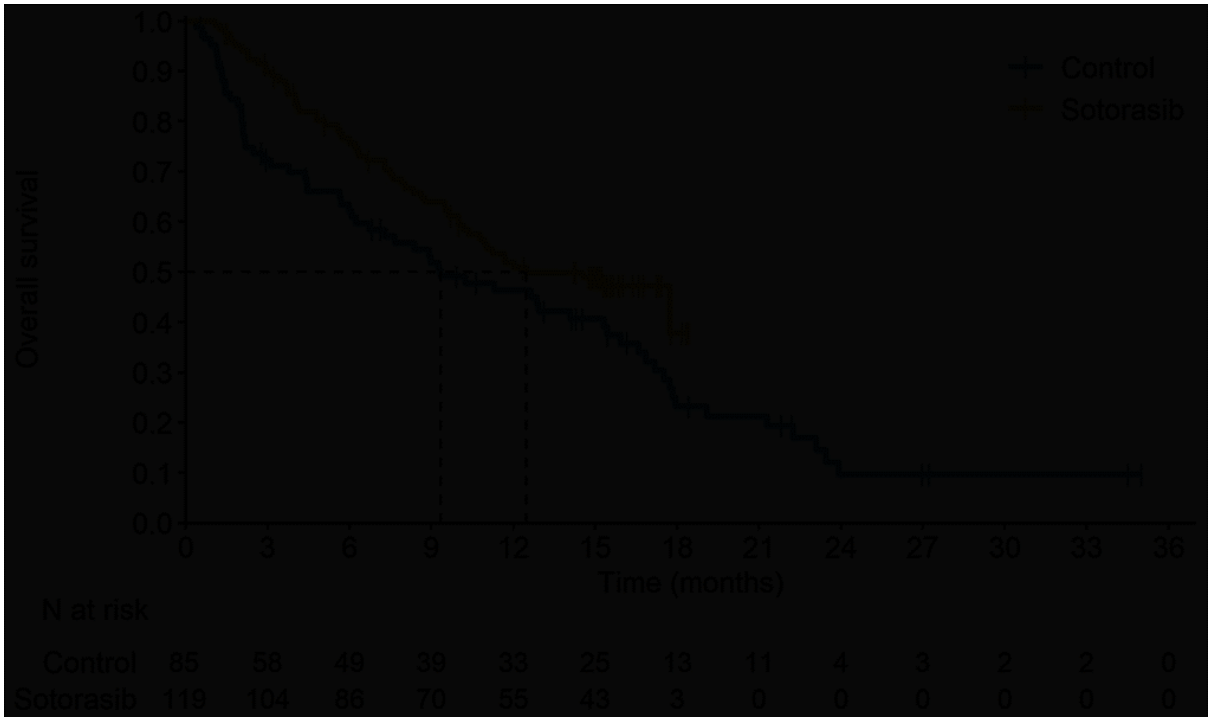
12.3.3 'p.G12C-only' analysis

12.3.3.1 Overall survival

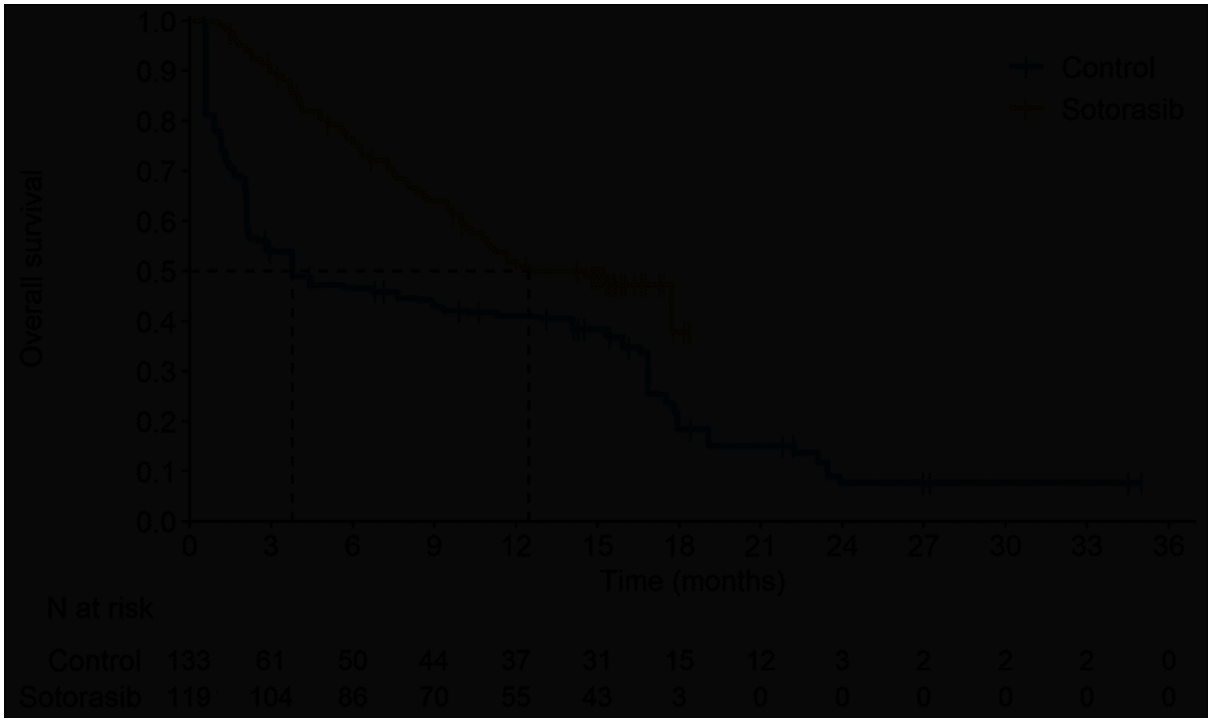
OS outcomes for the exploratory '*p.G12C*-only' analysis are shown as Kaplan-Meier curves before and after ATT weighting in **Error! Reference source not found.** and **Error! Reference source not found.**, respectively. In both cases, as with the main '*KRAS* mutant' analysis, outcomes show that OS is higher for the sotorasib cohort compared with the control cohort.

The OS hazard ratio for sotorasib versus chemotherapy based on the Cox proportional hazards model was estimated at [redacted] after ATT adjustment, indicating that sotorasib produces a statistically significant reduction in the rate of death versus chemotherapy-based treatment.

[redacted]



[redacted]

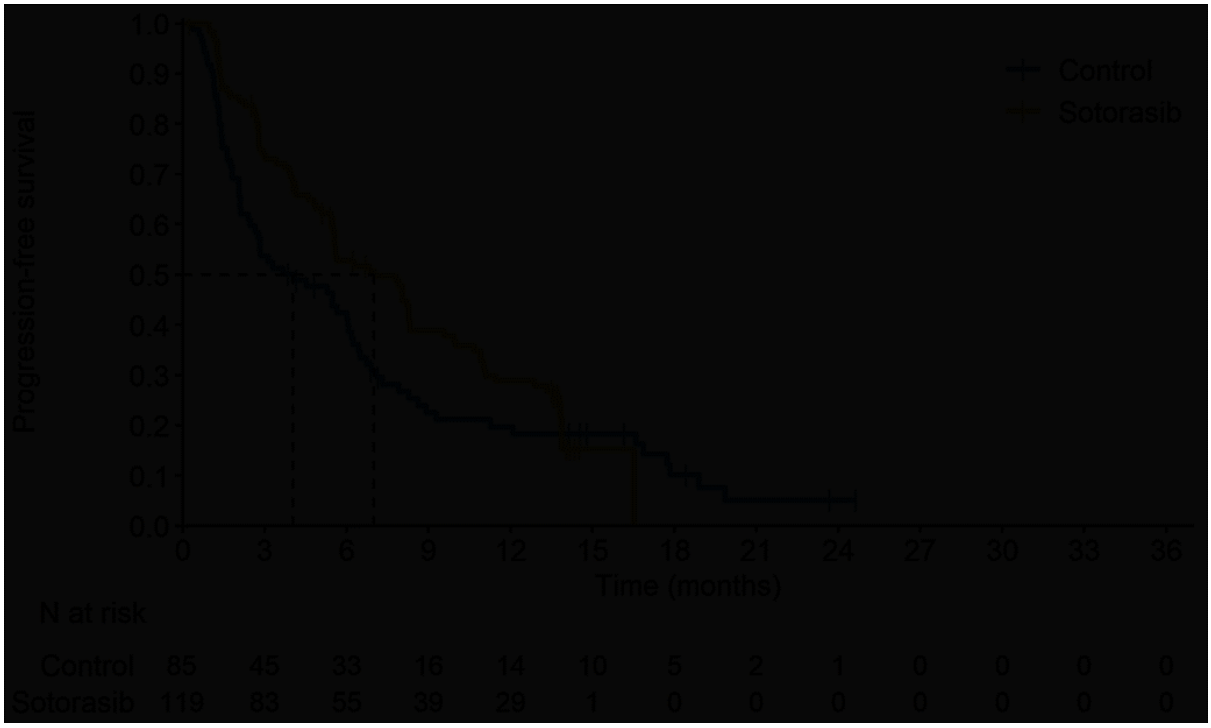


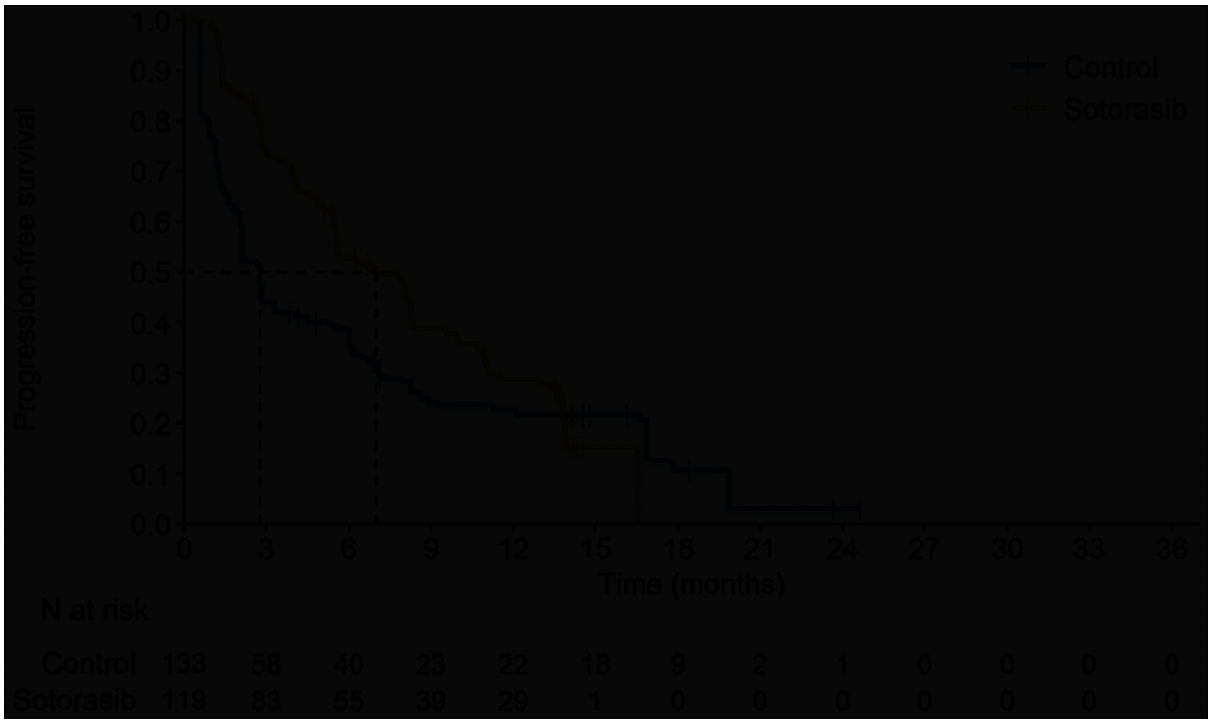
Key: ATT, Average treatment effect on the treated
Note: In the ATT-weighted analysis, the N at risk corresponds to the sum of weights in each arm

12.3.3.2 Progression-free survival

PFS outcomes for the '*p.G12C*-only' analysis are shown as Kaplan-Meier curves before and after ATT weighting in **Error! Reference source not found.** and **Error! Reference source not found.** respectively. In both cases, as with the main '*KRAS* mutant' analysis, outcomes show that PFS is higher for the sotorasib cohort versus the control cohort.

The PFS hazard ratio for sotorasib versus chemotherapy based on the Cox proportional hazards model was estimated at [redacted] after ATT adjustment, indicating that sotorasib produces an improvement in PFS (although this effect is not statistically significant).





Key: ATT, Average treatment effect on the treated
Note: In the ATT-weighted analysis, the N at risk corresponds to the sum of weights in each arm

Appendix M - HRQoL statistical methodology

Introduction

This report details the methods and results of analyses to estimate EQ-5D-5L health state utility values using data collected in the phase 2 NSCLC cohort of Study 20170543, to inform the economic models of sotorasib (AMG 510) in subjects with previously treated advanced NSCLC with KRAS G12C Mutation. The analyses described in this report are based on the 15th March 2021 data cut.

Phase 2 of Study 20170543 was a single-arm clinical trial (with AMG 510 as monotherapy), where quality of life data was collected from subjects using the following patient-reported outcome measures (PROMs): EORTC QLQ-C30, EORTC QLQ-LC13, NSCLC SAQ, PGIC, PGIS, EQ-5D-5L, and PRO-CTCAE. Utilities for health states are required for health economic modelling; therefore, the overall objective of this analysis was to provide such estimates. Additional objectives were to explore utilities over time and within subgroups.

Estimates in this report are based on Denmark-specific utilities.

Methodology

Study 20170543 (CodeBreak 100)

Phase 2 of this study was a multicentre, non-randomised, open-label, and aimed to evaluate efficacy and safety/tolerability of AMG 510 as monotherapy

PROM assessments

7 PROMs were assessed as part of this study: EORTC QLQ-C30, EORTC QLQ-LC13, NSCLC SAQ, PGIC, PGIS, EQ-5D-5L, and PRO-CTCAE. The remainder of this report will focus on the EQ-5D-5L.

PROMs were completed on Day 1 pre-dose of every cycle (cycle length: 21 days) until cycle 6, and then on Day 1 of every other cycle from cycle 7 until treatment discontinuation. Additional PROM completion occurred at the end of treatment visit and at the safety follow-up visit.

EQ-5D-5L

The EQ-5D is a generic instrument for describing and valuing health developed by the EuroQol group. It assesses health in 5 dimensions: mobility, self-care, usual activities, pain/discomfort, and anxiety/depression. Each dimension has 5 level of responses: no problems, slight problems, moderate problems, severe problems, and extreme problems.

Visual Analog Score (VAS): The last EQ-5D-5L question asks respondents to rate their present health status on a vertical 0 to 100 visual analogue scale, with 0 labelled as “the worst heath you can imaginable” and 100 labelled as “the best health you can imaginable.” The scale is marked in increments of “1”, with values labelled at each

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decile. A minimal important difference (MID) of 7 points has been proposed for the VAS in cancer patients (139, 140).

Derivation of utility scores

The EQ-5D-5L health states were converted into a single summary index (referred to as the EQ-5D-5L utility index) by applying a formula that attaches values (also called weights or tariffs) to each of the levels in each dimension

EQ-5D-5L Denmark Index

For the Denmark Index, utility scores were derived using the Denmark EQ-5D-5L value set(86). When scoring in this manner, utilities range from 1 (full health) to -0.757 (worse than death). To date, no specific MID has been proposed for the Denmark Index; therefore, the largest country-specific MID (UK Index: 0.08) will be used as a conservative estimate of the Denmark Index MID.

Health states of interest

Different health states defined in a variety of ways were explored. This included by progression status (pre- and post-progression response), tumor response (time-varying and Day 1 Cycle 3), ECOG score, treatment status, and time to death. Therefore, health states were defined as follows:

Progression status

The date of progression was derived from progression-free survival data, using the Independent Review Committee definition. PROM assessments were defined as pre-progression or post-progression as follows:

- Pre-progression
    - PROM assessment date prior to progression date, OR
    - Censored progression date
- Post-progression
    - PROM assessment date on or after progression date

Response status

Response status as per independent review committee definition was used. EQ-5D-5L assessments were assigned according to time-varying response status by looking at the 30 days prior to and including the date of EQ-5D-5L assessment. The tumor response assessment made closest to the date of EQ-5D-5L assessment within this window will be assigned. If there was no assessment of tumor response in a 30-day window, response status was coded as missing.

ECOG score

EQ-5D-5L assessments were assigned to ECOG categories by looking at the 30 days prior to and including the date of EQ-5D-5L assessment. The ECOG assessment made closest to the date of EQ-5D-5L assessment within this window was assigned. If there was no assessment of ECOG in a 30-day window, ECOG score were coded as missing.

Treatment status

The date of AMG510 discontinuation was used. EQ-5D-5L assessments were defined as on- or off- treatment as follows:

- On
    - PROM assessment date prior to discontinuation date, OR
    - Censored discontinuation date
- Off
    - PROM assessment date on or after discontinuation date

Time to death

Date of death was derived from overall survival data, in addition to the last known alive date. EQ-5D-5L assessments were defined as follows:

- Within 30 days of death
    - Death date - PRO assessment date ≤30
- 31-90 days until death
    - 31 ≤ Death date - PRO assessment date ≤90
- 91-183 days until death
    - 91 ≤ Death date - PRO assessment date ≤183
- ≥184 days until death
    - Death date - PRO assessment date ≥184, OR
    - Last known alive date - PRO assessment date ≥184

If death date was missing (i.e. censored) and 'last known alive date - PRO assessment date' ≤184, PRO assessment was excluded from the time to death analysis.

Adverse events - Anemia

EQ-5D-5L assessments were assigned to adverse event categories by looking at the 21 days prior to and including the date of EQ-5D-5L assessment. EQ-5D-5L assessments were assigned to severe, mild/moderate or absent as follows:

- Severe: A grade 3 or 4 adverse event (emergent or ongoing) within the 21 days prior to an EQ-5D-5L assessment
- Mild/moderate: A grade 1-2 adverse event (emergent or ongoing) within the 21 days prior to an EQ-5D-5L assessment
- Absent: No adverse event (emergent or ongoing) within the 21 days prior to an EQ-5D-5L assessment

Statistical methodology

This analysis primarily used the EQ-5D-5L analysis set, consisting of all subjects in the Phase 2 NSCLC cohort Full Analysis Set with a non-missing utility index (i.e. all five dimensions complete) for at least one timepoint across the whole study period. An alternate analysis set was used for change from baseline mixed models for repeated measures (MMRMs): the subset of the Phase 2 NSCLC cohort Safety Set who had both a baseline and at least one subsequent EQ-5D assessment. Analysis was performed using SAS version 9.4, with additional exploratory plots of missing data being produced using R version 3.6.0.

Completion rates and descriptive statistics

Completion rates for EQ-5D-5L scores for each utility index were assessed across timepoints at Baseline, Cycles 1-25, End of Treatment Phase, and Safety Follow-Up (total number of subjects completing assessments, percentage of Full Analysis Set, and number and total number and percentage of expected subjects to complete assessment).

Additionally, parallel boxplots(141) were produced exploring the association between scores at a visit and missing EQ-5D-5L score in the subsequent visit. These were designed to assess the likelihood of data being missing at random, a key assumption for the MMRM analyses.

Descriptive statistics for the scores by visit were produced for each utility index and VAS (e.g. number of observations, mean, standard deviation, minimum, maximum).

Change from baseline MMRM

MMRMs were fitted that included change from baseline scores as the dependent variable, study visit (categorical) and baseline score as fixed effects, and study visit as a repeated effect (repeated by subject). Models were fitted using a heterogeneous compound symmetry covariance structure. The number of subjects, least squares (LS) means, standard errors and 95% confidence intervals (CIs) for the value of utility scores was presented.

Health state utility values MMRM

To estimate mean utility values for each health state, a mixed model approach was used to account for repeated PROM assessments per subject within a health state using separate MMRMs under the assumption of missing at random.(142) Mixed models are appropriate for longitudinal PRO data and have been used to estimate health state utility values in previous studies.(143, 144)

Models were fitted with health utility index scores measured at any visit (baseline, cycles, and follow-up) as the dependent variable, with health state as a categorical fixed effect and a random intercept for each subject. Models were run using an unstructured covariance matrix. The following equation represents the model:

$$y_{ij} = \beta_0 + \beta_1 x_{ij} + \gamma_{0i} + \varepsilon_{ij}$$

Where y_{ij} represents utility index for subject i at visit j, β_0 is a fixed intercept, β_1 is a fixed effect on the categorical health state variable x (e.g. pre-/post-progression), γ_0 is a random intercept for each subject, and ε is a random error term.

These models also explored interactions with progression, by including health state variables and their interaction as covariates with:

- Progression status x Time to death
- Progression status x Treatment status

Results

Subject population

Overall, 124 subjects were present in the Phase 2 NSCLC Cohort Full Analysis Set. Of these, 124 had at least one EQ-5D assessment at any time point and thus comprised the EQ-5D-5L Full Analysis Set for analysis of completion rates, descriptive statistics, and health utility values (see main body). An alternate subset of subjects in the Safety

Set who had both a baseline utility and one subsequent EQ-5D assessment yielded 86 subjects for analysis of Change from Baseline MMRMs.

Completion rates

Table 69 shows that completion of the EQ-5D-5L at Baseline comprised 70.97% of the Full Analysis Set Completed, with number of participants dropping below 50% of the Full Analysis Set at Cycle 7. The proportion of completed assessments out of those expected to complete remained at least 70% until Cycle 23, at which point 10 assessments were available for analysis. As such, subsequent analyses exploring EQ-5D-5L scores over time focus on visits up to and including Cycle 23.

Table 69. EQ-5D-5L Completion rates by assessment time point

	Phase 2 Full Analysis Set (N=124)			
Assessment Timepoint	Number Completed	Number Expected	% of full analysis set	% of Expected
Baseline	88	124	70.97%	70.97%
Day 1 Cycle 2	98	120	79.03%	81.67%
Day 1 Cycle 3	92	106	74.19%	86.79%
Day 1 Cycle 4	81	95	65.32%	85.26%
Day 1 Cycle 5	78	90	62.90%	86.67%
Day 1 Cycle 6	64	75	51.61%	85.33%
Day 1 Cycle 7	44	62	35.48%	70.97%
Day 1 Cycle 9	37	49	29.84%	75.51%
Day 1 Cycle 11	32	44	25.81%	72.73%
Day 1 Cycle 13	22	30	17.74%	73.33%
Day 1 Cycle 15	23	29	18.55%	79.31%
Day 1 Cycle 17	18	23	14.52%	78.26%
Day 1 Cycle 19	20	25	16.13%	80.00%
Day 1 Cycle 21	17	21	13.71%	80.95%
Day 1 Cycle 23	10	16	8.06%	62.50%
Day 1 Cycle 25	0	1	0.00%	0.00%
End of Treatment Phase	41	99	33.06%	41.41%
Safety Follow-Up	10	40	8.06%	25.00%

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