Medicinrådet

Bilag til Medicinrådets anbefaling vedrørende tafasitamb til behandling af diffust storcellet B-celle lymfom

Vers. 1.0

Bilagsoversigt

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

Incyte's comments on Medicinrådets draft assessment report for Minjuvi. | August 30, 2022

Thank you for the opportunity to give feedback on the draft assessment. Medicinrådet's hesitancy for assessing relative efficacy versus current treatment options in Denmark when the market authorization approval consists of a single-arm, phase II trial (L-MIND) is evident throughout the full report, and we would like to raise a few concerns regarding how Medicinrådet has chosen to address the uncertainty that might be present in the evidence package.

The L-MIND trial was complemented with an indirect treatment comparison, based on a real-world, retrospective, observational cohort of patients, treated with ESMO/NCCN guideline-listed regimens. This was done in order to evaluate the comparative benefit of tafasitamab (in combination with lenalidomide) compared to existing treatment alternatives, including R-GemOx, which is relevant for the Danish context. From our point of view, we cover all levels of evidence needed, except for a head-to-head clinical trial. We want to stress that the lack of such trials is common for drugs treating orphan diseases where there is no approved therapy available. When the L-MIND study was conducted, no standard therapy was available to treat the indication of tafasitamab, hence no head-to-head trial was possible to perform.

We understand that the Danish system is designed to accept conclusions derived from randomised double-blind clinical trials against the standard of care (what you call formal conclusions) and that we do not provide such data for tafasitamab. That said, we have invested in the submitted indirect comparison methods in order to help Medicinrådet evaluate tafasitamab in the best possible way. This is useful in DLBCL, as it allows comparison with several treatment options - which is particularly important in R/R DLBCL, where treatment options are numerous and where an established treatment pathway is lacking. The treatment options that Medicinrådet points out (e.g., RDHAOx and R-ICE) are not used for the same patients that are being treated with R-GemOx. The options considered should be restricted to those suitable for the non-transplant eligible population, which is often too frail to be considered for high dose chemotherapy. Hence, we recognize a high unmet medical need for the patient population relevant for this assessment.

While we recognize that indirect comparisons often have limitations, we have gone to great lengths to minimize or exclude these limitations in the indirect comparisons provided in this submission. Specifically, like any indirect treatment comparison, the RE-MIND2 study aims to balance the treatment and comparison cohorts with respect to known and measurable prognostic factors and effect modifiers, in order to minimize the risk of bias when comparing the results in the two cohorts. The RE-MIND2 study is among few indirect comparisons who took the more advanced approach and leveraged individual patient data, both for the experimental and the comparators arms. This allows to leverage propensity score matching methods to adjust for differences in patient characteristics between trials and thus provide more accurate and reliable outcomes compared to other methodologies, such as MAIC or Bucher's. To this end, the data inclusion and exclusion criteria of the comparator used in the analyses were collected to match those of L-MIND as closely as possible, and the 1:1 matching was performed by balancing nine key variables for R-GemOx. It is correct that no matching based on international prognostic index (IPI) is performed in RE-MIND-2, but as Medicinrådet also mentions; age, LDH and Ann Arbor are, which are the major contributors to IPI. In addition, extensive sensitivity analyses were performed.

All these analyses indicate a significant additional advantage in terms of lifespan for patients treated with tafasitamab+lenalidomide compared to R-GemOx. Despite being somewhat lower, even the sensitivity analysis with a population matched on 11 covariates shows an added benefit of tafasitamab+lenalidomide over R-GemOx in terms of overall survival (OS) and progression-free survival (PFS). For instance, the sensitivity analysis consistently showed that a higher number of patients reached long-term survival with tafasitamab+lenalidomide than with R-GemOx. While in the base-case 18.9% of tafasitamab+lenalidomide patients reached OS over 36 months against 6.8% of R-GemOx, the sensitivity analysis estimated 18.6% and 5.1% for tafasitamab+lenalidomide and R-GemOx, respectively. Incyte wants to highlight that the extrapolation of long-term effect is highly relevant from a health economic perspective, and should be noticed by Medicinrådet. In addition, one may question how relevant the additional covariate 'cell of origin' is – according to a leading Danish clinical expert, it was invented over 20 years ago and clinicians do not base their decisions for treatment on cell of origin.

The additional clinical benefit of tafasitamab+lenalidomide, mediated by its high and durable response rates, has also been recognized by regulators (e.g. EMA) and has led to confirmation of the orphan drug status of tafasitamab. Indeed, in the context of the EMA's examination of the orphan designation criteria, the designation criteria set out in Article 3(1)(b) of Regulation (EC) No 141/2000 (i.e. "*Existence of no satisfactory methods of diagnosis prevention or treatment of the condition in question, or, if such methods exist, the medicinal product will be of significant benefit to those affected by the condition*.") must be satisfied. The validity of our data is therefore also confirmed externally by our orphan drug designation, as the data set was strong enough to maintain this designation, even according to the criterion of superiority over alternatives.

Based on these facts, we offer the maximum possible level of evidence at this stage, including: an authorization study (L-MIND) as well as two external comparison arms (RE-MIND and RE-MIND2); with consistent beneficial results through these studies.

Medicinrådet argues that the study population in L-MIND differs on a number of prognostic factors from the Danish population and therefore does not correspond to the Danish patient population. This implying that there is a high risk that the L-MIND study overestimates the effect in relation to a relevant Danish patient population.

We would like to raise a major concern regarding how Medicinrådet has decided to interpret this uncertainty for the evidence package and patient population, and transferred into the health economic evaluation. One of the major prognostic factors that influences the probability of survival is age. According to Danish registry data, 75% of all non-transplant eligible patients are not considered for autologous stem cell transplant due to their high age (above 70 years). In L-MIND, the median age was 72 years and the median age of diagnosis in the Nordic countries is 70-72 years of age. This implies that the L-MIND population correspond well to the real patient population in Denmark, in one of the most important prognostic factors.

As Medicinrådet states, they have decided to use the most conservative extrapolations of OS and PFS and not necessarily the best fit. Thus, Medicinrådet's assessment did not result in a *base case scenario*, rather a *worst-case scenario*. For instance, the plateau seen in the Kaplan-Meier for PFS (Figure 3 in the dossier) was not considered when Medicinrådet chose an exponential extrapolation. While the generalized gamma suggested by Incyte may be argued to have overestimated PFS, the exponential distribution suggested by Medicinrådet does not provide a good visual fit at all.

If an intermediate distribution is chosen, the ICER decreases approximately 30% when compared to the ICER estimated by Medicinrådet. Such a, still conservative but more appropriate extrapolation, clearly affects the results of figure 13 from Medicinrådet's report (showing the ICER at different price levels of tafasitamab).

Moreover, the same argumentation can be found for OS, if a slightly less conservative approach is chosen (Medicinrådet chose the only parametric distribution that did not produce a good relative statistical fit), together with the intermediate distribution for PFS, the ICER is heavily reduced from Medicinrådet base case (se figure 1 below).

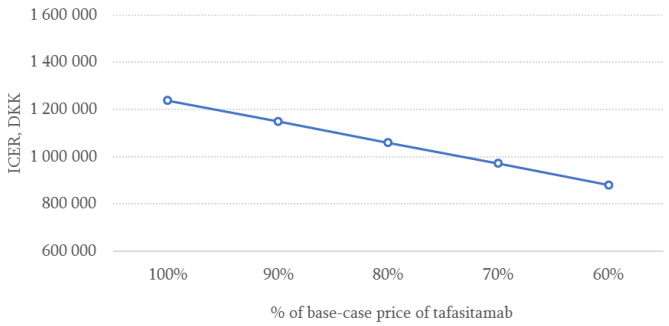

Figure 1. ICER at different price levels of tafasitamab with Medicinrådet's base case assumptions but parametric function for PFS changed to log-logistic and for OS to Weibull

The analyses described above with more appropriate assumptions on extrapolations made than Medicinrådet's, do not include the possibility to be cured (since Medicinrådet chose to not implement it in their analyses). However, there seems to be evidence for patients surviving more than five years and who can be considered cured, according to the leading Danish clinician.

The above reasoning, with more conservative assumptions compared to Incyte's base-case and more realistic assumptions compared to Medicinrådets worst-case, would result in an ICER of 1,240,000 DKK/QALY, at Incyte's base-case price. This is significantly higher compared to the approx. 730,000 DKK/QALY that Incyte presented in the application, but also significantly lower than the above 2,000,000 DKK/QALY suggested by Medicinrådet.

Patients who have relapsed and are refractory to first line therapy, and who are not eligible for autologous stem cell transplant (ASCT), have a poor prognosis and few available and effective treatment options. Despite the introduction of anti-CD20-based therapy such as rituximab, around 25% of DLBCL patients are expected to experience R/R disease within five years of diagnosis. For high-risk patients (IPI 4-5), this probability increases to approximately 34%. In addition, nearly 45% of R/R patients who receive second line therapy proceed to third line therapy, and there has been limited improvement in the survival of adult patients with DLBCL beyond the introduction of rituximab, highlighting a need for novel therapies earlier in treatment, especially for high-risk cases. Hence, this patient population face a huge unmet need for new innovative treatments that will delay progression and prolong survival, while improving or maintaining the patients' quality of life.

In Denmark, there are currently no innovative treatment options available for treating patients with relapse or refractory DLBCL, who have failed first line therapy. Tafasitamab in combination with lenalidomide has shown to be an effective, well-tolerated, chemotherapy-free option for the treatment of patient who are ineligible for ASCT. When comparing to the real-world standard of care treatments, tafasitamab+lenalidomide results in significantly improved PFS and OS. Tafasitamab in combination with lenalidomide therefore offers to fulfill the unmet need of new innovative treatments for patients with R/R DLBCL who are ineligible for ASCT in Denmark.

We hope that Medicinrådet will take this information into consideration in the final version of the assessment, and provide Incyte and Amgros with a more realistic health economic evaluation which will form the basis of the negotiations to ensure access to a medicine we believe Danish patients will benefit from.

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30-08-2022
MGK/CAF

Forhandlingsnotat

Dato for behandling i Medicinrådet	28.09.2022
Leverandør	Incyte
Lægemiddel	Minjuvi (tafasitamab)
Ansøgt indikation	Tafasitamab er i kombination med lenalidomid efterfulgt af tafasitamab monoterapi indiceret til behandling af voksne patienter med recidiverende eller refraktær diffust storcellet B-celle-lymfom, som ikke er egnede til autolog stamcelletransplantation.

Forhandlingsresultat

Leverandøren har valgt at givet to forskellige pristilbud, ét hvis Medicinrådet anbefaler Minjuvi (tafasitamab) som standardbehandling, og ét andet pristilbud, såfremt Medicinrådet ikke anbefaler Minjuvi (tafasitamab):

Tabel 1: Forhandlingsresultat – hvis Medicinrådet anbefaler Minjuvi (tafasitamab)

Lægemiddel	Styrke/form	Pakningsstørrelse	AIP	Forhandlet SAIP	Rabatprocent ift. AIP
Minjuvi (tafasitamab)	200mg/IV	1 stk.	5.815,26	[redacted]	[redacted]

Ovenstående pris er betinget af Medicinrådets anbefaling.

Tabel 2: Forhandlingsresultat - hvis Medicinrådet ikke anbefaler Minjuvi (tafasitamab)

Lægemiddel	Styrke/form	Pakningsstørrelse	AIP	Forhandlet SAIP	Rabatprocent ift. AIP
Minjuvi (tafasitamab)	200mg/IV	1 stk.	5.815,26	[redacted]	[redacted]

Ovenstående pris er ikke betinget af Medicinrådets anbefaling.

[redacted]

Informationer fra forhandlingen

[redacted]

Konkurrencesituationen

På nuværende tidspunkt er der indsendt anmodninger om vurdering til Medicinrådet på Polivy (polatuzumab vedotin) til diffust storcellet B-celle lymfom i 1. linje og Yescarta (axicabtagene ciloleucel) til behandling af diffust storcellet B-celle lymfom i 2. linje.

Tidligere er CAR-T behandlingerne Yescarta (axicabtagene ciloleucel) og Kymriah (tisagenleclucel) vurderet i Medicinrådet til behandling af diffust storcellet B-celle lymfom i 3. linje, men blev ikke anbefalet som standardbehandling.

Tabel 3: Årlige lægemiddelomkostninger

Lægemiddel	Dosis*	Pakningsstørrelse	Pakningspris** SAIP	Antal pakninger/år	Årlige lægemiddelomkostninger SAIP pr. år
Minjuvi (tafasitamab)	12mg/kg	200 mg (1 stk.)	[redacted]	155	[redacted]

**Den anbefalede dosis af Minjuvi er 12 mg pr. kg kropsvægt (gns. 78,1 kg) administreret som en intravenøs infusion i henhold til følgende tidsplan: Cyklus 1: infusion på dag 1, 4, 8, 15 og 22 i cyklussen. Cyklus 2 og 3: infusion på dag 1, 8, 15 og 22 i hver cyklus. Cyklus 4 indtil sygdomsprogression: infusion på dag 1 og 15 i hver cyklus. Hver cyklus har 28 dage.*
***Prisen er betinget af Medicinrådets anbefaling.*

Status fra andre lande

Norge: Under vurdering[1].
Sverige: Under vurdering[2].
England: Under vurdering[3].

Konklusion

Amgros vurderer, at det ikke er muligt at opnå en bedre pris på Minjuvi (tafasitamab) på nuværende tidspunkt.

[1] https://nyemetoder.no/metoder/tafasitamab-minjuvi
[2] https://janusinfo.se/download/18.2859d99b17e6d9cce3572ce8/1643013207939/Avvakta-Minjuvi-220124.pdf
[3] https://www.nice.org.uk/guidance/indevelopment/gid-ta10645

Medicinrådet

Application for the assessment of tafasitamab (Minjuvi®) with lenalidomide for relapsed or refractory diffuse large B-cell lymphoma

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1 Basic information

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Overview of the pharmaceutical	
Proprietary name	Minjuvi®
Generic name	Tafasitamab
Marketing authorization holder in Denmark	Incyte Biosciences Distribution B.V.
ATC code	L01XC35
Pharmacotherapeutic group	Lymphoma, Large B-Cell, Diffuse
Active substance(s)	Tafasitamab
Pharmaceutical form(s)	Powder for concentrate for solution for infusion (200 mg)
Mechanism of action	Tafasitamab is a monoclonal antibody that targets the CD19 antigen expressed on the surface of pre-B and mature B lymphocytes. Upon binding to CD19, tafasitamab mediates B-cell lysis through effector cells of the immune system, such as natural killer cells, gammadelta T cells and phagocytes, and direct induction of cell death (apoptosis).
Dosage regimen	Tafasitamab is administered via intravenous (IV) infusion. The recommended dose is 12 mg tafasitamab per kg body weight administered via IV according to the following schedule: • Cycle 1: Administer the infusion on day 1, 4, 8, 15 and 22 of the cycle. • Cycles 2 and 3: Administer the infusion on day 1, 8, 15, and 22 of each cycle. • Cycle 4 until disease progression: Administer the infusion on day 1 and 15 of each cycle. Each cycle has 28 days. Tafasitamab is used in combination with lenalidomide (oral administration). After a maximum of 12 cycles of combination therapy, stop treatment with lenalidomide, and continue tafasitamab infusions as single agent on day 1 and 15 of each 28-day cycle, until disease progression.
Therapeutic indication relevant for assessment (as defined by the European Medicines Agency, EMA)	Tafasitamab is indicated in combination with lenalidomide followed by tafasitamab monotherapy for the treatment of adult patients with relapsed or refractory diffuse large B-cell lymphoma (DLBCL) who are not eligible for autologous stem cell transplant (ASCT).
Other approved therapeutic indications	Not applicable
Will dispensing be restricted to hospitals?	Yes
Combination therapy and/or co-medication	Lenalidomide is self-administered in capsule form at the recommended starting dose of 25 mg daily on days 1 to 21 of each cycle.
Packaging – types, sizes/number of units, and concentrations	1 x 200 mg vial. Powder for concentrate for solution for infusion.
Orphan drug designation	Yes

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2 Abbreviations

Abbreviation	Definition
1L	First-line
2L	Second line
2L+	Second line or more
3L	Third line
3L+	Third line or more
ABC	Activated B-cell
ADCC	Antibody-dependent cellular cytotoxicity
ADCP	Antibody-dependent cellular phagocytosis
AE	Adverse event
AIC	Akaike Information Criterion
AICC	Corrected Akaike Information Criterion
AIDS	Acquired immunodeficiency syndrome
ALT	Alanine transaminase
ANC	Absolute neutrophil count
AP	Alkaline phosphatase
ASCT	Autologous stem cell transplant
AST	Aspartate aminotransferase
ATC	Anatomical Therapeutic Chemical
BCL	B-cell lymphoma
BEAM	Carmustine, etoposide, cytarabine and melphalan
BIC	Bayesian Information Criterion
BIM	Budget impact model
BR	bendamustine, rituximab
BSA	Body surface area
CAR	Chimeric antigen receptor
C-CEM	Core cost-effectiveness model
CEAC	Cost-effectiveness acceptability curve
CEM	Cost-effectiveness model
CI	Confidence interval
CLL	Chronic lymphocytic leukaemia
CNS	Central nervous system
COO	Cell of origin
CR	Complete response
CRR	Complete response rate
CRS	Cytokine release syndrome
CSF	Cerebrospinal fluid
CSR	Clinical study report
DCR	Disease control rate
DK	Denmark
DKK	Danish Krone
DLBCL	Diffuse large B-cell lymphoma
DLG	Danish Lymphoma Group
DMC	Danish Medical Council
DMCG	Danish Multidisciplinary Cancer Groups
DNA	Deoxyribonucleic acid
DOR	Duration of response
DP	Disease progression
DRG	Diagnosis-related group
DSA	Deterministic sensitivity analysis
DSU	Decision Support Unit
EBV	Epstein-Barr virus
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
EFS	Event-free survival
EJP	Economically justifiable price
EMA	European Medicines Agency
ENR	Enrolled patients

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Abbreviation	Definition
EOT	End of treatment
EP	Both effect modifier and prognostic factor
ERG	Evidence Review Group
ESMO	European Society for Medical Oncology
ESS	Estimated sample size
EU	European Union
FAS	Full Analysis Set
Fc	Fragment crystallizable
FDA	Food and Drug Administration
FISH	Fluorescence in situ hybridization
GCB	Germinal center B-cell
GEM	Gemcitabine
GEMOX	Gemcitabine and oxaliplatin
GEP	Gene expression patterns
GP	General practitioner
HAS	Haute Autorité de Santé
HBc	Hepatitis B core
HBs	Hepatitis B surface antibody
HbsAg	Hepatitis B surface antigen
HBV-DNA	Hepatitis B virus deoxyribonucleic acid
HDCT	High-dose chemotherapy
HIV	Human immunodeficiency virus
HR	Hazard ratio
HRQoL	Health-related quality of life
HSUV	Health state utility values
HTA	Health technology assessment
ICER	Incremental cost-effectiveness ratio
IFN-γ	Interferon gamma
IgG	Immunoglobulin G
IHC	Immunohistochemistry
IL-2	Interleukin-2
INV	Investigator
IPI	International Prognostic Index
IPT	Inverse probability of treatment
IPTW	Inverse probability treatment weighting
IQR	Interquartile range
IRC	Independent Radiology/Clinical Review Committee
ITT	Intent to treat
IV	intravenous
IWGRC	International Working Group Response Criteria
KM	Kaplan-Meier
KOL	Key opinion leader
LDH	Lactate dehydrogenase
LEN	Lenalidomide
LMV	Laboratoriemedicinsk vejledning
LY	Life years
MA	Marketing authorisation
MAS	Matched analysis set
MI	Multiple imputations
MRI	Magnetic resonance imaging
MUGA	Multiple-gated acquisition
NA	Not applicable
NCCN	National Comprehensive Cancer Network
NCT	National Clinical Trial
NE	Not estimable
NHL	Non-Hodgkin Lymphoma
NHS	National Health Service
NICE	The National Institute for Health and Care Excellence
NK	Natural killer

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Abbreviation	Definition
NN	Nearest Neighbour
NR	Not reached
NS	Not significant
NTE	Not transplant eligible
Ob-ENR	Observational enrolled analysis set
OR	Odds ratio
ORR	Objective response rate
OS	Overall survival
PAS	Patient Access Scheme
PD	Progressive disease
PET-CT	Positron Emission Tomography–Computed Tomography
PF	Prognostic factor
PFLY	Progression-free life year
PFS	Progression-free survival
PH	Proportional hazard
PIX	Pixantrone
PK	Pharmacokinetics
PO	Oral
Pola-BR	Polatuzumab vedotin, bendamustine and rituximab
PP	Per protocol
PPLY	Post-progression life year
PPS	Per Protocol Set
PR	Partial response
PS	Performance status
PSA	Probabilistic sensitivity analysis
PT	Preferred term
PYE	Patient-years of exposure
QALY	Quality adjusted life years
QAPFLY	Quality-adjusted progression-free life year
QAPPLY	Quality-adjusted post-progression life year
RBC	Red blood cell
R2	Rituximab and lenalidomide
R-CHOP	Rituximab, cyclophosphamide, doxorubicin, vincristine and prednisone
R-DHAP	Rituximab, dexamethasone, cytarabine, and cisplatin
R-GDP	Rituximab, gemcitabine, dexamethasone, cisplatin
R-GemOx	Rituximab, gemcitabine, oxaliplatin
R-ICE	Rituximab, ifosfamide, carboplatin and etoposide
REAL	Revised European American Lymphoma
RIPD	Reconstructed individual patient-level data
R/R	Relapsed of refractory
RTX	Rituximab
SAE	Serious adverse event
SAF	Safety Analysis Set
SAP	Statistical analysis plan
SC	Subcutaneous
SCT	Stem cell transplant
SD	Stable disease
SE	Standard error
SLR	Systematic literature review
SMD	Standardized mean difference
SOC	System organ class
SoC	Standard of care
STA	Single technology assessment
TAFA	Tafasitamab
TBD	To be determined
TEAE	Treatment-emergent adverse event
TE-AESI	Treatment-emergent adverse events of special interest
TESAE	Treatment-emergent serious adverse event
TNM	Tumour/Node/Metastasis

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Abbreviation	Definition
TTD	Time to treatment discontinuation
TTDD	Time to treatment discontinuation or death
TTNT	Time-to-next treatment
TTP	Time-to-progression
Tx	Treatment
UK	United Kingdom
ULN	Upper limit of normal
US	United States
UV	Ultraviolet
WHO	World Health Organisation
WTP	Willingness to pay

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4 Summary

Diffuse large B cell lymphoma (DLBCL) is the most common and aggressive type of B-cell non Hodgkin's lymphoma. DLBCL is a heterogenous disease and, for the vast majority of patients, the aetiology is unknown. Age, diet, genetic mutations, infections environmental factors, immunodeficiency, and chronic inflammation may all play a role. Approximately 60% of patients will present with advanced stage DLBCL. If left untreated, DLBCL patients have a life expectancy of less than one year.

Approximately 500 new cases of DLBCL are diagnosed every year in Denmark. The incidence of DLBCL increases with age, most cases occurring in adults >54 years of age. Less than 25% of DLBCL patients are expected to experience relapse of refractory disease within 5 years of diagnosis. Nearly 45% of relapse or refractory (R/R) patients who received second-line treatment proceed to third-line.

For newly diagnosed DLBCL, the first-line therapy consists of chemoimmunotherapy, usually a combination of rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone (R-CHOP-regimen), sometimes combined with additional doses of rituximab or radiation therapy. High-dose chemotherapy (HDCT) with rituximab, dexamethasone, cytarabine, and cisplatin (R-DHAP) or rituximab, ifosfamide, carboplatin and etoposide (R-ICE) and ASCT remain the best chance for a secondary cure for patients who are below 65-70 years of age and with chemosensitive relapse without significant comorbidity [1]. Ultimately, 50% of ASCT-eligible patients will relapse after transplantation [2]. Patients who are not eligible for HDCT and ASCT or are R/R to 1 line treatment have a poor prognosis and few available and effective treatment options. Newer treatments for this patient population, such as polatuzumab vedotin in combination with bendamustine and rituximab (pola-BR) and chimeric antigen receptor T-cell therapy (CAR T-cell therapies) offer limited efficacy and considerable AEs. Furthermore, the Danish Medical Council (DMC) does not recommend CAR T-cell therapies or pola-BR for the treatment of R/R DLBCL. Thus, there remains an urgent unmet need for Danish patients with R/R DLBCL who are ineligible or fail ASCT.

According to the DLBCL treatment guidelines, the treatment alternatives for R/R DLBCL patients who are not eligible for transplant are rituximab in combination with chemotherapy (R-GDP, R-GemOx or R-ICE). Based on a consultation with a key-opinion leader (KOL), chemotherapy regimens containing gemcitabine, such as R-GemOx, are becoming more accepted over the past years. Thus, R-GemOx should be seen as the most relevant treatment alternative in Denmark and it was chosen as the comparator in the health economic analysis.

Minjuvi (tafasitamab) is indicated in combination with lenalidomide followed by Minjuvi monotherapy for the treatment of adult patients with R/R DLBCL who are not eligible for autologous stem cell transplant (ASCT). Tafasitamab is a fragment crystallizable (Fc) enhanced, humanized antibody that targets the CD19 antigen expressed on the surface of pre-B and mature B lymphocytes. Upon binding to CD19, tafasitamab mediates B-cell lysis through direct induction of cell death (apoptosis) and the engagement of immune effector cells like NK cells, γδ T cells, and macrophages. The combination of tafasitamab with the immunomodulatory drug lenalidomide was investigated for enhanced antitumour activity. Lenalidomide activates T cells to release the cytokines interferon gamma (IFN-γ) and interleukin-2 (IL-2), which stimulate NK cell activity and induce an increase in NK cell numbers. In addition, lenalidomide increases NK-cell expression of FcγRIII, the receptor with high-affinity binding to tafasitamab.

Tafasitamab is administered via intravenous (IV) infusion and lenalidomide is administered orally. The recommended dose is 12 mg tafasitamab per kg body weight administered via IV according to the following schedule:

- Cycle 1: Administer the infusion on day 1, 4, 8, 15 and 22 of the cycle.
- Cycles 2 and 3: Administer the infusion on day 1, 8, 15, and 22 of each cycle.
- Cycle 4 until disease progression: Administer the infusion on day 1 and 15 of each cycle.

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Each cycle has 28 days.

Evidence of the clinical effectiveness of the combined therapy tafasitamab+lenalidomide is supported by the phase II, single-arm study (L-MIND). The comparative efficacy of tafasitamab+LEN against R-GemOx was generated by a real-world, retrospective, observational study (RE-MIND2) against a cohort of patients treated with systemic NCCN/ESMO guideline listed regimens administered in routine clinical care.

In L-MIND—tafasitamab in combination with lenalidomide followed by tafasitamab monotherapy demonstrated high and durable clinical efficacy, including in difficult-to-treat NTE R/R DLBCL patients, and a manageable short- and long-term safety profile. The combination has proven to be a generally well tolerated, chemotherapy free, treatment option with a manageable safety profile in the short and long term. In the pre-specified analysis of the RE-MIND2 study, tafasitamab in combination with lenalidomide followed by tafasitamab monotherapy demonstrated a statistically significant improvement in median OS of over 20 months as compared to R GemOx.

A core cost-effectiveness model (C-CEM) was developed in Microsoft Excel® to assess the cost effectiveness of tafasitamab vs. relevant comparators (for the Danish setting this is R-GemOx) for the treatment of patients with DLBCL who are ineligible for receiving transplants. A survival partition approach was selected given it is recognised as one of the most commonly adopted model structures for oncology treatments. This approach was also in line with the previous HTA assessments reviewed for R/R DLBCL. The model was developed based on clinical and treatment pathways for patients with R/R DLBCL; the considerations of key clinical aspects (progression-free survival [PFS] and overall survival [OS]) that affect clinical outcomes, costs, and treatment decisions; a thorough review of published and available health technology assessment (HTA) submission reports; and interviews with KOLs.

This analysis used the limited societal perspective and considered all relevant treatment related costs, including drug costs, drug administration costs (e.g., co-medications), monitoring, management of AEs, subsequent treatment costs, and disease management costs. Transportation costs incurred by the patient were also included. The model inputs were based on Danish sources where possible.

In the base case results, tafasitamab in combination with lenalidomide followed by tafasitamab monotherapy, provided a gain of [redacted] LYs and [redacted] QALYs over a life time horizon (35 years), when compared to R-GemOx. The treatment with tafasitamab in combination with lenalidomide was also associated with higher costs (incremental costs of [redacted] DKK), leading to an ICER of [redacted] DKK per QALY gained. The uncertainty of the model results was assessed with deterministic sensitivity analyses (DSA), a probabilistic sensitivity analysis (PSA) and several scenarios. The results of sensitivity analyses show that the results were robust through several parameter changes, where starting age and efficacy assumptions (single parametric fit of OS and PFS) showed the greatest impact.

Bristol-Myers Squibb Pharma EEIG (current MAH of lenalidomide in Denmark) is expected to lose patent in January 2022.

In summary, tafasitamab in combination with lenalidomide is a clinically meaningful and cost-effective treatment option for adult patients with R/R DLBCL who are not eligible for ASCT.

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

5.1 Diffuse large B-cell lymphoma (DLBCL)

Non-Hodgkin's lymphoma (NHL) is a heterogeneous group of haematological malignancies that originate in the lymphocyte cells of the immune system [3]. Approximately 85%–90% of NHL originates from B cells (B-cell lymphoma) and 10%–15% of NHL originates from T cells or natural killer (NK) cells. There are at least 30 subtypes of mature B-cell NHL malignancies [3]. These subtypes are broadly categorised as indolent (slow growth) or aggressive (fast growth), with the aggressive subtypes having a worse prognosis than the indolent forms.

DLBCL is the most common and aggressive type of B-cell non-Hodgkin's lymphoma (NHL) [3-5]. DLBCL is a heterogenous disease and, for the vast majority of patients, the aetiology is unknown. Age, diet, genetic mutations, infections (eg, Epstein-Barr virus), environmental factors (eg, UV radiation, hair dyes, and pesticides), immunodeficiency (including due to AIDS and immunosuppressant medications), and chronic inflammation may all play a role [6-8]. Approximately 60% of patients will present with advanced stage DLBCL (Ann Arbor stage III or IV disease). If left untreated, DLBCL patients have a life expectancy of less than one year [9, 10].

Following a thorough history and physical exam, diagnosis should be based on an excisional biopsy of an involved lymph node or a tumour in another organ. If necessary, a cutting-needle biopsy may be conducted if it is the only practical choice. Diagnosis from a fine-needle aspiration or cytology from an effusion should be avoided [4]. A sufficient tissue sample should be taken in order to allow immunohistochemical and genetic studies on the material, thereby increasing the chance of the pathologist reaching the correct diagnosis. After a definitive diagnosis, staging should be undertaken. The process includes serum studies to assess the function of the bone marrow and other organs and to measure the concentration of lactate dehydrogenase in the serum, and imaging studies to determine the degree of lymphadenopathy and the presence of extranodal involvement [4]. There are several systems for disease staging; such as the Ann Arbor staging, which is summarised in Table 1.

Table 1. Ann Arbor staging system in DLBCL

Staging system	Description	Criteria	
Cotswolds modification Ann Arbor Staging	• Adds information regarding the prognostic significance of bulky disease (denoted by an X designation) and regions of lymph node involvement (denoted by an E designation) • The A and B designations denote the absence or presence of symptoms, respectively; the presence of symptoms correlates with treatment response • The importance of imaging modalities such as CT scanning is underscored	Stage	Area of involvement
		I	Single lymph node group
		II	Multiple lymph node groups on same side of diaphragm
		III	Multiple lymph node groups on both sides of diaphragm
		IV	Multiple extranodal sites or lymph nodes and extranodal disease
		X	Bulk >10 cm
		A/B	B symptoms: weight loss >10%, fever, drenching night sweats

Abbreviations: ECOG, Eastern Cooperative Oncology Group; PET-CT, Positron Emission Tomography–Computed Tomography.

Sources: Armitage et al. 2017 [4]; Lister et al. 1989 [11]; PDQ Cancer Information Summaries [12]; Quarles van Ufford et al. 2010 [13].

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In approximately 40% of cases, the disease arises in extranodal medullary tissues [14]. The most common sites of primary extranodal disease are the stomach/gastrointestinal tract, but disease can arise in virtually any tissue. Depending on site of involvement and stage of disease, patients with DLBCL may present with organ dysfunction or compressive symptoms, infections, or central nervous system involvement.

There is no clear consensus on a widely applicable prognostic score that captures the natural history and biology of DLBCL. The most commonly used tool for prognostication in patients with DLBCL is the International Prognostic Index (IPI). The IPI consists of a 0-5 score (or 0-3 for patients younger than 60 years) obtained by summing the number of risk factors presented by the patient. The risk factors are elevated serum LDH level, ECOG performance status higher than 2, Ann Arbor stage III or IV, age higher than 60 years and more than one extranodal involvement [4]. The prognostic significance of the IPI has been validated in several studies both prior to the introduction of rituximab and post-rituximab (modified IPI: R-IPI and NCCN-IPI) [15].

5.1.1 Incidence and prevalence of DLBCL in Denmark

The observed 5-year prevalence of NHL in Denmark in 2020 was 4,754 patients (82.08 per 100,000), leading to 340 deaths [16]. The incidence of NHL in Denmark has been increasing over time (Table 2), reaching approximately 1,460 new cases in 2020 [16, 17]. There is a difference between the incidence rates of NHL among men and women. In 2019, the incidence rate of NHL for men was 14.1 per 100,000 for men and 10.2 per 100,000 for women [17].

Table 2. Incidence and prevalence of NHL in the past 5 years

Year	2015	2016	2017	2018	2019
Incidence in Denmark [18]	1,378	1,476	1,494	1,447	1,441
5-year prevalence in Denmark [19]	4,935	5,249	5,512	5,651	5,657

DLBCL accounts for approximately 37% of all NHL newly diagnosed cases [3-5]. Until 2019, there were 9,880 DLBCL patients in the Danish National Lymphoma Registry, with approximately 500 new cases diagnosed every year (Table 3) [20].

Table 3. Estimated incidence of DLBCL in Denmark in the past 5 years

Year	2015	2016	2017	2018	2019
Incidence in Denmark [18]	510	546	553	535	533

The incidence of DLBCL increases with age and rises from <1/100,000 in children to 10–15/100,000 in patients aged 65 years and older, with most cases occurring in adults >54 years of age [21]. The median age at diagnosis in Denmark is 67 years [1]. Less than 25% of DLBCL patients are expected to experience relapse of refractory disease (R/R) within 5 years of diagnosis. For high-risk patients (IPI 4-5), this probability increases to approximately 34% [22]. Nearly 45% of R/R patients who receive second-line treatment (2L) proceed to third-line (3L) [23].

Table 4. Estimated number of patients eligible for treatment

Year	2022	2023	2024	2025	2026
Number of patients in Denmark eligible for treatment	149	148	159	161	155
Number of patients in Denmark who are expected to use the pharmaceutical in the coming years	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

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5.1.2 Patient populations relevant for this application

No agent recommended by the European Society for Medical Oncology (ESMO) guidelines is specifically approved as a 2L treatment for DLBCL, and there is no consensus regarding the optimal treatment, and—with no curative option available–there is no consensus regarding the optimal treatment to prolong survival [24]. The efficacy of immunochemotherapy regimens in the 2L setting is decreased largely due to acquired rituximab resistance following 1L treatment with the standard of care (SoC) rituximab-based regimen, (rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone [R-CHOP]). Re-challenging with salvage, rituximab-based, chemotherapy regimens in not transplant eligible (NTE) R/R DLBCL brings only limited treatment responses: only a small percentage of patients experience prolonged disease-free survival [2].

Newer treatments such as polatuzumab vedotin with bendamustine and rituximab (pola-BR) and chimeric antigen receptor (CAR) T-cell therapies offer limited efficacy and considerable AEs [25-29]. Furthermore, the Danish Medical Council (DMC) does not recommend CAR T-cell therapies or pola-BR for the treatment of R/R DLBCL [30-32]. Thus, there remains an urgent unmet need for Danish patients with R/R DLBCL who are ineligible or fail autologous stem cell transplantation (ASCT).

5.2 Current treatment options and choice of comparator(s)

The Danish Multidisciplinary Cancer Groups (DMCG.dk) together with the Danish Lymphoma Group (DLG) provide treatment guidelines for DLBCL in Denmark. The recommendations are divided into first (1L), second (2L) and third line (3L) treatments. Special recommendations are provided for patient subgroups, such as patients with cardiac insufficiency or DLBCL leg type [1].

5.2.1 Current treatment options

5.2.1.1 First-line treatment

For newly diagnosed DLBCL, the first-line therapy consists of chemoimmunotherapy, usually R-CHOP-regimen, sometimes combined with radiation therapy [33]. According to the key opinion leader (KOL), etoposide can be added for high-risk patients. The number and length of R-CHOP cycles will depend on the patient's age-adjusted IPI and disease stage. First approved in the late 1990s, rituximab is directed against the CD20 protein found on the surface of normal and malignant lymphocytes [34].

5.2.1.2 Therapy for relapsed or refractory patients

Patients who are R/R to 1L treatment have a poor prognosis and few available and effective treatment options [35, 36]. Despite the introduction of anti-CD20-based therapy such as rituximab, as mentioned above, less than 25% of DLBCL patients are expected to experience relapse of refractory disease (R/R) within 5 years of diagnosis. For high-risk patients (IPI 4-5), this probability increases to approximately 34% [22]. Nearly 45% of R/R patients who receive 2L treatment proceed to 3L [23].

There has been limited improvement in the survival of adult patients with DLBCL beyond the introduction of rituximab, highlighting a need for novel therapies earlier in treatment, especially for high-risk cases [37, 38].

Outcomes for patients with R/R DLBCL who were refractory or relapsed after 1L treatment with R-CHOP are dismal and patients face limited treatment options with chemoimmunotherapy [2, 39-41]. High-dose chemotherapy (HDCT) with rituximab, dexamethasone, cytarabine, and cisplatin (R-DHAP) or rituximab, ifosfamide, carboplatin and etoposide (R-ICE) and ASCT remain the best chance for a secondary cure for patients who are below 65-70 years of age and with chemosensitive relapse without significant comorbidity [1]. Ultimately, 50% of ASCT-eligible patients will relapse after transplantation [2].

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Nevertheless, approximately 50% of patients are not transplant eligible, either because they are chemo-refractory to salvage chemotherapy administered prior to ASCT; they are not candidates for ASCT due to advanced disease or comorbidities, severe concomitant medical or psychiatric illness, active central nervous system involvement, or HIV seropositivity; or they have failed after a prior ASCT [42, 43]. Retrospective studies have shown that only 25%–38% of patients who relapsed following rituximab-chemotherapy underwent ASCT. These patients have little chance at prolonged control of disease and are limited to palliative care [24, 42]. Transplant-ineligible patients have a median overall survival (mOS) of only 6–8 months, representing an important unmet need [33]. If left untreated, R/R DLBCL patients have a life expectancy of merely 3–9 months [42, 44, 45].

There is no particular regimen recommended as 2L treatment of DLBCL patients who cannot be treated with HDCT. Patients who are in good performance can be treated with potentially curative platinum regimens, such as rituximab, gemcitabine, dexamethasone, cisplatin (R-GDP); rituximab, gemcitabine and oxaliplatin (R-GemOx); or R-ICE. Otherwise, patients can be enrolled in clinical trials if they meet the inclusion criteria [1].

Further lines of therapy may include allogeneic transplant, a clinical trial, or CAR T-cell therapy (if ≥2 lines of systemic therapy) [24, 46]. Allogeneic stem cell transplant can be used as 3L for patients who are below 70 years of age and developed a chemo-sensitive relapse after ASCT or who were not able to harvest stem cells for ASCT [1]. Even though the treatment guideline mentions that CAR-T therapy can be recommended for patients who are refractory to 2L or later line therapy or who relapsed after ASCT, neither tisagenlecleucel nor axicabtagene ciloleucel are recommended by the DMC for treating adult patients with R/R DLBCL after two or more lines of systemic therapy [1, 31, 32].

Finally, the DMC does not recommend pola-BR for the treatment of adult patients with R/R DLBCL that are not candidates for haematopoietic stem cell transplantation [30]. In the pola-BR treatment arm of the phase IB/II clinical trial, 33.3% of patients discontinued all treatment due to AEs, most commonly due to thrombocytopaenia and neutropaenia. Peripheral neuropathy (including peripheral motor neuropathy, peripheral sensory neuropathy, decreased vibratory sense, hypaesthesia, and paraesthesias) occurred in 43.6% of patients in the pola-BR combination treatment arm (all grade 1–2) and resulted in treatment delays in one patient [29]. Pola-BR has other limitations; the treatment targets the CD20 protein, which has been shown to undergo a negative transformation in up to 60% of patients after treatment with rituximab-containing chemotherapy [47-50]. Therefore, pola-BR may not be appropriate for treatment in this potentially large proportion of patients who experience a loss of CD20 antigen expression after rituximab therapy.

5.2.2 Choice of comparator: R-GemOx

According to the DLBCL treatment guidelines, the treatment alternatives for R/R DLBCL patients who are not eligible for transplant are R-GDP, R-GemOx or R-ICE [1]. Based on a consultation with a KOL, chemotherapy regimens containing gemcitabine, such as R-GemOx, are becoming more accepted over the past years. Thus, R-GemOx should be seen as the most relevant treatment alternative in Denmark.

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5.2.3 Description of the comparator

Information on the comparator R-GemOx, is presented in Table 5.

Table 5. Description of comparator: R-GemOx

Comparator: R-GemOx	
Generic name(s) (ATC-code)	Rituximab, gemcitabine and oxaliplatin
Mode of action	Rituximab is a monoclonal antibody designed to attach to CD20 present on B lymphocytes. When rituximab attaches to CD20, it causes the death of B lymphocytes, which helps in lymphoma. Gemcitabine and oxaliplatin, two chemotherapies, prevent DNA replication and transcription, causing cell death.
Pharmaceutical form	Rituximab: powder for solution for infusion Gemcitabine: powder for solution for infusion Oxaliplatin: powder for solution for infusion
Posology [51]	Day 1: rituximab 375 mg/m^2, 90 minutes infusion gemcitabine 1000 mg/m^2, 100 minutes infusion oxaliplatin 100 mg/m^2, 2 hours infusion Cycle repeated every 15 days
Method of administration [51]	Intravenous (IV) infusion
Should the pharmaceutical be administered with other medicines? [51]	Premedication for rituximab with paracetamol 1000 mg orally, clemastine 2 mg intravenously or cetirizine 10 mg orally. Steroids can be considered in case of previous reaction or according to local routine.
Treatment duration/criteria for end of treatment [51]	Initially, 4 cycles. Upon response, 4 more cycles can be administered.
Necessary monitoring, both during administration and during the treatment period	
Need for diagnostics or other tests (i.e. companion diagnostics)	

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5.3 The intervention: Minjuvi® (tafasitamab)

5.3.1 Indication

Minjuvi (tafasitamab) is indicated in combination with lenalidomide followed by Minjuvi monotherapy for the treatment of adult patients with relapsed or refractory diffuse large B-cell lymphoma (DLBCL) who are not eligible for autologous stem cell transplant (ASCT).

5.3.2 Mechanism of action

Tafasitamab is a fragment crystallizable (Fc) enhanced, humanized antibody that targets the CD19 antigen expressed on the surface of pre-B and mature B lymphocytes (Figure 1). CD19 is broadly and homogeneously expressed across different B-cell malignancies, including DLBCL, and amplifies B-cell receptor signalling, as well as tumour cell proliferation and survival. Tafasitamab contains an Immunoglobulin G (IgG) 1/2 hybrid Fc-domain with 2 amino acid substitutions to enhance the Fc-mediated functions of the antibody. The Fc modification results in more potent immune effector cell mechanisms, including enhanced ADCC and antibody-dependent cellular phagocytosis (ADCP).

Upon binding to CD19, tafasitamab mediates B-cell lysis through direct induction of cell death (apoptosis) and the engagement of immune effector cells like NK cells, γδ T cells, and macrophages.

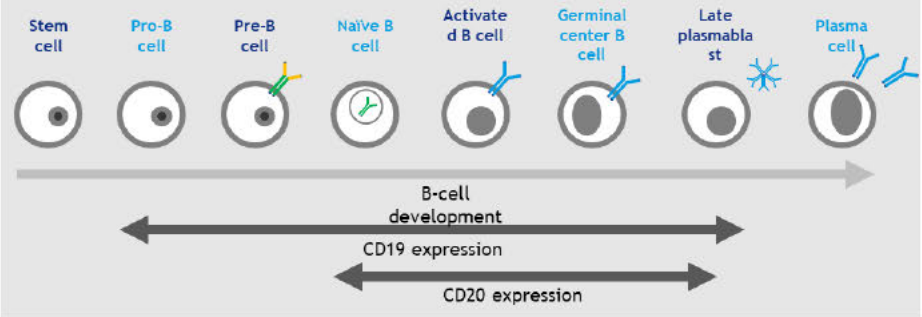

Figure 1. CD19 is expressed from the early pre-B stage up to mature B cells, before it is down-modulated at the plasma cell stage

Source: Blanc et al. 2011 [52]

The combination of tafasitamab with the immunomodulatory drug lenalidomide was investigated for enhanced antitumour activity. Lenalidomide activates T cells to release the cytokines interferon gamma (IFN-γ) and interleukin-2 (IL-2), which stimulate NK cell activity and induce an increase in NK cell numbers [53, 54]. In addition, lenalidomide increases NK-cell expression of FcγRIII, the receptor with high-affinity binding to tafasitamab [55].

The enhancement of tafasitamab-mediated NK-cell activation and ADCC activity, and consequently malignant B-cell lysis, by lenalidomide was demonstrated in previously published in vitro and in vivo experiments [53, 54, 56-58]. In studies conducted in vitro in DLBCL tumour cells, tafasitamab in combination with lenalidomide resulted in increased ADCC activity, as compared to either agent alone. In one study, the addition of lenalidomide to tafasitamab resulted in a 20.6% increase in ADCC (95% CI: 2.0%–39.2%; p=0.03; compared to the tafasitamab analogue, XmAb5603).

The novel mechanism of action of tafasitamab and synergism with lenalidomide is an innovative treatment approach that has been demonstrated to be an effective, well tolerated, immunomodulatory, chemotherapy-free treatment option for patients with R/R DLBCL who are ineligible for ASCT or who have relapsed after ASCT.

5.3.3 Method of administration and dosage

Tafasitamab is administered via intravenous (IV) infusion and lenalidomide is administered orally. The recommended dose is 12 mg tafasitamab per kg body weight administered according to the following schedule:

- Cycle 1: Administer the infusion on day 1, 4, 8, 15 and 22 of the cycle.
- Cycles 2 and 3: Administer the infusion on day 1, 8, 15, and 22 of each cycle.
- Cycle 4 until disease progression: Administer the infusion on day 1 and 15 of each cycle.

Each cycle has 28 days.

Tafasitamab is for IV use after reconstitution and dilution.

- For the first infusion of cycle 1, the intravenous infusion rate should be 70 mL/h for the first 30 minutes. Afterwards, the rate should be increased to complete the first infusion within a 2.5-hour period.
- All subsequent infusions should be administered within a 1.5 to 2-hour period.
- In case of adverse reactions, consider the recommended dose modifications provided in Table 1.
- Tafasitamab must not be co-administered with other medicinal products through the same infusion line.
- Tafasitamab must not be administered as an intravenous push or bolus

In addition, patients should self-administer lenalidomide capsules at the recommended starting dose of 25 mg daily on days 1 to 21 of each cycle. The starting dose and subsequent dosing may be adjusted according to the lenalidomide Summary of Product Characteristics (SmPC).

Tafasitamab plus lenalidomide in combination is given for up to twelve cycles.

Treatment with lenalidomide should be stopped after a maximum of twelve cycles of combination therapy. Patients should continue to receive MINJUVI infusions as single agent on day 1 and 15 of each 28-day cycle, until disease progression or unacceptable toxicity.

5.3.4 Need for diagnostics or other tests

No additional tests or investigations are needed for the treatment with tafasitamab in combination with lenalidomide.

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6 Literature search and identification of efficacy and safety studies

6.1 Identification and selection of relevant studies

Evidence of the clinical effectiveness of the combined therapy tafasitamab+lenalidomide is supported by one phase II, single-arm study (L-MIND) and one observational study (RE-MIND). The RE-MIND study aimed to characterise the effectiveness of lenalidomide monotherapy in the treatment of R/R DLBCL patients and compare the effectiveness of lenalidomide monotherapy with the efficacy outcomes reported with tafasitamab+lenalidomide therapy in the L-MIND study. Since a comparison of the combination tafasitamab+lenalidomide vs lenalidomide in monotherapy is not relevant for the Danish setting (not the comparator in question), the results of RE-MIND trial are not presented in this dossier, but can be provided upon request.

As mentioned in section 5.2.2 the comparator in focus for Danish setting is R-GemOx. Since no head-to-head trial was available, Incyte investigated other possibilities to show comparative evidence. A systematic literature review (SLR) for efficacy and safety was conducted to supplement the data described above, with the objective to compile clinical evidence specific for the R/R DLBCL population. For R-GemOx, four studies were identified in the literature search, a PRISMA diagram following the selection process of relevance for this specific context can be found in Appendix A – Literature search for efficacy and safety of intervention and comparator(s) (figure 41).

For further details, please see Appendix A and the attached documents:

- 9_SLR DLBCL Clinical v3.pdf
- 10_SLR DLBCL Clinical Update Final 3.0.pdf

Of the four studies identified for R-GemOx for R/R patients with DLBCL in the SLR, one study was comparative vs bendamustine/rituximab (BR). This study together with two additional studies (Cazelles et al. and Schade et al.) were retrospective, observational studies that are not well suited to include in a matching adjusted indirect treatment comparison (MAIC), which is a commonly accepted methodology by HTA bodies across Europe. One identified study (Mounier et al.) was interventional and could therefore possibly be used to integrate in a MAIC. However, a MAIC methodology has several intrinsic limitations, such as limited availability of specific patient baseline characteristics in published studies and sample size reduction due to weighting. This could impact ability to avoid bias and achieve statistically significant results. If one compare the L-MIND study to Mounier et al, the following limitations were identified:

- Imbalances in unreported or unobserved patients' characteristics (e.g. history of primary refractoriness) could potentially bias the results as these cannot be included in the population-adjustment.
- Due to the poor overlap of L-MIND and Mounier et al. patient populations, a population adjustment is limited. As such, no adjustment can be made on refractoriness of patients to their prior therapy, older patients were kept in the L-MIND population while patients above 75 should not have been candidate for inclusion in the Mounier et al. study, and no adjustment on the number of prior lines of therapy received by patients could be made beyond the exclusion of patients treated in the fourth-line setting or beyond in L-MIND. As a consequence, any results produced by a MAIC are expected to be biased in favor of R-GemOx.
- As the type of assessment of surrogate outcomes (i.e. by an independent review committee or through the investigator) in Mounier et al. could not be determined, there is some uncertainties on the comparison of PFS and ORR.
- The Mounier et al. study enrolled numerous patients that were rituximab naïve, who were shown to benefit more from R-GemOx. As it is unclear whether rituximab-naïve patients would benefit more from tafasitamab+lenalidomide, there are some concerns about the shared effect modifier assumption in this comparison.

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- The effective sample size was small (n=20) and therefore any results of such an analysis would be uncertain.

These limitations could partially be mitigated by performing a large observational retrospective study which quantified the incremental added benefit of tafasitamab using 1:1 matching of individual patients based on key baseline characteristics. Therefore, the comparative efficacy of tafasitamab+LEN against R-GemOx was generated from a real-world, retrospective, observational study (RE-MIND2) against a cohort of patients treated with systemic NCCN/ESMO guideline listed regimens administered in routine clinical care. The first results from RE-MIND 2 versus Pola-BR, rituximab+lenalidomide and CAR T was published in November 2021 and data on the pooled cohort, BR and R-GemOx was recently published. [59]

The RE-MIND2 study enabled indirect comparisons against a diverse set of comparators including a pooled cohort, which effectively represented clinical practice or physician's choice at the time, in a setting where no established standard of care exists and treatment is heterogeneous across regions, countries, and centers.

The comparability across patients is discussed in Appendix C and rationale for comparative evidence in Appendix F.

6.2 List of relevant studies

A list of the relevant studies for tafasitamab+lenalidomide and R-GemOx is presented in Table 6. L-MIND and RE-MIND 2 was used to inform the efficacy data in the health economic model. The interventional single arm study for R-GemOx (Mounier et al) identified in the clinical SLR does inform some of the model inputs for R-GemOx (verified by Danish KOL or where KOL input was not sufficient), please see table 16 for more information. Therefore, Mounier et al is also presented in the table below.

Table 6. Relevant studies included in the assessment

Reference (title, author, journal, year)	Trial name	NCT number	Dates of study (start and expected completion date)
Long-term outcomes from the Phase II L-MIND study of tafasitamab (MOR208) plus lenalidomide in patients with relapsed or refractory diffuse large B-cell lymphoma *Düll et al, Haematologica, 2021*	L-MIND	NCT02399085	Study start date: March 2016 Primary Completion Date: Nov 2018 Estimated Study Completion Date: Nov 2022
Improved Efficacy of Tafasitamab plus Lenalidomide versus Systemic Therapies for Relapsed/Refractory DLBCL: RE-MIND2, an Observational Retrospective Matched Cohort Study *Nowakowski et al, Clinical Cancer Research, 2022*	RE-MIND 2	NCT04697160	Study Start Date: April 1, 2020 Primary Completion Date: May 7, 2021 Study Completion Date: May 7, 2021
Supportive evidence			
Rituximab plus gemcitabine and oxaliplatin in patients with refractory/relapsed diffuse large B-cell lymphoma who are not candidates for high-dose therapy. A phase II Lymphoma Study Association trial, Mounier et al, Haematologica, 2013	N/A	NCT00169195	Study start: April 2003 Completion: November 2012

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Furthermore, there are five ongoing clinical studies investigating tafasitamab (in combination with other treatment and as monotherapy) in 1L and 2L+ R/R DLBCL which were not included in this assessment (Table 7).

1. The pivotal study, L-MIND, a phase 2 open-label, multicentre study characterising the safety and efficacy of tafasitamab in combination with lenalidomide in adults with R/R DLBCL is ongoing [60]
2. B-MIND, an open-label, phase 2/3 randomised, two-arm, multicentre study of tafasitamab in combination with bendamustine vs rituximab in combination with bendamustine in R/R DLBCL patients who are 2L or 3L and who are not candidates for HDCT and ASCT (thus have exhausted their therapeutic options) [61].
3. An expanded access study for tafasitamab in patients who are R/R DLBCL [62].
4. FIRST-MIND, investigating tafasitamab monotherapy or tafasitamab+lenalidomide, both in addition to R-CHOP in 1L patients with DLBCL [63].
5. FrontMIND, comparing the efficacy and safety of Tafasitamab + lenalidomide in addition to R-CHOP against R-CHOP in 1L, high-intermediate and high-risk patients with newly-diagnosed DLBCL [64].

Table 7. Ongoing studies for tafasitamab in DLBCL, not included in the assessment

Reference (title, author, journal, year)	Trial name	NCT number	Dates of study (start and expected completion date)
Ongoing studies			
Phase Ib Study to Assess Safety and Preliminary Efficacy of Tafasitamab or Tafasitamab Plus Lenalidomide in Addition to R-CHOP in Patients With Newly Diagnosed DLBCL	*MOR208C107 FIRST-MIND*	*NCT04134936*	Active, not recruiting Start: December 11, 2019 Estimated completion: January 2023
A Study to Evaluate the Safety and Efficacy of Lenalidomide With MOR00208 in Patients With R-R DLBCL	*MOR208C203 L-MIND*	*NCT02399085*	Active, not recruiting Start: March 2016 Estimated completion: December 2022
A Trial to Evaluate the Efficacy and Safety of Tafasitamab With Bendamustine (BEN) Versus Rituximab (RTX) With BEN in Adult Patients With Relapsed or Refractory Diffuse Large B-cell Lymphoma (DLBCL)	*MOR208C204 B-MIND*	*NCT02763319*	Active, not recruiting Start: June 2016 Estimated completion: March 2024
Expanded Access Program for Tafasitamab (MOR00208) in R/R DLBCL	*MOR208N001*	*NCT04300803*	Approved for marketing Start: n/a Estimated completion: n/a
Tafasitamab + Lenalidomide + R-CHOP Versus R-CHOP in Newly Diagnosed High-intermediate and High Risk DLBCL Patients	*FrontMIND*	*NCT04824092*	Recruiting Start: May 11, 2021 Estimated completion: May 2026

7 Efficacy and safety

7.1 Efficacy and safety of tafasitamab+lenalidomide compared to R-GemOx for R/R DLBCL

As mention in chapter 6, evidence for the clinical effectiveness of the combined therapy tafasitamab+lenalidomide (LEN) is supported by the phase II, single-arm study (L-MIND) whose updated efficacy analysis was published by Düll et al. These results are presented in section 7.1.2. For the comparator of interest, R-GemOx, three single-arm studies in R/R DLBCL were identified in the literature search [65-67] but they where not used in the comparative analysis of efficacy

and safety (however, one of them was used to inform some of inputs for R-GemOX in the health economic model and is therefore presented in list in table 6 above as supportive evidence). Instead, the comparative efficacy of tafasitamab+LEN against R-GemOx was generated by a real-world, retrospective, observational study (RE-MIND2) against a cohort of patients treated with systemic NCCN/ESMO guideline listed regimens administered in routine clinical care. The RE-MIND2 results are presented in section 7.1.3.

7.1.1 Relevant studies

An overview of the relevant studies to demonstrate clinical efficacy and safety for tafasitamab+LEN and R-GemOx is presented in Table 8. Detailed study characteristics are available in appendix B and baseline characteristics of patients included in the studies used in the comparative analysis are presented in appendix C.

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Table 8. Overview of relevant studies to demonstrate clinical efficacy and safety for tafasitamab+LEN and R-GemOx

Study Name	Study design	Population (n)	Intervention	Comparator	Main outcomes	Study used in health economic model
Tafasitamab + LEN						
L-MIND	Phase 2, open-label, single-arm, multicentre study	81	12 tafasitamab + LEN 28-day cycles followed by tafasitamab monotherapy (in patients with stable disease or better) until disease progression	Not applicable (Single arm)	• Primary: ORR • Secondary: o DoR o PFS o OS	Yes
R-GemOx						
RE-MIND 2	A real-world, retrospective, observational study, using a propensity score-based, 1:1 matched comparison	Total: 3,454 Matched systemic therapies pooled : 76 Matched R-GemOx: 74	• Systemic therapies pooled cohort • BR cohort • R-GemOx cohort • Rituximab + lenalidomide (R-Len) cohort • CAR T-cell cohort • Pola-BR cohort • Pixantrone monotherapy Based on the choice of comparator, this documentation describes the results for the comparison against R-GemOx, as well as the overall results for the pooled analysis considering all comparators	Tafasitamab + lenalidomide	• Primary: OS • Secondary: o ORR o CRR o DoR o Event-free survival (EFS) o PFS o TTNT o Treatment discontinuation rate due to AEs o Duration of treatment exposure	Yes

Abbreviations: DLBCL, diffuse large B-cell lymphoma; GEM, gemtcitabine; GemOx, gemcitabine and oxaliplatin; LEN, lenalidomide; DoR, duration of response; ORR, objective response rate; OS, overall survival, PFS, progression-free survival, R-GemOx, rituximab, gemcitabine and oxaliplatin; RTX, rituximab. Notes: *Patients receiving R-GemOx in second line. **If at least a PR was achieved after 4 cycles, 8 cycles were planned. †Cycles were postponed until the absolute neutrophil count reached 1.0x109/L and the platelet count reached 100x109/L. ‡The dose of oxaliplatin was adjusted in the event of peripheral neuropathy.

7.1.2 Efficacy and safety: L-MIND

L-MIND was a single-arm, multicentre, open-label, phase 2 study of tafasitamab in combination with lenalidomide followed by tafasitamab monotherapy in adult patients with DLBCL who had relapsed after or were refractory to at least one, but no more than three, previous systemic regimens, and who were not candidates for HDCT and subsequent ASCT. Tafasitamab in combination with lenalidomide was administered for up to 12 cycles (28 days each), followed by tafasitamab monotherapy until progression in patients with a response of SD or better [58]. Detailed characteristics of the L-MIND study are provided in Appendix B.

Tafasitamab in combination with lenalidomide followed by tafasitamab monotherapy demonstrated outstanding efficacy and offered high and durable response rates in patients with NTE R/R DLBCL after 1–3 prior systemic therapies (including an anti-CD20 therapy). The IRC-reported best ORR was 57.5%, with a CRR of 40%, which translated to long OS [68].

Taken together, the long-term outcomes from L-MIND show that the combination of tafasitamab and lenalidomide demonstrated a high CR rate with long lasting remissions and a very favourable survival benefit in this population of adult patients with R/R DLBCL who are not eligible for ASCT, including in difficult-to-treat subgroups [69].

7.1.2.1 Primary outcome: ORR

The best objective response was CR for 32 patients (n=32/80; 40.0%) and PR for 14 patients (n=14/80; 17.5%). Based on these data, the Independent Radiology/Clinical Review Committee (IRC)-assessed best ORR was 57.5% (95% CI: 45.9%–68.5%). Twenty-six patients had SD or PD (n=13/80; 16.3% for each group) as their best objective response. As in the initial analysis, eight (n=8/80; 10.0%) patients were not evaluable, as no valid post-baseline radiological examination for response assessment was available or the baseline scan was inadequate. These patients were included as non-responders in the analysis [69]. The best ORR data are summarised in Table 9.

Table 9. Best objective response rate: L-MIND (long-term outcomes data cut-off 30 October 2020; FAS; IRC assessed)

	Tafasitamab+lenalidomide (N=80)
Best objective response,* n (%)	
CR [95% CI]	32 (40.0) [29.2–51.6]
PR [95% CI]	14 (17.5) [9.9–27.6]
SD	13 (16.3)
PD	13 (16.3)
Not evaluable	8 (10.0)
Best ORR† [95% CI]	46 (57.5) [45.9–68.5]

Abbreviations: CI, confidence interval; CR, complete response; FAS, Full Analysis Set; IRC, Independent Radiology/Clinical Review Committee; ORR, objective response rate; PD, progressive disease; PR, partial response; SD, stable disease.

Note: After the CSR addendum (dated 13 Mar 2020), the Sponsor detected an error in the radiology adjudication of the response assessment by the IRC for one patient (patient 36001-05), for which the comment of the adjudicating radiologist (the 'Adjudicator') did not match the selection of the best response by the Adjudicator. The Adjudicator's comment indicated that he/she agreed with radiology Reviewer 1 who assessed a best response of SD but selected the response of CR assessment provided by radiology Reviewer 2 by mistake. Upon detection of this discrepancy, clarification was sought from the adjudicating radiologist, and he/she confirmed that the response assessment of SD as per the comment provided was correct, and that the selected response assessment of CR was incorrect. Subsequently, the Sponsor reviewed and reconciled the comments of the adjudicating radiologist against the selection for the other 21 cases that had required adjudication by the IRC process. Based on this review, the Sponsor confirms that no other human errors during the adjudication process were detected. As a result, the adjudication error for patient 36001-05 was corrected and the corrected efficacy analyses are described in this table.

*New tumour imaging and/or clinical data accumulated between the data cut offs of 30 November 2019 and 30 October 2020 were assessed by IRC for 19 of 22 patients ongoing on tafasitamab treatment. For two patients the best response changed from CR to PR. For two additional patients the best response changed from PR to CR.

†CR+PR

Sources: Düll et al. 2021 [70]; Incyte, Data on file (L-MIND CSR Addendum 3) [69].

7.1.2.2 Secondary outcomes

The secondary efficacy outcomes from L-MIND are summarised in Table 10.

Table 10. Secondary endpoint results: L-MIND (long-term outcomes data cut-off 30 October 2020; FAS; IRC assessed)

	Tafasitamab+lenalidomide (N=80)
DoR*	
Patients with response	46
Progression, n (%)	13 (28.3)
Death, n (%)	2 (4.3)
Censored, n (%)	31 (67.4)
Median, months [95% CI]	43.9 [26.1, NR]
36 months, % [95% CI]	64.3 [46.8, 77.4]
48 months, % [95% CI]	NR [NR, NR]
Patients with CR	
Median, months [95% CI]	NR [43.9, NR]
36 months, % [95% CI]	80.1 [58.1, 91.3]
42 months, % [95% CI]	80.1 [58.1, 91.3]
Patients with PR	
Median, months [95% CI]	5.6 [2.2, NR]
PFS†	
Median follow-up,‡ months [95% CI]	33.9 [26.5, 35.4]
Progression, n (%)	34 (42.5)
Death, n (%)	8 (10.0)
Censored, n (%)	38 (47.5)
Median, months [95% CI]	11.6 [6.3, 45.7]
36 months, % [95% CI]	41.1 [29.1, 52.7]
48 months, % [95% CI]	34.3 [19.3, 49.9]
OS§	
Median follow-up,‡ months [95% CI]	42.7 [38.0, 47.2]
Death, n (%)	41 (51.3)
Censored, n (%)	39 (48.8)
Median, months [95% CI]	33.5 [18.3, NR]
36 months, % [95% CI]	47.3 [35.5, 58.2]
54 months, % [95% CI]	41.0 [28.2, 53.4]
Patients with CR	
Median, months [95% CI]	NR [45.7, NR]
36 months, % [95% CI]	81.3 [62.9, 91.1]
54 months, % [95% CI]	68.8 [44.8, 83.9]
Patients with PR	
Median, months [95% CI]	22.5 [8.6, NR]

Abbreviations: CI, confidence interval; CR, complete response; DoR, duration of response; FAS, Full Analysis Set; IRC, Independent Radiology/Clinical Review Committee; NR, not reached; OS, overall survival; PFS, progression-free survival; PR, partial response. *DoR [months] = (date of assessment of tumour progression or death–date of assessment of firstdocumented response of (CR or PR)+1)/30.4375.

†The PFS time was defined as the time (in months) from the date of the first administration of any study drug to the date of tumour progression or death from any cause.

‡The median follow-up time for PFS and OS was calculated using the reverse Kaplan-Meier method, considering the censored patients as events and patients with events as censored.

§OS was defined as the time from the date of the first administration of any study drug until death from any cause (documented by the date of death).

Sources: Düll et al. 2021 [70]; Incyte, Data on file (L-MIND CSR Addendum 3) [69].

7.1.2.2.1 Duration of response

As of the 30 October 2020 data cut-off, the median DoR among patients achieving CR or PR was 43.9 months (95% CI: 26.1%–NR). Of the 46 responders, 13 (n=13/80; 28.3%) patients progressed, two (n=2/80; 4.3%) patients died, and a further 31 (n=31/80; 67.4%) patients were censored. Kaplan–Meier probability estimates for DoR at 12 months was 73.7% (95% CI: 57.4%–84.5%), at 24 months was 67.9% (95% CI: 51.0%–80.1%), and at 36 and 42 months was 64.3% (95% CI: 46.8%–77.4%) [69, 70].

A Kaplan–Meier plot of DoR by best objective response CR or PR for patients in the FAS (IRC evaluation) is presented in Figure 2 [68]. Of the 32 patients with a best objective response of CR, five patients progressed (n=5/32; 15.6%), one patient died (n=1/32; 3.1%), and a further 26 patients were censored (n=26/32; 81.3%).[69] The estimate of the median DoR for patients with a best objective response of CR was not reached. The Kaplan–Meier probability estimate for patients with a best objective response of CR was 93.1% (95% CI: 74.9%–98.2%) at 12 months, 85.1% (95% CI: 64.9%–94.2%) at 24 months, and 80.1% (95% CI: 58.1%–91.3%) at 36 and 42 months.[69] Of the 14 patients (n=14/80; 18%) with PR, the median DoR was 5.6 months (95% CI: 2.2–NR); eight patients progressed (n=8/14; 57.1%), one patient died (n=1/14; 7.1%), and a further five patients were censored (n=5/14; 35.7%) [69].

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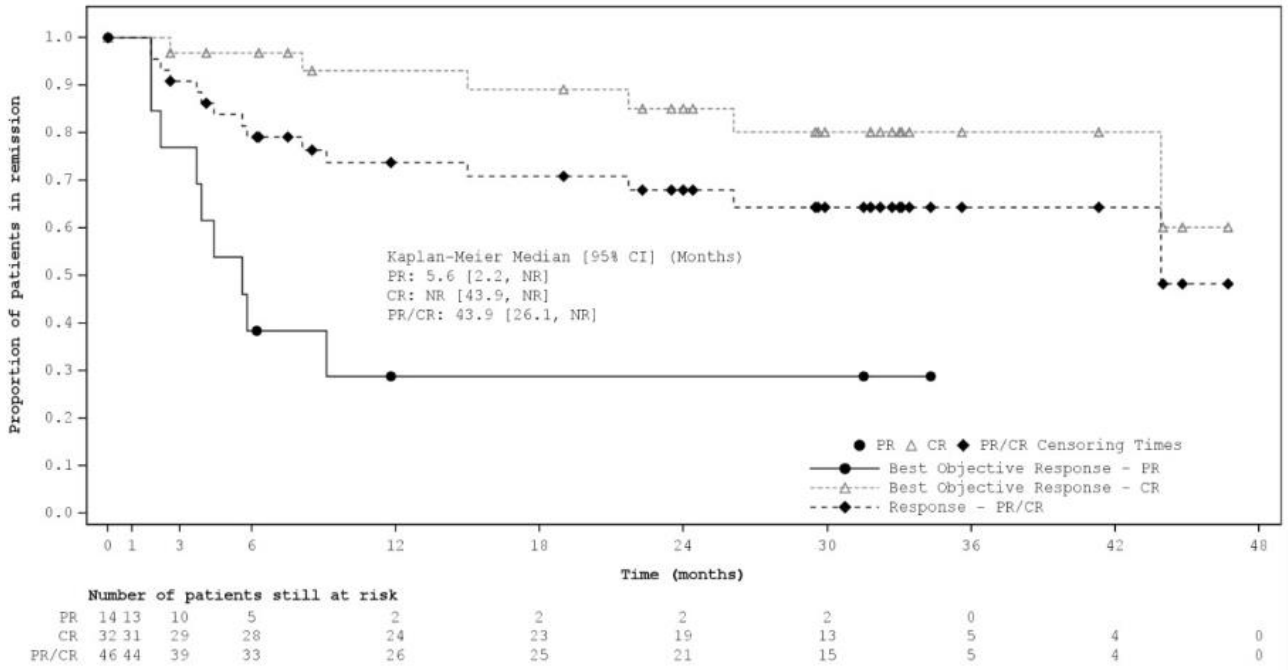

Figure 2. Kaplan–Meier plot of duration of response by best objective response (long-term outcomes data cut-off 30 October 2020; FAS; IRC assessed; L-MIND)

Notes: In case the median or the respective confidence limits were not calculable by the Kaplan–Meier method, NR is displayed instead. The 34 patients with best objective response not PR or CR were not included in this subgroup analysis.

Abbreviations: CI, confidence interval; CR, complete response; FAS, Full Analysis Set; IRC, Independent Radiology/Clinical Review Committee; NR, not reached; PR, partial response.

Source: Duell et al, 2021 [68]

7.1.2.2.2 Progression-free survival

In the updated efficacy analysis, PFS events were observed in 42 patients (n=42/80; 52.5%). A Kaplan–Meier curve of PFS in the FAS is presented in Figure 3. The Kaplan–Meier estimate for the median PFS was 11.6 months (95% CI: 6.3–45.7 months) with a median follow-up time of 33.9 months (95% CI: 26.5–35.4 months) [68, 70]. At 24 months, the Kaplan–Meier estimate of PFS was 43.1% and at 36 months it was 41.1% [70, 71]

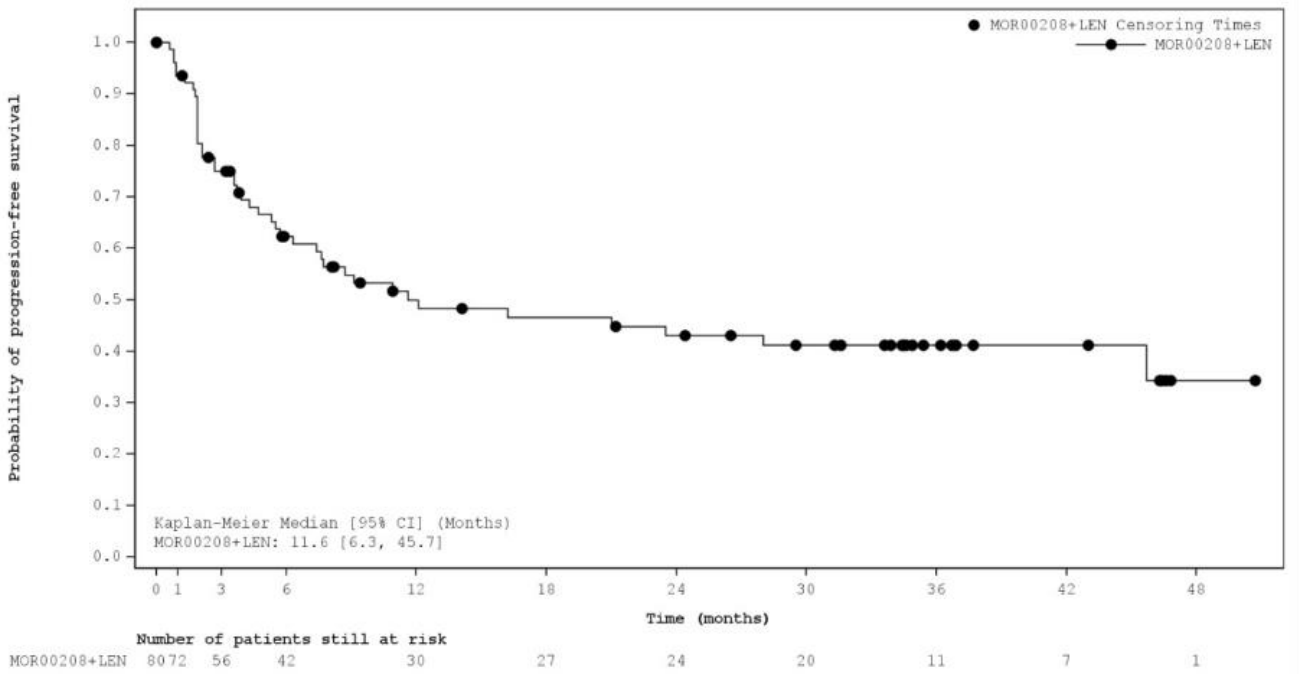

Figure 3. Kaplan–Meier plot of progression-free survival (long-term outcomes data cut-off 30 October 2020; FAS; IRC assessed; L-MIND)

Note: In case the median or the respective confidence limits were not calculable by the Kaplan–Meier method, NR is displayed instead.

Abbreviations: CI, confidence interval; FAS, Full Analysis Set; IRC, Independent Radiology/Clinical Review Committee; LEN, lenalidomide; NR, not reached.

Sources: Düll et al. 2021;[70] Incyte, Data on file (L-MIND CSR Addendum 3).[69]

7.1.2.2.3 Overall survival

The Kaplan–Meier estimate for median OS was 33.5 months (95% CI: 18.3 months–NR; Figure 4) with a median follow-up time of 42.7 months (95% CI: 38.0–47.2 months). Overall, 41 patients died (n=41/80; 51.3%). Thirty-nine patients were censored in the OS analysis, including one patient due to being lost-to-OS follow-up. The Kaplan–Meier probability estimate of OS at 12 months was 73.7% (95% CI: 62.2%–82.2%), 57.2% (95% CI: 45.1%–67.5%) at 24 months, 47.3% (95% CI: 35.5%–58.2%) at 36 months, and 41.0% (95% CI: 28.2%–53.4%) at 54 months [69].

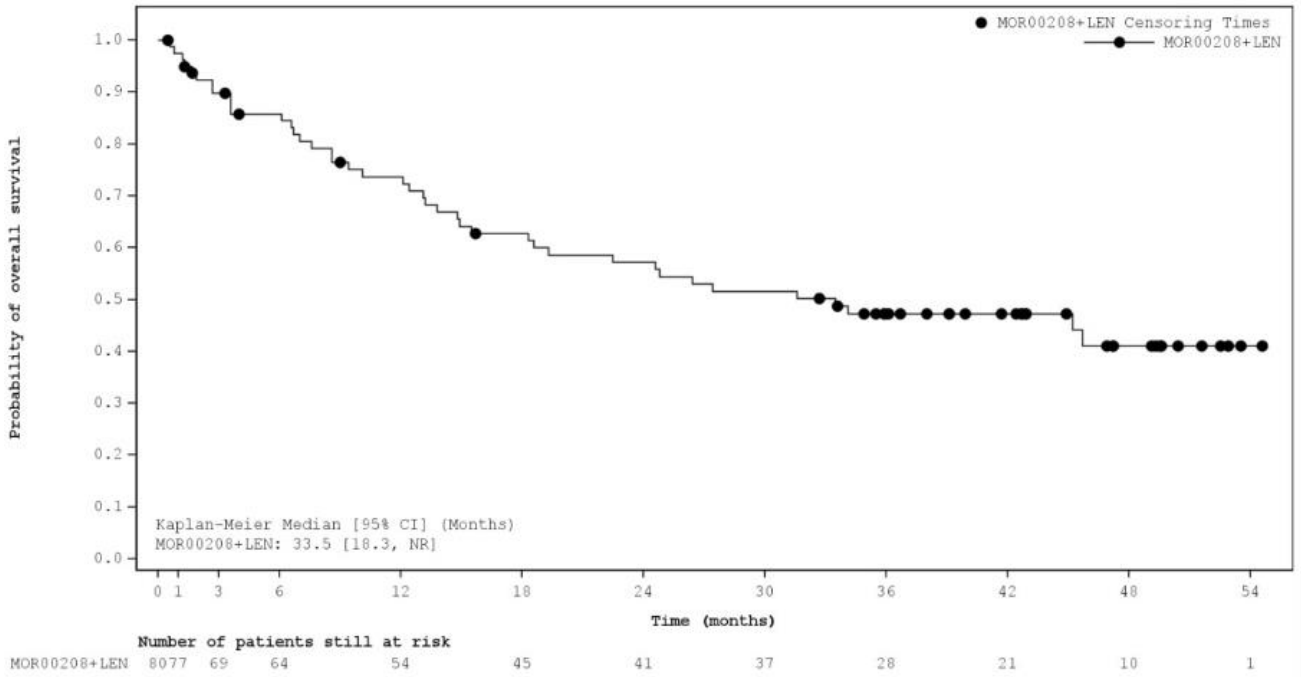

Figure 4. Kaplan–Meier plot of overall survival (long-term outcomes data cut-off 30 October 2020; FAS; IRC assessed; L-MIND)

Note: In case the median or the respective confidence limits were not calculable by the Kaplan-Meier method, NR is displayed instead.

Abbreviations: CI, confidence interval; FAS, Full Analysis Set; LEN, lenalidomide; NR, not reached.

Source: Düll et al. 2021;[70] Incyte, Data on file (L-MIND CSR Addendum 3).[69]

The Kaplan–Meier estimate for median OS by best objective response of CR (IRC) was not reached (95% CI: 45.7 months–NR; FAS;Figure 5) at the 30 October 2020 cut-off date [69]. For this subgroup of patients, the Kaplan–Meier probability estimate of OS was 96.9% (95% CI: 79.8%–99.6%) at 12 months, 90.6% (95% CI: 73.7%–96.9%) at 24 months, 81.3% (95% CI: 62.9%–91.1%) at 36 months, and 68.8% (95% CI: 44.8%–83.9%) at 54 months.[69] The Kaplan–Meier estimate for median OS by best objective response of PR was 22.5 months (95% CI: 8.5 months–NR; FAS;Figure 5).

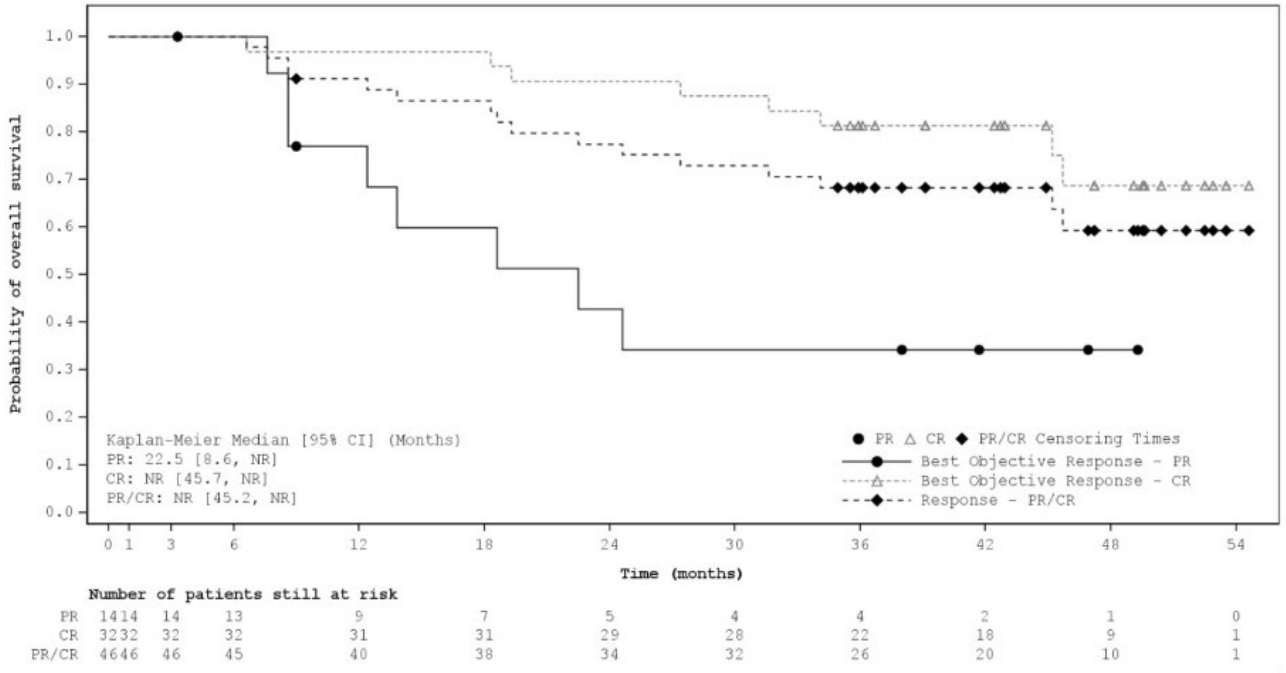

Figure 5. Kaplan–Meier plot of overall survival by best objective response (long-term outcomes data cut-off 30 October 2020; FAS; IRC assessed; L-MIND)

Note: In case the median or the respective confidence limits were not calculable by the Kaplan–Meier method, NR was displayed instead. Thirty-four patients with best objective response not PR or CR were not included in this subgroup analysis.

Abbreviations: CI, confidence interval; CR, complete response; FAS, Full Analysis Set; NR, not reached; PR, partial response.

Sources: Düll et al. 2021;[70] Incyte, Data on file (L-MIND CSR Addendum 3) [69].

7.1.2.3 Subgroup analysis

The L-MIND efficacy results were consistent across various subgroups of interest. In particular, in poor prognosis subgroups—patients with two or more lines of treatment, refractory to prior treatment, or GCB cell of origin disease—results were comparable to the overall study population (Table 11) [70, 71].

Table 11. Outcomes across patient subgroups of interest (L-MIND)

Subgroup (FAS)	ORR % (95% CI)	CR %	mDoR % (95% CI)	mPFS months (95% CI)	mOS months (95% CI)
[redacted]					
[redacted]					
[redacted]					
[redacted]					
[redacted]					

Abbreviations: CR, complete response; mDoR, median duration of response; FAS, Full Analysis Set; GCB, germinal centre B-cell; mOS, median overall survival; mPFS, median progression-free survival; NR, not reached.

Sources: Düll et al. 2021 [70]; Incyte, Data on file (L-MIND CSR Addendum 3) [69]; Incyte, Data on File (Analysis tables) [71].

7.1.2.4 Safety

In the pivotal L-MIND clinical trial, treatment-emergent AEs (TEAEs) of any grade occurred in all 81 patients. Of these, 84% (n=68/81) experienced a TEAE suspected to be related to any study drug [69]. Based on their single-agent safety profiles, no new safety signals were identified for either agent or the combination during this study. The observed TEAEs during treatment with tafasitamab in combination with lenalidomide followed by tafasitamab monotherapy reflect the established safety profile of lenalidomide.

As of the 30 October 2020 data cut-off, the most frequently reported grade ≥3 haematological TEAEs (≥5% of patients) were: neutropaenia (49.4%; n=40/81); thrombocytopaenia (17.3%; n=14/81); febrile neutropaenia (12.3%; n=10/81); leukopaenia (11.1%; n=9/81); and anaemia (7.4%; n=6/81). Pneumonia (9.9%; n=8/81) and hypokalaemia (6.2%; n=5/81) were the most frequent non-haematological TEAEs (≥5% of patients) [69].

Forty-three patients (53.1%; n=43/81) experienced treatment-emergent serious adverse events (TESAEs) during the study with the most frequently experienced (≥2 patients) grade ≥3 TESAEs being pneumonia (8.6%; n=7/81) and febrile neutropaenia (6.2%; n=5/81) [69].

In total, 20 patients (24.7%; n=20/81) discontinued treatment with one or both study drugs because of TEAEs during the study. Eight discontinuations were related to one of or both treatments, one was found to be exclusively related to

tafasitamab (bronchitis), three were found to be exclusively related to lenalidomide (tumour flare, diarrhoea, and neutropaenia) and four discontinuations were found to be related to both (allergic dermatitis, thrombocytopaenia, and two times neutropaenia) [69].

Eight patients died during study treatment (9.9%; n=8/81; as of the 30 November 2018 data cut-off) and no new on-treatment deaths occurred as of the 30 October 2020 data cut-off. TEAEs leading to death occurred in three patients (3.7%; n=3/81) due to sudden death, respiratory failure, and cerebrovascular accident. None were considered related to the study treatment. The remaining five deaths were due to disease progression [58, 69].

Detailed safety information for the L-MIND study is provided in Appendix E.

7.1.3 Comparative analysis of efficacy and safety Tafasitamab+LEN compared to systemic therapies for patients with R/R DLBCL: RE-MIND2

RE-MIND2 established the comparative benefit of tafasitamab in combination with lenalidomide followed by tafasitamab monotherapy against a real-world, retrospective, observational cohort of patients treated with ESMO/NCCN guideline-listed regimens administered in routine clinical care. Using a propensity score-based, 1:1 matched comparison (Nearest Neighbour (NN) 1:1 matching methodology was utilised to balance the cohorts by means of baseline covariates such as number of prior lines of therapy and Ann Arbor stage) — this company-sponsored, large (N=3454), observational, retrospective study served as an external control to trial data from L-MIND [74, 75]. Further information on the L-MIND study is provided in section 7.1.2.

Although the RE-MIND2 study included patients treated with other systemic regimens for R/R DLBCL, this section describes the results for the comparison against R-GemOx. Detailed characteristics of the RE-MIND2 study are provided in Appendix B, baseline characteristics of patients included in the RE-MIND2 study are presented in Appendix C and detailed methods and results are presented in Appendix F.

7.1.3.1 Primary outcome: OS

Overall survival was the primary endpoint and was met in all primary analysis sets (MAS_Pool, and MAS_R-GemOx, see Table 85 for definitions) conducted in the pre-specified analysis of the RE-MIND2 study results based on 1:1 matching with nine baseline covariates. Tafasitamab in combination with lenalidomide followed by tafasitamab monotherapy provided 22.5 months of incremental median OS when compared with systemic therapies pooled and 20.6 months compared to R-GemOx [74]. The difference in OS between cohorts was statistically significant in favour of tafasitamab in combination with lenalidomide followed by tafasitamab monotherapy compared to the pooled systemic therapies (HR=0.553 [95% CI: 0.358–0.855]; Cox proportional hazard model p=0.0076); and R-GemOx (HR=0.467 [95% CI: 0.305–0.714]; Cox proportional hazard model p=0.0004), respectively [74]. Kaplan−Meier plots of OS are provided in Figure 6.

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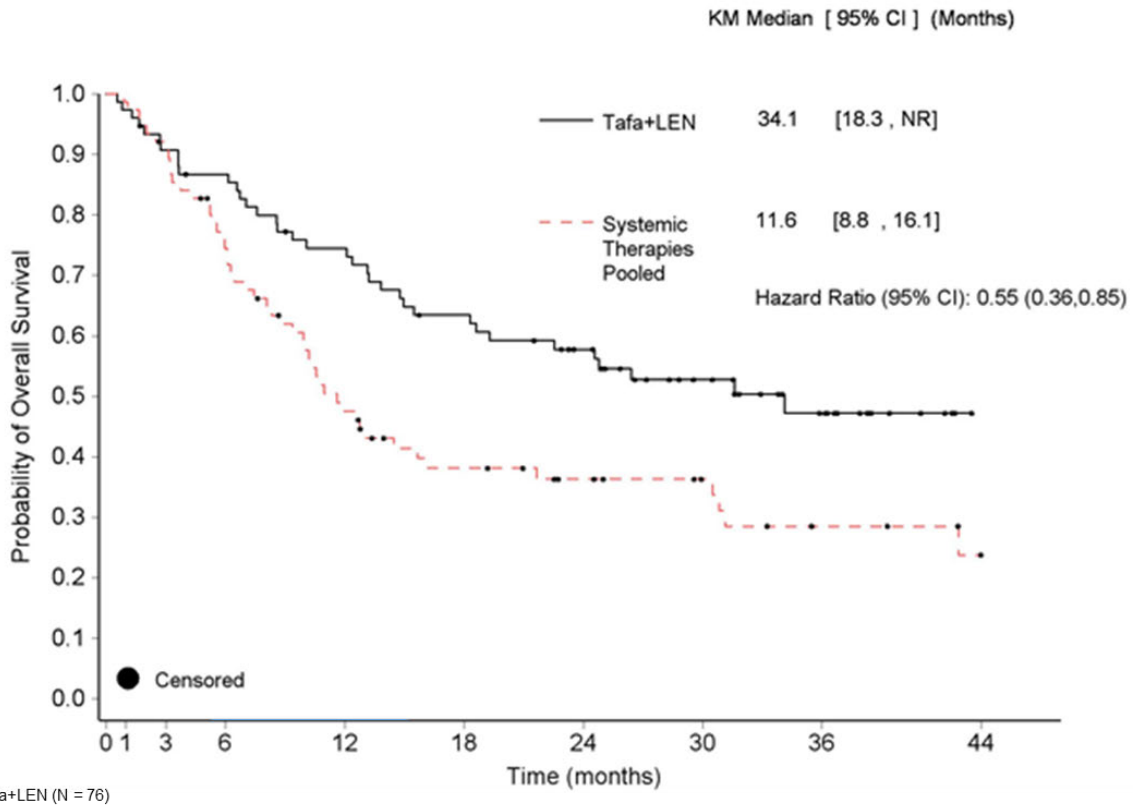


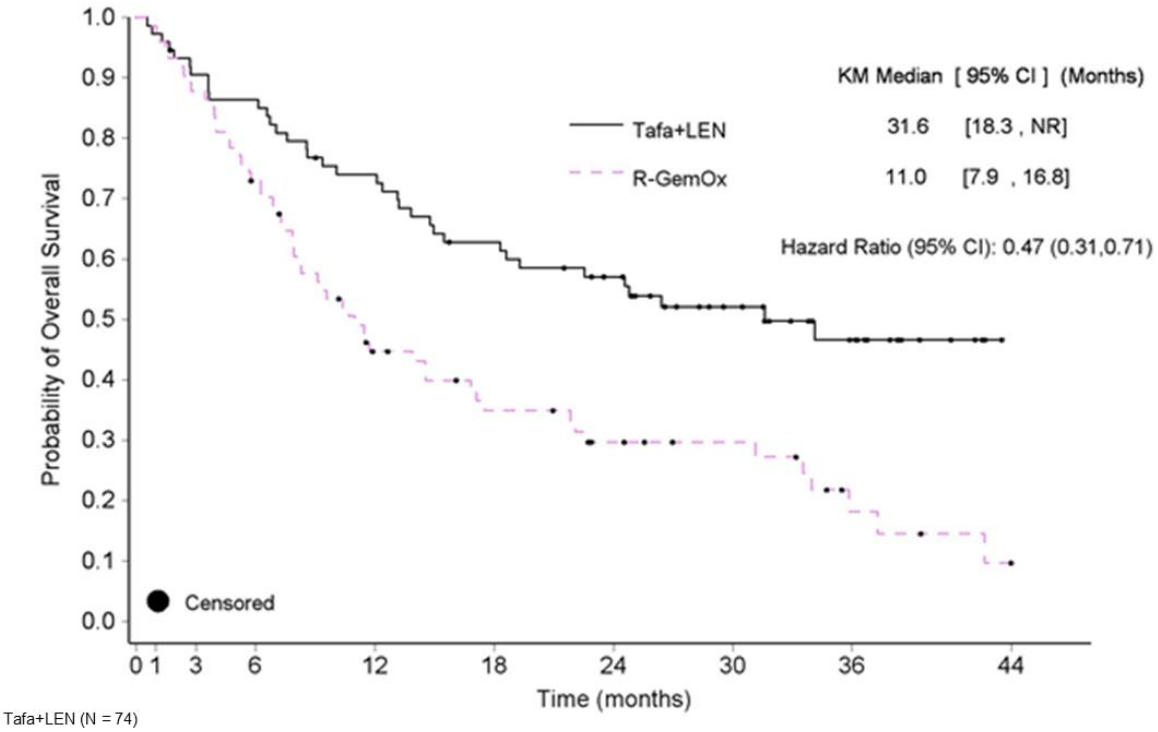
Tafa+LEN (N = 76)

at risk	76	74	68	64	54	45	37	24	14	0
event(s)	0	2	7	10	19	27	31	34	35	36
censored	0	0	1	2	3	4	8	18	25	40

Systematic Therapies Pooled (N = 76)

at risk	76,	75	68	54	33	23	18	14	8	0
event(s)	0	1	7	19	38	44	45	45	48	49
censored	0	0	1	3	5	9	13	17	20	27

(a) Subset of L-MIND patients matched with the observational cohort for pooled systemic therapies (MAS_Pool)



Tafa+LEN (N = 74)									
at risk	74	72	66	63	53	44	37	24	14	0
event(s)	0	2	7	10	19	27	31	34	36	36
censored	0	0	1	1	2	3	6	16	24	48
R-GemOx (N = 74)										
at risk	74	73	65	53	29	21	15	12	5	0
event(s)	0	1	9	20	40	46	49	49	53	55
censored	0	0	0	1	5	7	10	13	16	19

(b) Subset of L-MIND patients matched with the observational cohort of patients taking R-GemOx (MAS_R-GemOx)

Figure 6. RE-MIND2: Kaplan–Meier plot for overall survival: MAS_Pool and MAS_R-GemOx

Abbreviations: CI, confidence interval; KM, Kaplan–Meier; LEN, lenalidomide; MAS, matched analysis set; NR, not reached; R-GemOx, rituximab + gemcitabine + oxaliplatin; Tafa, tafasitamab.

Notes: MAS_Pool included 1:1 matched patients from the L-MIND study and the observational cohort using 9 baseline covariates. MAS_R-GemOx included 1:1 matched patients from the L-MIND study and R-GemOx as pre-specified treatment. See Table 85 for definitions on MAS_Pool and MAS_R-GemOx.

The median was calculated with Kaplan–Meier method. The 95% CI was calculated by means of Greenwood formula.

HR was calculated with Cox proportional hazard model.

Source: Incyte, Data on file (RE-MIND2 CSR) [74].

Subgroup analysis of OS was consistent with the primary matched analysis results. Median Kaplan–Meier estimates of OS for each primary analysis set showed notable differences in favour of tafasitamab+lenalidomide for the following subgroups [74]:

- MAS_Pool: Age: <70 and ≥70, Ann Arbor stage: III+IV, Refractoriness to last therapy line: Yes; Number of prior lines of therapy: 2/3, History of primary refractoriness: No, and Prior ASCT: Yes and No.
- MAS_R-GemOx: Age: <70, Ann Arbor stage: III+IV, Refractoriness to last therapy line: Yes; History of primary refractoriness: No, and Prior ASCT: Yes and No.

Also, for both primary analysis sets, the difference in the median Kaplan−Meier estimates of OS showed favourable OS trends for tafasitamab+lenalidomide in the subgroups of Ann Arbor stage: I+II, Refractoriness to last therapy line: No, and Number of prior lines of therapy: 1.

7.1.3.2 Secondary efficacy outcomes

This section describes the main secondary outcomes from the RE-MIND2 study, namely ORR and PFS. Other secondary outcomes are presented in Appendix F.

7.1.3.2.1 Overall/objective response rate (ORR)

The percentage of patients with best ORR for tafasitamab in combination with lenalidomide followed by tafasitamab monotherapy was 67.1% (95% CI: 55.4%–77.5%) vs 48.7% (95% CI: 37.0%–60.4%) for the comparison with pooled systemic therapies; and 68.9% (95% CI: 57.1%–79.2%) vs 45.9% (95% CI: 34.34%–57.9%) for the comparison with R-GemOx. The difference of ORR between cohorts was statistically significantly in favour of tafasitamab+lenalidomide for MAS_Pool (18.42%; 95% CI: 1.905%–34.204%; p=0.0323) and MAS_R-GemOx (22.97%; 95% CI: 6.285%–38.722%; p=0.0076) [74]. A forest plot of ORR for different analysis sets is provided in Figure 7.

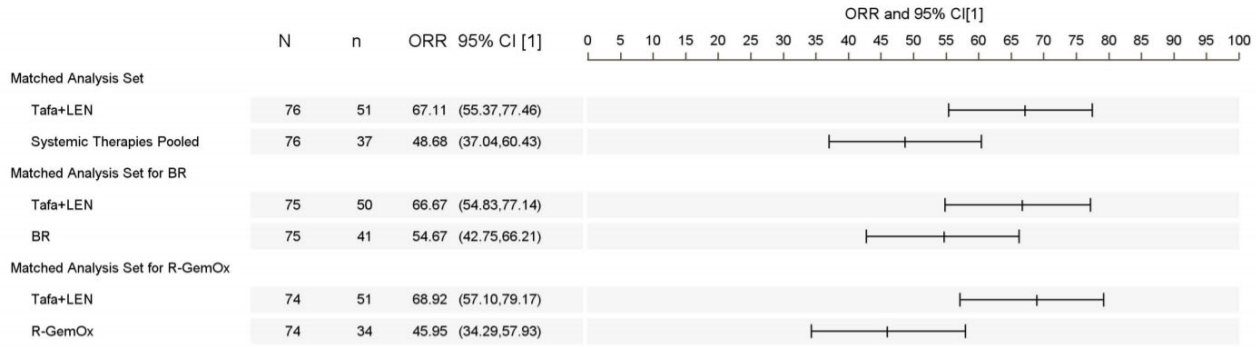


Figure 7. RE-MIND2: Forest plot of ORR for different analysis sets

Abbreviations: BR, bendamustine + rituximab; CR, complete response; CI, confidence interval; LEN, lenalidomide; ORR, objective response rate; R-GemOx, rituximab + gemcitabine + oxaliplatin; N, number of patients in each cohort.

[1] Chan-Zhang method [76]. See Table 85 for definitions on MAS_Pool and MAS_R-GemOx.

The vertical gray line indicates a rate of 0.

HR was calculated using the observational cohort as reference cohort. HR <1.0 is in favour of tafasitamab+lenalidomide. Difference in ORR rate = [(ORR rate of tafasitamab+lenalidomide cohort) − (ORR rate of observational cohort)]. Source: Incyte, Data on file (RE-MIND2 CSR) [74].

Data on the comparison against BR is not presented in this submission.

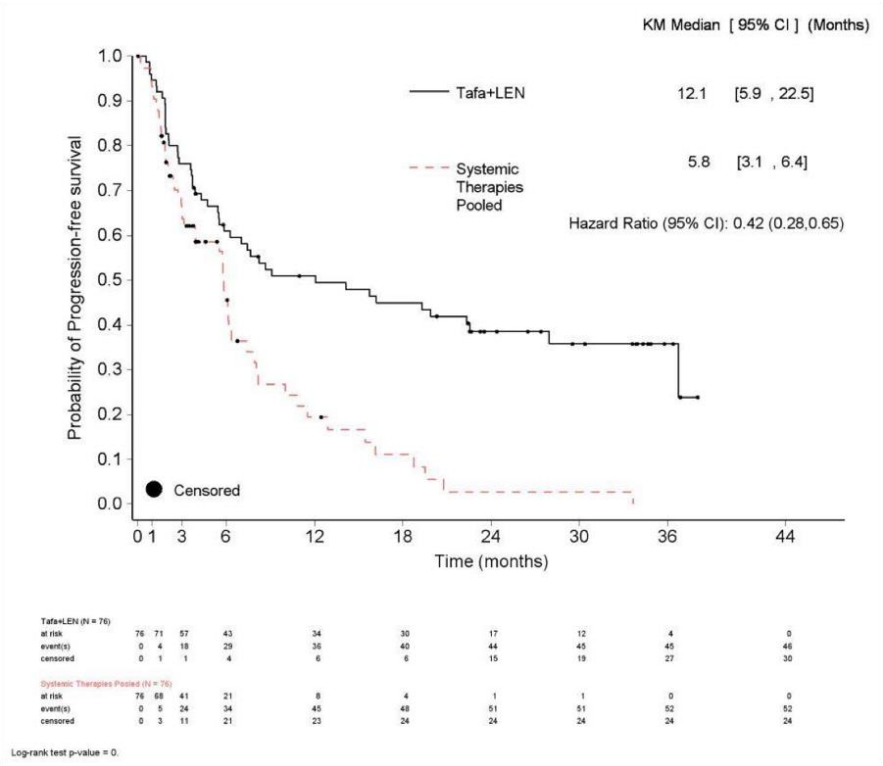
Overall, the subgroup analysis of ORR was consistent with the primary matched analysis results. The percentage of patients with overall response as the best response was higher in the tafasitamab+lenalidomide cohort compared to the cohorts of systemic therapies pooled, and R-GemOx across all the subgroups [74].

7.1.3.2.2 Progression-free survival (PFS)

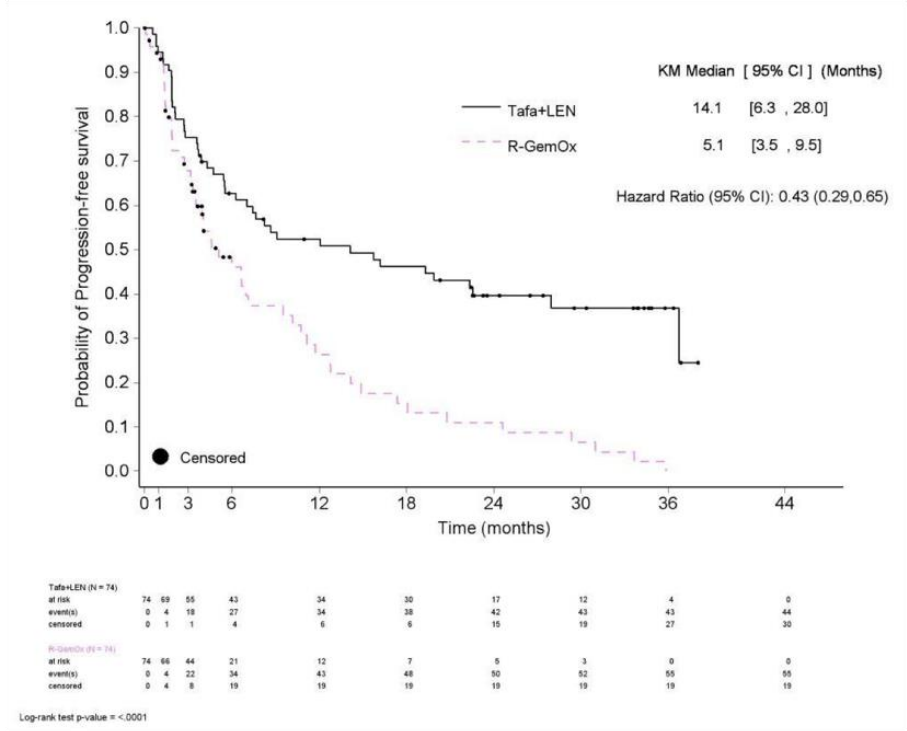
The median PFS with tafasitamab in combination with lenalidomide followed by tafasitamab monotherapy was longer compared to the cohorts of systemic therapies pooled (12.1 vs 5.8 months), and R-GemOx (14.1 vs 5.1 months). The PFS statistically significantly improved in the tafasitamab+lenalidomide cohort compared to the cohorts of systemic therapies pooled (HR=0.424 [95% CI: 0.278–0.647]; Cox proportional hazard model p<0.0001), and R-GemOx (HR=0.433 [95% CI: 0.288–0.653]; Cox proportional hazard model p<0.0001) [74].

The proportion of patients who had a PFS event (of progression or death) was lower in the tafasitamab+lenalidomide cohort compared to the cohorts of systemic therapies pooled (60.5% vs 68.4%), and R-GemOx (59.5% vs 74.3%). Disease

progression was the most frequent PFS event across the cohorts. The probability of PFS was also higher in the tafasitamab+lenalidomide cohort at all timepoints after Month 1. Kaplan−Meier plots of PFS are presented in Figure 8 [74].



(a) Subset of L-MIND patients matched with the observational cohort for pooled systemic therapies (MAS_Pool)



(b) Subset of L-MIND patients matched with the observational cohort of patients taking R-GemOx (MAS_R-GemOx)

Figure 8. RE-MIND2: Kaplan–Meier plot of progression-free survival for MAS_Pool and MAS_R-GemOx

Abbreviations: CR, complete response; CI ,confidence interval; KM, Kaplan–Meier; LEN, lenalidomide; R-GemOx, rituximab+gemcitabine+oxaliplatin; MAS, matched analysis set; N, number of patients in each cohort; Tafa, tafasitamab.

Notes: MAS_Pool included 1:1 matched patients from the L-MIND study and the observational cohort using 9 baseline covariates.

MAS_R-GemOx included 1:1 matched patients from the L-MIND study and MAS_R-GemOx as pre-specified treatment, respectively. See Table 85 for definitions on MAS_Pool and MAS_R-GemOx.

The median was calculated with Kaplan–Meier method. The 95% CI was calculated by means of Greenwood formula.

The hazard ratio was calculated with Cox proportional hazard model.

Source: Incyte, Data on file (RE-MIND2 CSR) [74].

Further information about RE-MIND2 outcomes and results are provided in Appendix D.

7.1.3.3 Safety

[redacted] This difference can be attributed to the respective treatment regimens. In the L-MIND study, tafasitamab+lenalidomide was administered for 12 cycles (approximately 12 months), followed by tafasitamab monotherapy until disease progression. In comparison, the majority of therapies administered in the systemic therapies pooled cohort, as well as the R-GemOx regimen in the comparator cohort, were immunochemotherapies, which are typically administered over a fixed, limited treatment duration of approximately 2–6 months. The longer duration of exposure in the tafasitamab+lenalidomide cohort also signifies a long DoR and indicates a favourable tolerability profile of this regimen [74].

Additionally, the observed difference between the tafasitamab+lenalidomide cohort and the other treatment cohorts may be associated with the limitations of safety data recorded during routine clinical care compared to the stringently collected data during the prospectively conducted L-MIND study. Of note, the rate of treatment discontinuation due to toxicities reported in the literature for R-GemOx is 10.0% [66].

8 Health economic analysis

8.1 Model description

A core cost-effectiveness model (C-CEM) was developed in Microsoft Excel® to assess the cost effectiveness of tafasitamab vs. relevant comparators for the treatment of patients with DLBCL who are ineligible for receiving transplants. The comparator considered in the model to reflect the Danish context is R-GemOx. A survival partition approach was selected given it is recognised as one of the most commonly adopted model structures for oncology treatments [77]. This approach was also in line with the previous HTA assessments reviewed for R/R DLBCL [78-80].

8.1.1 Model structure

A partitioned survival model structure with three health states was used to follow patients from their second line (2L) of treatment after being diagnosed to their next line of treatment until death. The model was developed based on clinical and treatment pathways for patients with R/R DLBCL; the considerations of key clinical aspects (progression-free survival [PFS] and overall survival [OS]) that affect clinical outcomes, costs, and treatment decisions; a thorough review of published and available health technology assessment (HTA) submission reports; and interviews with KOLs. Figure 9 illustrates the survival partition health states for the model. This approach applies treatment specific and independent OS and PFS curves for each comparator.

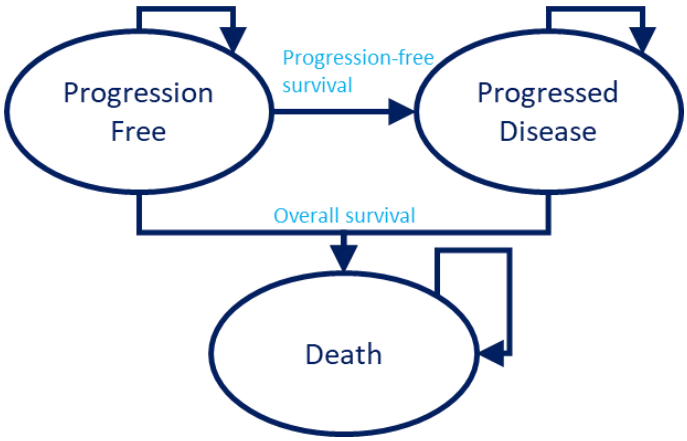


Figure 9. Model Diagram

The three health states modelled were pre-progression, post-progression, and death. Patients with R/R DLBCL who had received at least one line of treatment and were ineligible for receiving a transplant entered the model, initiated treatment, and experienced an interval of PFS. Patients who experienced disease progression and did not die during the initial modelled line of treatment continued to the post-progression health state where they may have received subsequent treatments. Patients could discontinue treatment or die at any time in the model. The model also allowed for the incorporation of long-term disease freedom assumptions and reduced resource use in case of prolonged PFS.

The model also captures the proportion of patients on and off treatment within each health state using the same partition approach: patients falling under the time-to-treatment discontinuation (TTD) curve are on treatment, while the patients between the TTD and PFS curves must be in the pre-progression health state and are off treatment. This means that during the pre-progression health state, patients could stop receiving treatment based on the duration and could stop accruing treatment-related costs; however, these patients will not switch to subsequent treatments unless they progress.

Costs were assigned to each health state, and utilities were applied according to the patients' disease-progression status. Costs and utilities were accrued and summarised for each cycle of the model (four weeks), so the difference in cumulative costs and utilities could be analysed and compared across comparators. Health outcomes and costs were discounted at 3.5% per annum according to Danish guidelines.

8.1.2 Target Population

The population in the L-MIND trial included adults with DLBCL, transformed low-grade lymphoma, composite lymphoma or grade 3b follicular lymphoma. Patients who were ineligible for HDCT and ASCT were included if they had received at least one but no more than three prior lines of therapy including one line of a CD 20 targeted therapy. The mean age at the baseline of the L-MIND population was 69.3 years (standard error [SE] 1.06 years, standard deviation 9.53 years) and 54.3% were male [81]. The mean body weight was 78.09 kg [81]. The mean body surface area (BSA), was calculated based on the average height and the weight reported in L-MIND case study report (CSR). The calculated BSA was 1.91 m^2. This analysis mainly focused on the overall L-MIND population who were on at least their second line of treatment (i.e., with at least one prior line of treatment, referred to as '2L+ patients'). The population who were in their second line of treatment (i.e., with one prior line of treatment, referred to as '2L patients') was considered in a scenario analysis.

8.1.3 Perspective

This analysis used the limited societal perspective and considered all relevant treatment related costs, including drug costs, drug administration costs (e.g., co-medications), monitoring, management of AEs, subsequent treatment costs, and disease management costs. Transportation costs incurred by the patient were also included.

8.1.4 Cycle Length

In line with the treatment cycle for tafasitamab and lenalidomide, a four-week cycle length was selected for this CEM. This cycle length was deemed sufficiently short to accurately capture clinical outcomes and differences in treatment administrations.

8.1.5 Time Horizon and Discounting

The time horizon for this model is flexible with up to a maximum of 35 years. A 35-year time horizon was used in the base case, covering a lifetime for patients in the target population. This time horizon was considered long enough to capture the long-term clinical and economic consequences of DLBCL for patients who are ineligible for HDCT and ASCT. Given the median age of 69.3 years in the L-MIND trial, 35 years was considered long enough to cover the lifetime of every patient. Overall survival was capped by general mortality using DK life tables and PFS was capped by OS in the model, such that risk of progression or death of patients is less than or equal to the mortality risk. Cost and health-related (like quality-adjusted life years [QALY]) outcomes were discounted at a rate of 3.5% in the base case in accordance with Danish guidelines [82].

8.1.6 Comparators

As described in section 5.2.2, R-GemOx are becoming the most accepted treatment in Denmark for R/R DLBCL patients who are not eligible for transplant and is therefore viewed as the most relevant comparator.

8.1.7 Model inputs

The model inputs were based on Danish sources where possible. The efficacy inputs—including PFS, OS, and treatment discontinuation for tafasitamab and lenalidomide—were taken from the L-MIND study, with efficacy data for comparators from the RE-MIND2 study. Frequencies on monitoring tests and dosing for R-GemOX was based on Danish clinical expert opinion. Other relevant inputs for R-GemOx were sourced from relevant HTA submissions to NICE for

treatments to lymphoma, Pola-BR and axicabtagene ciloleucel, and literature and they are assumed to reflect the Danish clinical practice [79, 83]. The efficacy inputs are further presented in sections 8.2, 8.3 and 8.4.

The cost inputs (presented in section 8.5) included drug costs (induction and maintenance), administration (induction and maintenance), co-medication costs (induction and maintenance), monitoring costs, subsequent treatment costs, AE and disease management costs for pre- and post-progression, one-off progression, and one-off death, and non-medical direct costs (transportations costs).

8.1.8 Model outputs

The model health outcomes included life years (LY), progression-free life years (PFLY), long-term disease free LYs, post-progression life years (PPLY) as well as on and off treatment time. Quality-adjusted life years (QALY) were also reported for each of the health states listed above as well as adverse events (AE), progression, and death, with their associated disutilities.

The model aggregates the health outcomes and costs from each health state and reports the discounted outcomes (costs and health-related outcomes discounted at 3.5% per annum):

- Life years (LY), progression-free life years (PFLY), post-progression life years (PPLY), long-term disease freedom, on treatment time, and off treatment time
- QALYs, quality-adjusted progression-free life years (QAPFLY), quality-adjusted post-progression life years (QAPPLY), and long-term disease freedom QALYs
- Disutilities associated with AEs, progression, and death
- Total, induction and maintenance drug, administration, co-medication, monitoring, AE management, disease management, and subsequent treatment costs
- Incremental cost-effectiveness ratios (ICER): cost per QALY gained and cost per LY gained

The incremental outcomes included cost per QALY gained, cost per LY gained, the incremental net monetary benefit, and the economically justifiable price (EJP). Deterministic sensitivity analyses (DSA), probabilistic sensitivity analyses (PSA), and scenario analyses were used to test the influence of uncertainty of the model parameters on the results.

8.1.9 Mortality within PFS

Patients experiencing death in the pre-progression health state need to be modelled in order to avoid overestimating the incidence of progression and, therefore, post-progression costs. Death during the pre-progression state was modelled by assuming a constant ratio of death to progression among PFS events:

$$Pre - progression\ Deaths(t) = [PFS(t-1) - PFS(t)] \times Ratio\ of\ Death\ during\ PFS$$

8.1.10 Long-term disease freedom

The KM curves of the OS in L-MIND study show a distinct plateau towards the end of the study follow-up period (see Figure 10 and Figure 11 in section 8.3.1.1). As a similar pattern was observed in the PFS (Figure 20 and Figure 21 in section 8.3.2.1), this plateau could implicate a long-term aspect of the therapy. Therefore, a long-term disease freedom option was incorporated into the model to allow for analysis to be conducted with patients who are disease free.

The model allows for the user to select the timepoint at which patients could move to the long-term disease free state. The cut-off time could be selected in 0.5-year increments starting at two years and going up to five years. A two-year time point has been selected for the base case based on the early discussions with clinical experts. This was also in line with previous HTA submissions to NICE and TLV. [78-80, 83-86].

According to the European Society for Medical Oncology (ESMO) guidelines, all patients with DLBCL who are event-free at two years have an identical OS to that of the general population [24]. However, this may not be generalisable to the R/R DLBCL population, where patients are in more advanced lines of treatment with limited treatment choices. Therefore, it was assumed that only a proportion of the patients who are progression free in two years can be considered as being long-term disease fee (i.e., have a mortality equivalent to the general population). This means that after two years of being progression free, a proportion of patients who were in the progression-free state moved over to being long-term disease free. The mortality rates of these long-term disease free patients are then restored to the age- and gender-matched mortality of the general population.

Long-term disease freedom could also have an impact on the treatment intake. For treatments that should continue up to progression, the physician might decide to stop the treatment without reaching progression, in case evidence of a long-term disease freedom is present. Therefore, the model provides an option to discontinue treatment for these patients. It must be noted that the long-term disease freedom assumptions are not treatment specific (i.e., patients who are progression free for two years on different treatments have the same chance at being disease free). Also note that patients who are classified as long-term disease free will not experience any relapses.

8.1.11 Prolonged PFS

An optional prolonged PFS state is included in the model to reflect the potential reduced resource usage when patients are progression free for a long time. This function only impacts the resource use and does not have an impact on health outcomes. The model allows for the user to select the timepoint at which patients could move to the prolonged progression-free state. These are selected in 0.5-year increments starting at two years and going up to five years. A two-year time point has been selected for the base case following discussions with the KOLs. The model user can also enter a proportion of patients among those who are progression free at two years. This proportion will be considered in the prolonged progression-free state, thus consuming limited resources from this point onwards.

The proportion of prolonged PFS among patients who reached two years without experiencing a progression was assumed to be the same as the long-term disease free proportion in the base case (i.e., 78.6% calculated based on CR rate).

8.1.12 Model validation

The model was assessed by two internal peer reviewers who were not involved with the original programming. Throughout the validation process, a comprehensive and rigorous quality check was fulfilled, which included validating the logical structure of the model, mathematical formulas, sequences of calculations, and values of the numbers supplied as model inputs. Unexpected model behaviour/implementation and typing errors were all identified through this review. The company who developed the model followed a standard operating procedure with detailed checklists to ensure that the validation was complete and thorough. The process involved checking the intermediate calculations for references (whether they are linked to the correct cells, etc.), implementation (whether correct signs for the parameters are used, etc.), and evaluation of the face validity of the predicted results. The expected functions of the parameters were checked with an extreme-value sensitivity analysis. The process also involved checking the functionality of any built-in macro programs. The quality check was a repeatable process that produced a checklist spreadsheet indicating the specific tasks performed and results returned. The appropriateness of distributions used in the probabilistic analysis of the model was also checked. Following the validation, corrections of any identified errors or bugs were incorporated into the revised model.

As external validation, the model predictions for OS and PFS were checked against data observed in the long-term clinical trials to drive the selection of the most appropriate parametric fits.

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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 inputs for clinical effect and utility values are summarized in Table 12, and for adverse events in Table 13 (further information is provided in sections 8.3 and 8.4). The clinical documentation presented in section 7 describes relevant efficacy measures for the treatment with tafasitamab+LEN. Also, the relative efficacy outcomes are in line with the current clinical practice in Denmark, as mentioned in section 5.2.

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Table 12. Input data used in the model

Estimates	Input value used in the model	How is the input value obtained / estimated	Source
OS approach: tafasitamab and lenalidomide	Parametric Single Fit; lognormal	Best statical fit and relatively good visual fit to the data	L-MIND [81]
OS approach: R-GemOx	Lognormal	Best statistical fit of models with most plausible long-term extrapolations in relation to external data	RE-MIND2 [74]
PFS approach: tafasitamab and lenalidomide	Parametric single fit; generalized Gamma	Best statistical fit and visual fit to the data	L-MIND [81]
PFS approach: R-GemOx	Exponential	Best statistical fit and joint best visual fit to observed data	RE-MIND2 [74]
Treatment discontinuation rule: tafasitamab	Treatment discontinuation curve; lognormal	Best statistical fit, good visual fit; aligned with PFS assumptions	L-MIND [81]
Treatment discontinuation rule: lenalidomide	Treatment discontinuation curve; KM curve	Lenalidomide has a fixed duration thus no extrapolations were needed	L-MIND [81]
Treatment discontinuation rule: R-GemOx	KM curves	Best available source	RE-MIND2 [74]
Mortality within PFS	[redacted]	Ratio of death within the PFS events based on data for tafasitamab and lenalidomide from the L-MIND study [67]	L-MIND[81]
Long-term disease free proportion	[redacted] of patients who reached 2 years without experiencing progression. Long-term disease free patients are assumed to discontinue treatment.	Interview with KOLs. Proportion of patients with CR within the population of those who are progression-free in two years. Calculated with PFS KM curves from the L-MIND population, stratified by the level of response	L-MIND [81]
Prolonged PFS proportion	[redacted] Prolonged PFS patients will continue to spend limited resources up to their progression time.	Assumed to be the same as the cure proportion.	L-MIND [81]
Utility: Progression-free survival	0.72, SE 0.03	EQ-5D-5L (UK population utilities). Further information on section 8.4.2.	NICE Single Technology appraisal - Polatuzumab vedotin with rituximab and bendamustine for treating R/R DLBCL [ID1576] Company evidence submission July 2019 [79]

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Utility: Long-term disease free	0.72, SE 0.03	Assumed same as PFS health state	Assumption
Utility: Post-progression survival	0.65, SE 0.06	EQ-5D-5L (UK population utilities). Further information on section 8.4.2.	NICE Single Technology appraisal - Polatuzumab vedotin with rituximab and bendamustine for treating R/R DLBCL [ID1576] Company evidence submission July 2019 [79]

Abbreviations: DLBCL, diffuse large B-cell lymphoma; KM, Kaplan-Meier; NICE, National Institute for Health and Care Excellence; OS, overall survival; PFS, progression-free survival; R-GemOx, rituximab, gemcitabine and oxaliplatin; SE, standard error; UK; United Kingdom; R/R, Relapsed of refractory.

Table 13. Adverse event inputs used in the model

AE	Cumulative probability		Disutility	Disutility Duration (Days)	Data source (Disutility)	Data source (Disutility Duration)
	Tafasitamab + LEN (Source: L-MIND CSR)	R-GemOx (Source: ID1576)				
Anaemia	[redacted]	33.00%	0.25	16	NICE Single Technology appraisal - Polatuzumab vedotin with rituximab and bendamustine for treating R/R DLBCL [ID1576] Company evidence submission July 2019 [79]	For polatuzumab NICE submission, duration of adverse event (AE) was sourced from GO29365 and TA306; however most of these data were redacted from the submission. Where data were not available from either of these two sources, then the polatuzumab NICE submission assumed longest duration of an AE from GO29365 (72 days). [79]
Febrile neutropenia	[redacted]	-	0.15	7.1	NICE Single Technology appraisal - Polatuzumab vedotin with rituximab and bendamustine for treating R/R DLBCL [ID1576] Company evidence submission July 2019 [79]	Pixantrone monotherapy for RR NHL NICE STA ID414 company evidence 20nov2012 table 34 p158-160 [79]
Hypokalaemia	[redacted]	-	0.09	72	Assumed same as leukopenia	For polatuzumab NICE submission, duration of adverse event (AE) was sourced from GO29365 and TA306; however most of these data were redacted from the submission. Where data were not available from either of these two sources, then the polatuzumab NICE submission assumed longest duration of an AE from GO29365 (72 days). [79]
Leukopenia	[redacted]	-	0.09	14	NICE Single Technology appraisal - Polatuzumab vedotin with rituximab and bendamustine for treating R/R DLBCL [ID1576] Company evidence submission July 2019 [79]	Pixantrone monotherapy for RR NHL NICE STA ID414 company evidence 20nov2012 table 34 p158-160 [87]

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AE	Cumulative probability		Disutility	Disutility Duration (Days)	Data source (Disutility)	Data source (Disutility Duration)
	Tafasitamab + LEN (Source: L-MIND CSR)	R-GemOx (Source: ID1576)				
Neutropenia	[redacted]	73.00%	0.09	15.1	NICE Single Technology appraisal - Polatuzumab vedotin with rituximab and bendamustine for treating R/R DLBCL [ID1576] Company evidence submission July 2019	Pixantrone monotherapy for RR NHL NICE STA ID414 company evidence 20nov2012 table 34 p158-160 [87]
Pneumonia	[redacted]	-	0.20	14.9	NICE Single Technology appraisal - Polatuzumab vedotin with rituximab and bendamustine for treating R/R DLBCL [ID1576] Company evidence submission July 2019	Pixantrone monotherapy for RR NHL NICE STA ID414 company evidence 20nov2012 table 34 p158-160 [87]
Thrombocytopenia	[redacted]	23.00%	0.11	23.2	NICE Single Technology appraisal - Polatuzumab vedotin with rituximab and bendamustine for treating R/R DLBCL [ID1576] Company evidence submission July 2019	Pixantrone monotherapy for RR NHL NICE STA ID414 company evidence 20nov2012 table 34 p158-160 [87]

Abbreviations: AE, adverse event; DLBCL, diffuse large B-cell lymphoma; LEN, lenalidomide; NICE, National Institute for Health and Care Excellence; R/R, Relapsed of refractory; R-GemOx, rituximab, gemcitabine and oxaliplatin.

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

8.2.2.1 Patient population

Patient population in the clinical documentation submitted: The patient population of the L-MIND study consisted of adult patients with R/R DLBCL who were not candidates for HDCT and subsequent ASCT. Further details are provided in Appendix B.

Patient population in the health economic analysis submitted: The patient population considered for the base case analysis reflects that of the L-MIND trial for tafasitamab and lenalidomide, which is described in Table 14.

The Danish patient population: A retrospective study with 653 newly diagnosed DLBCL patients in Denmark identified the patient characteristics presented in Table 14. Based on the study results, it is possible to infer that the Danish patient population is similar to the patients enrolled in L-MIND [81, 88].

Table 14. Patient population at the baseline

Patient population Important baseline characteristics	Clinical documentation / indirect comparison etc. (including source)	Used in the model (number / value including source)	Danish clinical practice (including source)
Age, years	Mean: 69.3 [81]	Same as clinical documentation	Median: 66.3 [88]
Males, percentage	54.3 [81]		56.5 [88]
Weight, kg	Mean: 78.09 [81]		Median: 75 [88]
Height, cm	Mean: 167.56 [81]		Median: 171 [88]
BSA*, m^2	Mean: 1.91 [81]		Median: 1.9 [88]

Source: L-MIND study [81]; Bendtsen et al. 2017 [88].

8.2.2.2 Intervention

Intervention as expected in Danish clinical practice (as defined in section 2.2): Given that tafasitamab+LEN is a novelty treatment, there are no treatment guidelines describing how it is used in clinical practice. Is it expected that tafasitamab+LEN will be used as described in the SmPC.

Intervention in the clinical documentation submitted: In the L-MIND study, 12 tafasitamab + LEN 28-day cycles, followed by tafasitamab monotherapy (in patients with stable disease or better) were administered until disease progression. Further details on the posology are presented in section 7.1.2

Intervention as in the health economic analysis submitted: The model inputs for tafasitamab+LEN are mostly obtained from the L-MIND study. The detailed inputs are presented in Table 15.

Patients who have not discontinued treatment by the end of induction treatment could move on to maintenance treatment. A conservative assumption was made that all patients will proceed to maintenance treatment (increasing the drug costs in the intervention arm).

Dose intensities are included in the model to adjust the drug costs based on the actual dosage received by the patient. For treatments on which no information was available, a 100% dose intensity was assumed.

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Table 15. Model inputs for tafasitamab+LEN

Intervention	Clinical documentation (including source)			Used in the model (number / value including source)	Expected Danish clinical practice (including source if known)
	Tafasitamab	Lenalidomide	Source		
Induction					
Dependency	Weight	Fixed dose	L-MIND CSR [81]	Same as clinical documentation	Expected to be used as described in SmPC
Dose	12 mg/kg	25 mg			
# of Weeks per Treatment Cycle	4	4			
Treatment schedule (Number of administrations per treatment cycle)	• Cycle 1: 5 • Cycles 2 – 3: 4 • Cycles 4-12: 2	Cycles 1-12: 21			
Dose intensity	Up to cycle 33: 100%	• Cycles 1 to 8: 100% • Cycles 9 to 12: 80%	L-MIND CSR page 186 [81]		
Percentage of Patients Moving to Maintenance (if not discontinued by end of induction)	100%		Assumption[1]	Same assumption	
Maintenance					
Dependency	Weight	Fixed dose	L-MIND CSR [81]	Same as clinical documentation	Expected to be used as described in SmPC
Dose	12.0 mg/kg	---			
# of Weeks per Treatment Cycle	4	---			
Treatment schedule (Number of administrations per treatment cycle)	Cycle +13: 2	---			

[1] All tafasitamab patients who do not discontinue treatment before 12 cycles continue to the maintenance treatment Comparators.

The current Danish clinical practice: In Denmark, R-GemOx is being used more and more frequently as 2L treatment for DLBCL patients who cannot be treated with HDCT. Further information is provided in section 5.2. According to a local clinical expert, the only difference between Danish clinical practice and the information obtained from clinical documentation is that, in Denmark, R-GemOx is administered in every 3 weeks [89]. This difference was incorporated in the health economic model.

Comparator in the clinical documentation submitted: R-GemOx is a treatment regimen that consists of rituximab, gemcitabine and oxaliplatin. In the induction phase, R-GemOx is administered in 2-week cycles and in 4-week cycles during the maintenance phase.

Comparator in the health economic analysis submitted**:** The model inputs for R-GemOx are mostly obtained from the study published by Mounier et al. The detailed inputs are presented in **Table 16**. As dsscribed above, the treatment with R-GemOx consist of an induction phase, followed by a maintenance phase. Maintenance treatment for R-GemOx consisted of 4 cycles (4 cycles of induction therapy and 4 cycles of maintenance, so 8 cycles in total for patients on R-GemOx). The health economic model is based on the Danish clinical expert's advice that T-GemOX is administrated every 3 weeks and that approximately 80 % continue on to maintenance phase.

Table 16. Model inputs for R-GemOx

Intervention	Clinical documentation (including source)				Used in the model (number / value including source)	Expected Danish clinical practice (including source if known)
	Rituximab	Gemcitabine	Oxaliplatin	Source		
Induction						
Dependency	BSA			Mounier et al [65]	Same as clinical documentation	Same as clinical documentation [89]
Dose	375mg/m^2	1000 mg/m^2	100 mg/m^2			
# of Weeks per Treatment Cycle	2				3 [89]	3 [89]
Treatment schedule (Number of administrations per treatment cycle)	Cycles 1-4: 1	Cycles 1-4: 1	Cycles 1-4: 1		Same as clinical documentation	Same as clinical documentation [89]
Dose intensity	100%			No information available, assumed 100%		
Percentage of Patients Moving to Maintenance (if not discontinued by end of induction)	78%			Mounier et al[1] [65] confirmed by local clinical expert		
Maintenance						
Dependency	BSA			Mounier et al [65]	Same as clinical documentation	Same as clinical documentation [89]
Dose	375mg/m^2	1000 mg/m^2	100 mg/m^2			
# of Weeks per Treatment Cycle	4				3 [89]	3 [89]
Treatment schedule (Number of administrations per treatment cycle)	Cycles 5-8: 1	Cycles 5-8: 1	Cycles 5-8: 1	Mounier et al. 2013 [65] El Gnaoui et al. 2007 [90]	Same as clinical documentation	Same as clinical documentation [89]

Abbreviations: BSA, body surface area.

1 Out of the 36 patients that completed induction in Mounier et al study, 28 started the consolidation phase of treatment (thus 78%). *Maintenance treatment for R-GemOx consisted of 4 cycles (4 cycles of induction therapy and 4 cycles of maintenance, so 8 cycles in total for patients on R-GemOx).

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8.2.2.3 Relative efficacy outcomes

The clinical documentation from where the relative efficacy outcomes for tafasitamab+LEN and R-GemOx were obtained are described in section 7.

Relevance of the documentation for Danish clinical practice: The clinical documentation is relevant for the Danish population as it describes relevant efficacy measures for the proposed treatment in Denmark. Also, the relative efficacy outcomes are in line with the current clinical practice, as mentioned in section 5.2.

Relative efficacy outcomes in the submitted health economic analysis: The main efficacy inputs presented in the model are OS, PFS and TTD. The base case inputs were obtained through the RE-MIND2 study.

Table 17. Summary of text regarding *value*

Clinical efficacy outcome	Clinical documentation	Used in the model (value)
Overall survival (OS)	Tafasitamab+LEN: L-MIND R-GemOx: RE-MIND2	See section 8.3.1
Progression-free survival (PFS)		See section 8.3.2
Time to treatment discontinuation (TTD)		See section 8.3.3

Table 18. Summary of text regarding *relevance*

Clinical efficacy outcome	Clinical documentation (measurement method)	Relevance of outcome for Danish clinical practice	Relevance of measurement method for Danish clinical practice
Overall survival (OS)	Kaplan-Meier curves	Very relevant	Very relevant
Progression-free survival (PFS)	Kaplan-Meier curves	Very relevant	Very relevant
Time to treatment discontinuation (TTD)	Kaplan-Meier curves	Relevant	Relevant

8.2.2.4 Adverse reaction outcomes

Adverse reaction outcomes in the clinical documentation submitted: Information on adverse events with tafasitamab+LEN was obtained from the L-MIND study (Section 7.1.2.4). For R-GemOx, safety data was obtained from RE-MIND2 (Section 7.1.3.3).

Adverse reaction outcomes in the health economic analysis submitted: Only grade ≥3 AEs occurring in ≥5% of study subjects in the L-MIND population are used within the model (Table 19). In the model, AEs affect costs and utilities of patients receiving treatment. AEs are assumed to occur only in the first year of treatment. Therefore, patients who remain 'on treatment' for subsequent years do not incur further AE-related costs.

The model uses the cumulative probabilities of AE occurrence during the treatment period. The cumulative probabilities of AEs are assumed to be independent of PFS and treatment duration. To account for differences in exposure time, treatment-specific cumulative probabilities for the intent to treat population over the entire trial duration are used to calculate an overall cost of AEs. A per-patient overall AE cost and utility decrement is applied as a one-off lump sum at the start of treatment.

Table 19. Cumulative probability of AEs during the treatment period

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AE	Tafasitamab and Lenalidomide	R-GemOx
Anaemia	[redacted]	33.00%
Febrile neutropenia	[redacted]	
Hypokalaemia	[redacted]	
Leukopenia	[redacted]	
Neutropenia	[redacted]	73.00%
Pneumonia	[redacted]	
Thrombocytopenia	[redacted]	23.00%
Source	L-MIND CSR [91]	ID1576 [79]
Used in model	Yes	Yes

Abbreviations: AE = adverse event; R-GemOx = rituximab + gemcitabine and oxaliplatin

8.3 Extrapolation of relative efficacy

This section presents the methods and inputs used to simulate the time patients on tafasitamab + lenalidomide and R-GemOx spent in each health state, which ultimately drove the aggregated costs, LYs, and QALYs.

The key efficacy inputs in the model are OS and PFS and TTD. The L-MIND trial was used to derive clinical data for tafasitamab and lenalidomide. For the efficacy inputs, the 30 October 2020 data cut for the L-MIND study was used [92]. For R-GemOx, data was generated from the RE-MIND2 study, where patients from L-MIND were statistically matched to real-world patients. For details on methods used for survival extrapolations, refer to Appendix G.

An overview of the recommended parametric models for the base-case and scenario analyses is shown in Table 20.

Table 20. Summary of selected parametric models for base-case and scenario analyses

Treatment	OS		PFS		TTD	
	Base-case	Scenario analysis	Base-case	Scenario analysis	Base-case	Scenario analysis
Tafa+LEN	Lognormal	Generalised gamma; Log-logistic	Generalised gamma	Gompertz	Lognormal	Log-logistic
R-GemOx	Lognormal	Generalised gamma; Log-logistic	Exponential	Log-logistic	NA (Complete KM curve from RE-MIND2)	NA

Abbreviations: KM = Kaplan Meier;LEN = lenalidomide; NA = not applicable; OS, overall survival; PFS = progression-free survival; R-GemOx = rituximab + gemcitabine and oxaliplatin; TTD = time to treatment discontinuation; tafa = tafasitamab.

8.3.1 OS

8.3.1.1 Tafasitamab + LEN

The following section provides details on how OS was modelled for tafasitamab and lenalidomide. Figure 10 shows the OS KM curve for the whole L-MIND population. The median follow-up time for OS was 42.7 months (95% CI: 38.0, 47.2) in the L-MIND trial [92].

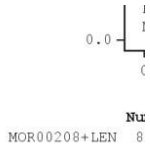

Figure 10. OS: KM Curve for the Whole L-MIND Population (data cut: 30 October 2020)

Abbreviations: CI = confidence interval; KM = Kaplan-Meier; LEN = lenalidomide; NR = not reported; OS = overall survival

Figure 11 shows the OS KM curve stratified by the different prior lines of treatment received by patients. As mentioned in section 8.1.2, the population of interest for the current analysis was the 2L+ group (i.e., patients with at least one prior line of treatment).

[redacted]

Figure 11. OS: KM Curve Stratified by Prior Line of Treatment

Abbreviation: KM = Kaplan-Meier; OS = overall survival

Parametric survival model parameters and fit statistics are shown in Table 21, with relative statistical fit classifications shown in Table 22. The lognormal model produced the lowest AICC and BIC, indicating the best statistical fit to the observed data, closely followed by the Gompertz model. However, based on the modified Burnham/Anderson and Kass/Raftery rules described in Appendix G, most other models produced good relative fits (0- to 4-point difference) according to AICC and reasonable relative fits (0- to 10-point difference) according to BIC compared to the lognormal model, with the exception of the exponential model which in terms of AICC generated a neutral relative fit (4- to 7-point difference) compared with the lognormal model.

Table 21. OS Parametric Distribution Fit Statistics for Tafasitamab and Lenalidomide

Distribution	Parameter 1		Parameter 2		Parameter 3		Parameter 4		AICC	BIC
	Intercept	SE	Scale	SE	Shape	SE	Gamma	SE		
Weibull	4.0809	0.2123	1.2676	0.1745	0.7889	0.1086			408.651	413.259
Lognormal	3.5797	0.2440	1.7944	0.2158					405.060	409.668
Log-logistic	3.5635	0.2286	1.0426	0.1384					406.569	411.178
Exponential	3.9726	0.1562	1.0000	0.0000	1.0000	0.0000			409.804	412.135
Generalised gamma	3.2662	0.5925	1.9453	0.2841	-0.4767	0.7584			406.817	413.647
Gompertz	3.4627	0.2443					-0.0286	0.0123	405.916	410.524

Abbreviations: AICC = corrected Akaike Information Criterion; BIC = Bayesian Information Criterion; OS = overall survival; SE = standard error

Table 22. OS Parametric Distribution Statistical Fit Classifications for Tafasitamab and Lenalidomide

Distribution	Difference from lowest AICC	AICC relative goodness-of-fit classification	Difference from lowest BIC	BIC relative goodness-of-fit classification
Weibull	3.591	Good (0-4 difference)	3.591	Reasonable (0-10 difference)
Lognormal	Lowest AICC	Reference	Lowest BIC	Reference
Log-logistic	1.509	Good (0-4 difference)	1.510	Reasonable (0-10 difference)
Exponential	4.744	Neutral (4-7 difference)	2.467	Reasonable (0-10 difference)
Generalised gamma	1.757	Good (0-4 difference)	3.979	Reasonable (0-10 difference)
Gompertz	0.856	Good (0-4 difference)	0.856	Reasonable (0-10 difference)

Abbreviations: AIC = Akaike Information Criterion; AICC = corrected Akaike Information Criterion; BIC = Bayesian Information Criterion; OS = overall survival

The long-term OS extrapolations for tafasitamab and lenalidomide among patients treated in the 2L+ setting are shown in Figure 12. The exponential model produced a relatively poor visual fit to the data by overestimating most of the KM curve until the tail, where it appeared to underestimate OS. Similarly, the Weibull model appeared to slightly overestimate the early to middle section of the KM curve before appearing to underestimate the tail, albeit to a lesser extent than the exponential model. All other models appeared to produce broadly good visual fits to the observed KM data until the tail, where the generalised gamma and Gompertz models appeared to generate the closest fit.

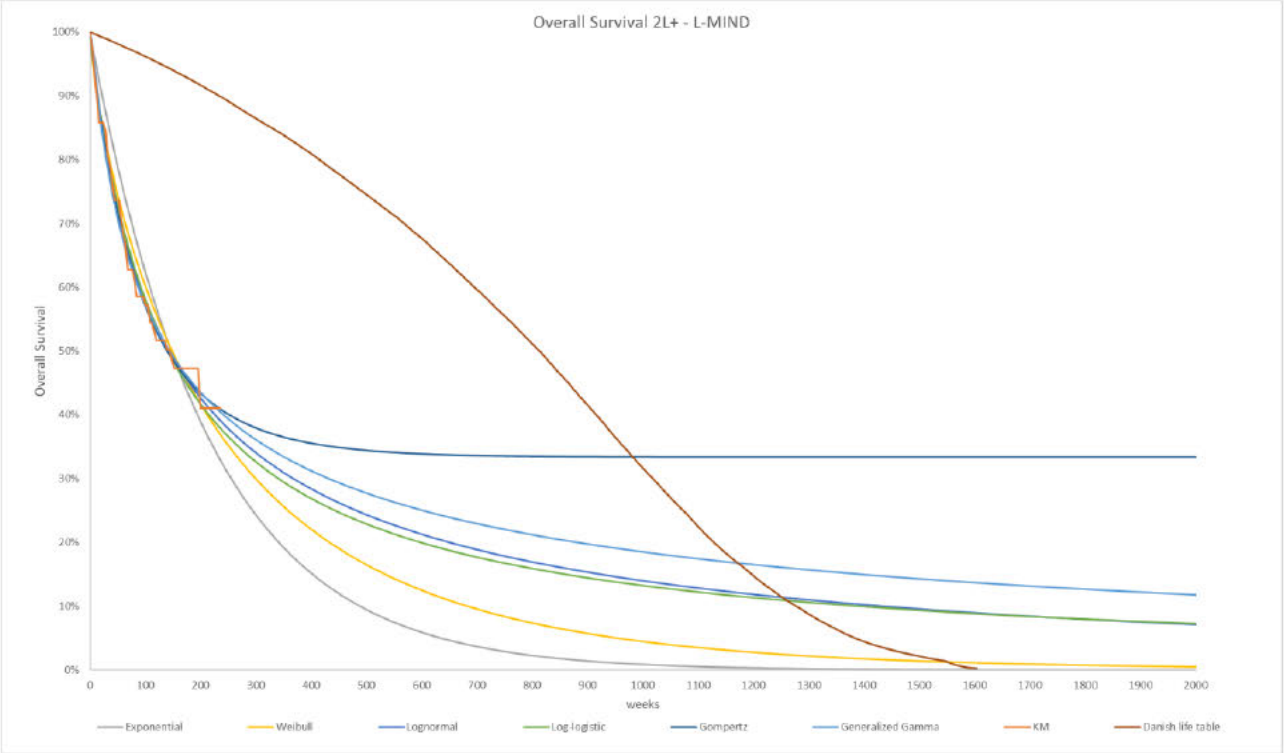

Figure 12. OS Extrapolations: Parametric Fits for Tafasitamab and Lenalidomide

Abbreviations: 2L+ = second line or more; KM = Kaplan Meier

Table 23 presents the predicted median OS in cycles using each of the parametric distributions, alongside with the predicted percentage of patients who are still alive at two, five, and ten years among patients treated in the 2L+ setting. The Gompertz distribution led to a potentially unrealistic long-term plateau due to a statistical artefact of the parametric fitting where a gamma parameter <0 is estimated. Therefore, this distribution may be implausible for OS, but is presented for completeness.

Table 23. OS: Median and Percentage Survived for Tafasitamab and Lenalidomide

	Median (cycles)	2-year OS	5-year OS	10-year OS
Exponential	33.9	61%	29%	9%
Weibull	34.2	59%	34%	16%
Log-logistic	32.5	57%	36%	22%
Lognormal	33.0	57%	37%	24%
Generalised gamma	33.1	57%	39%	27%
Gompertz	35.0	56%	40%	34%

Abbreviation: OS = overall survival

Figure 13 shows the smoothed hazard plots for OS. The generalised gamma and lognormal models had short-term increasing rates of death (up to 3 and 2 model cycles respectively) followed by long-term decreasing rates of death, with the generalised gamma model producing a slightly sharper short-term increase and slightly sharper long-term decline in mortality risk. The Weibull, log-logistic and Gompertz generated a decreasing risk of death over time, with the risk of mortality from the Gompertz model declining faster than other parametric models and matching mortality from the general population at ~80 months. The exponential model (by definition) generated a constant rate of death over time.

Figure 13. OS Parametric Model Smoothed Hazard Plots for Tafasitamab plus Lenalidomide for the 2L+ L-MIND Population

Abbreviations: 2L+ = second line or more; OS = overall survival

Based on statistical and visual fit to the observed data, the lognormal model was selected for the base case analysis. This was also in line with clinical validation (although collected for the 2L population, and not 2L+ which is relevant for the Danish setting) where experts from the NICE submission recommended choosing the curve with the AIC/BIC [93]. However, generalised gamma was also explored in scenario analysis as it appeared to produce a slightly better visual fit to the tail, with log-logistic also explored via scenario analysis as the next best statistical fit and a reasonable visual fit to the tail (although slightly worse than generalised gamma and lognormal).

8.3.1.2 R-GemOx

For the Re-MIND2 comparison of tafasitamab and lenalidomide against R-GemOx for OS, proportional hazards were first assessed by visual inspection of the log cumulative hazard plots (Figure 14) and Schoenfeld residuals test (Figure 15). While the middle to late section of the log cumulative hazard plot appeared to be broadly parallel, the log cumulative hazard plots crossed twice in the early to middle section of the curve. Furthermore, there appeared to be some potential divergence in the log cumulative hazard plots towards the end of follow-up. The global test of proportionality from the Schoenfeld residuals test generated a statistically non-statistically significant relationship between the residuals and time (p-value=0.1598), suggesting that proportional hazards may hold. However, the p-value may have been driven by the parallel nature of the hazards for part of the follow-up (as shown on the middle to late section of the log cumulative hazard graph), and the assumption of proportionality might not be appropriate given the crossings and potential divergence at the tails of the log cumulative hazard plots, and the Schoenfeld residual plot indicating a downward trend in the residuals over time, and a fitted regression line non-parallel to the 0 line. Therefore, independent parametric models were fitted to the R-GemOx OS KM curve from RE-MIND2.

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Figure 14. Log Cumulative Hazard Plot for RE-MIND2: Tafasitamab and Lenalidomide vs R-GemOx OS

Abbreviations: LEN = lenalidomide; OS = overall survival; R-GemOx = rituximab + gemcitabine and oxaliplatin; TAFA = tafasitamab

Figure 15. Schoenfeld Residuals Plot for RE-MIND2: Tafasitamab and Lenalidomide vs R-GemOx OS

Abbreviations: CI = confidence interval; OS = overall survival; R-GemOx = rituximab + gemcitabine and oxaliplatin

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For the RE-MIND2 comparison against R-GemOx, 74 out of the original 80 tafasitamab and lenalidomide patients from L-MIND were matched 1:1 with R-GemOx patients and were therefore fairly representative of the original L-MIND population. An overlay of the unmatched 2L+ and total L-MIND population OS KM curves for tafasitamab and lenalidomide with the matched tafasitamab and lenalidomide curves for RE-MIND2 versus R-GemOx are shown in Figure 16. As there was considerable overlap between the unmatched and matched tafasitamab and lenalidomide populations, with only a small sample of the original population lost to the matching process, individual parametric fits were used to model R-GemOx OS from RE-MIND2 vs. tafasitamab and lenalidomide from the original L-MIND population.

Figure 16. Overlaid Plots of Unmatched Tafasitamab and Lenalidomide OS KM Curves from L-MIND with 1:1 Matched Curves from RE-MIND2 against R-GemOx

Abbreviations: KM = Kaplan-Meier; LEN = lenalidomide; OS = overall survival; R-GemOx = rituximab + gemcitabine and oxaliplatin; TAFA = tafasitamab

AICC and BIC estimates for the parametric models are shown in Table 24, with relative statistical fit classifications based on modified Burnham/Anderson and Kass/Raftery rules shown in Table 25.

The lognormal model produced the lowest AICC and BIC indicating the best statistical fit. However, based on modified Burnham/Anderson rules applied to AICC and Kass/Raftery rules for BIC, most models produced good relative statistical fits in terms of AICC (0- to 4-point difference) and all produced a reasonable relative statistic fits for BIC (0- to 10-point difference) compared to the lognormal model. For AIC, the Weibull and Gompertz models both produced a neutral goodness of fit (4- to 7-point difference) in comparison to the lognormal model.

Table 24. Statistical Fit for RE-MIND2: OS 2L+ for R-GemOx

Distribution	AICC	AICC rank	BIC	BIC rank	Sum of AICC and BIC
Weibull	449.525	6	453.964	6	903.489
Lognormal	444.145	1	448.584	1	892.729
Log-logistic	445.527	2	449.966	3	895.493
Exponential	447.449	4	449.697	2	897.146
Generalised gamma	446.262	3	452.832	4	899.094
Gompertz	449.096	5	453.535	5	902.631

Abbreviations: 2L+ = second line or more; AICC = corrected Akaike Information Criterion; BIC = Bayesian Information Criterion; OS = overall survival; R-GemOx = rituximab + gemcitabine and oxaliplatin

Table 25. Statistical Fit for RE-MIND2: OS 2L+ R-GemOx Relative Statistic Fit Classifications

Distribution	Difference from lowest AICC	AICC relative goodness-of-fit classification	Difference from lowest BIC	BIC relative goodness-of-fit classification
Weibull	5.380	Neutral (4-7 difference)	5.380	Reasonable (0-10 difference)
Lognormal	Lowest AICC	Reference	Lowest BIC	Reference
Log-logistic	1.382	Good (0-4 difference)	1.382	Reasonable (0-10 difference)
Exponential	3.304	Good (0-4 difference)	1.113	Reasonable (0-10 difference)
Generalised gamma	2.117	Good (0-4 difference)	4.248	Reasonable (0-10 difference)
Gompertz	4.951	Neutral (4-7 difference)	4.951	Reasonable (0-10 difference)

Abbreviations: 2L+ = second line or more; AICC = corrected Akaike Information Criterion; BIC = Bayesian Information Criterion; OS = overall survival; R-GemOx = rituximab + gemcitabine and oxaliplatin

Parametric fits for R-GemOx are shown in Figure 17. All models produced fairly similar visual fits to most of the observed KM data, with reasonably good visual fits to the first half of the KM curve, and consistent underpredictions of the middle to late part of the KM curve. The Weibull and exponential models appeared to give close fits to the tail, with all other models appearing to produce overpredictions. However, given the slightly sudden step downwards at the end of the KM curve where a relatively small number of patients were at risk, the other models may still represent reasonable visual fits to the tail given they fit better to the section of the tail of the KM prior to this drop.

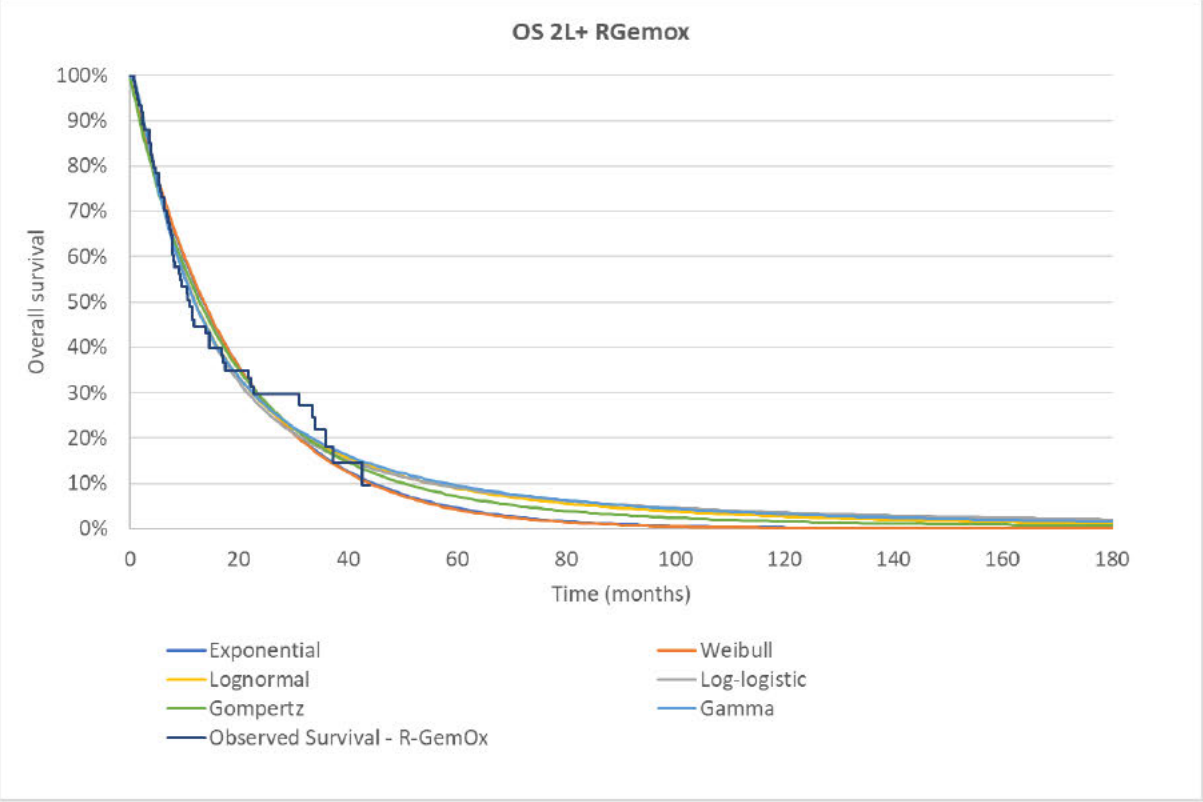

Figure 17. Parametric Survival Fits for RE-MIND2: OS 2L+ for R-GemOx

Abbreviations: 2L+ = second line or more; R-GemOx = rituximab + gemcitabine and oxaliplatin

OS predictions at 2, 5, and 10 years from each of the parametric models are shown in Table 26. Although the lognormal, log-logistic and generalised gamma curves produced slightly lower two-year predictions than most other curves, these distributions produced the most optimistic 5- and 10-year predictions at 9% to 10% and 3% to 4%, respectively. The

Weibull and exponential models generated the most pessimistic predictions with 4% to 5% at five years and 0% OS at 10 years.

Although clinical expert feedback has not been collected for the 2L+ population, all of the extrapolations appear clinically plausible in relation to the predictions provided by clinicians from the UK ad board. During the ad board, clinicians estimated an expectation of survival beyond two to three years of 10% to 15%. As the parametric curves produced figures of less than 10% to 15% at five years and less than 5% at 10 years, and the expectation that a 2L population would have higher survival than a 2L+ population, the figures appear potentially clinically plausible.

Table 26. Expected OS per Distribution for RE-MIND2: OS 2L+ for R-GemOx

Distribution	2-year OS prediction	5-year OS prediction	10-year OS prediction
Weibull	29%	4%	0%
Lognormal	28%	9%	3%
Log-logistic	27%	9%	4%
Exponential	29%	5%	0%
Generalised gamma	28%	10%	3%
Gompertz	29%	7%	2%

Abbreviation: 2L+ = second line or more; OS = overall survival; R-GemOx = rituximab + gemcitabine and oxaliplatin

Smoothed hazard plots for each parametric model are shown in Figure 18, along with the mortality rates from Danish life tables (using the model baseline age of 69.3 years).

The lognormal, log-logistic and generalised gamma models all produced similar short-term increasing then long-term decreasing hazard profiles. The Gompertz model produced a decreasing risk of death over time, while the Weibull model produced increasing but plateauing hazards before producing an almost constant rate of death over the long-term. By definition, the exponential model generated a constant risk of death over time.

Figure 18. Smoothed Hazard Plots for RE-MIND2: OS 2L+ for R-GemOx

Abbreviations: OS = overall survival; R-GemOx = rituximab + gemcitabine and oxaliplatin

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In terms of available external data, estimates from the RE-MIND2 parametric models were compared against two- and five-year OS estimates from the clinical trial by Mounier et al [65]. A screenshot of the OS and PFS plots from Mounier 2013 is shown in Figure 19. The OS curve indicated two-year and five-year OS of approximately 36% and 14%, respectively. All the parametric models appeared to slightly underpredict the two-year OS (27% to 29%) and five-year OS (4% to 10%).

Based on the five-year OS predictions, the lognormal, log-logistic and generalised gamma (9%, 9%, and 10% respectively) produced the most plausible extrapolations, although they still appeared to slightly underpredict five-year OS compared to Mounier 2013 publication. It is important to note however that potential differences in the underlying characteristics of the 2L+ R-GemOx population from RE-MIND2 and Mounier 2013 trial population may limit the ability to directly compare outcomes from the two studies.

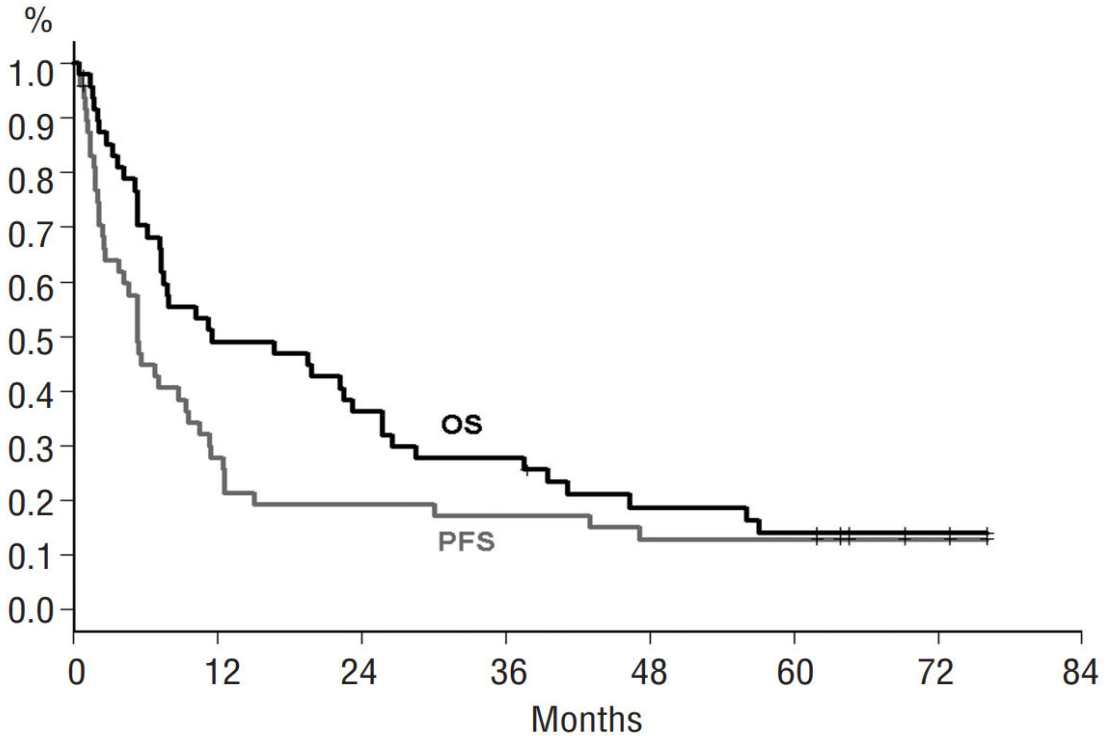

Figure 19. OS for R-GemOx from Mounier 2013

Abbreviations: OS = overall survival; PFS = progression-free survival; R-GemOx = rituximab + gemcitabine and oxaliplatin

Based on review of the statistical and visual fit, clinical plausibility of long-term extrapolations and hazard profiles, as well as comparisons to external data, the lognormal, log-logistic and generalised gamma models appeared to be the most plausible parametric fits for the 2L+ population for R-GemOx for the RE-MIND2 analysis, with limited differences in long-term predictions and hazard profiles. Given the limited differentiation between these models, the lognormal was selected on the basis of statistical fit, with the log-logistic and generalised gamma explored in scenario analyses. The choice of lognormal was supported by clinical experts from the NICE submission (note that this was validated for the 2L population and not the 2L+ population), as there are few patients that benefit in the long-term, the lognormal distribution includes decay over time, with a hazard profile that increases in the short term and decreases in the long-term [93]. However, limited clinical expert feedback was available to inform the selection of the parametric models.

8.3.2 PFS

8.3.2.1 Tafasitamab + LEN

Figure 20 shows the PFS KM curve for the whole L-MIND population (data cut: 30 October 2020). The median PFS was 11.6 months from the L-MIND trial [92]. A trend indicating a possible plateau towards the end of the follow-up time can be observed in PFS, indicating that tafasitamab and lenalidomide may be curative.

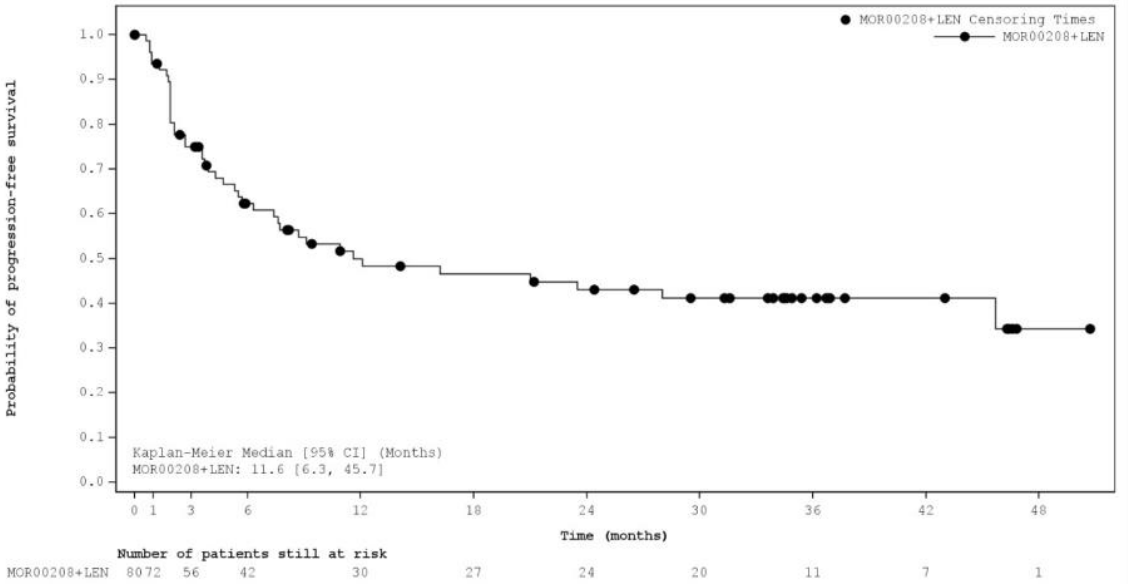

Figure 20. PFS KM Curve for the Whole L-MIND Population (Data Cut: 30 October 2020)

Abbreviations: CI = confidence interval; KM = Kaplan-Meier; LEN = lenalidomide; NR = not reported; PFS = progression-free survival

Figure 21 shows the KM curve stratified by different lines of treatment. As mentioned in section 8.1.2, the population of interest for the current analysis is the 2L+ group (patients with at least one prior line of treatment).

Figure 21. PFS KM Curve Stratified by Prior Lines of Treatment

Abbreviations: IRC = independent review committee; KM = Kaplan-Meier; PFS = progression-free survival

The parameters and fit statistics of each distribution are shown in Table 27, with classifications of relative statistical fit shown in Table 28. The generalised gamma produced the best statistical fit with the lowest AICC and BIC. Most models produced a poor relative statistical fit in terms of AICC and BIC (>10-point difference). The Gompertz model produced an inferior relative statistical fit according to AICC (7- to 10-point difference) and the Gompertz and lognormal both generated reasonable relative statistical fits in terms of BIC (0- to 10-point difference).

Table 27. PFS Parametric Distribution Fit Statistics for Tafasitamab and Lenalidomide

Distribution	Parameter 1		Parameter 2		Parameter 3		Parameter 4		AICC	BIC
	Intercept	SE	Scale	SE	Shape	SE	Gamma	SE		
Weibull	3.5776	0.2532	1.5731	0.2034	0.6357	0.0822			361.54	366.149
Lognormal	2.8566	0.2594	1.9329	0.2302					350.981	355.589
Log-logistic	2.7954	0.2651	1.1903	0.151					354.828	359.436
Exponential	3.4337	0.1543	1	0	1	0			374.483	376.813
Generalised gamma	0.9285	0.4522	1.3239	0.2963	-2.7937	0.9566			339.483	346.313
Gompertz	2.472	0.2127					-0.0845	0.0197	348.702	353.31

Abbreviations: AICC = corrected Akaike Information Criterion; BIC = Bayesian Information Criterion; PFS = progression-free survival; SE = standard error

Table 28. PFS Parametric Distribution Statistical Fit Classifications for Tafasitamab and Lenalidomide

Distribution	Difference from lowest AICC	AICC relative goodness-of-fit classification	Difference from lowest BIC	BIC relative goodness-of-fit classification
Weibull	22.057	Poor (>10 difference)	19.836	Poor (>10 difference)
Lognormal	11.498	Poor (>10 difference)	9.276	Reasonable (0-10 difference)
Log-logistic	15.345	Poor (>10 difference)	13.123	Poor (>10 difference)
Exponential	35.000	Poor (>10 difference)	30.500	Poor (>10 difference)
Generalised gamma	Lowest AICC	Reference	Lowest BIC	Reference
Gompertz	9.219	Inferior (7-10 difference)	6.997	Reasonable (0-10 difference)

Abbreviations: AICC = corrected Akaike Information Criterion; BIC = Bayesian Information Criterion; OS = overall survival

The long-term PFS extrapolations for tafasitamab and lenalidomide are shown in Figure 22. The generalised gamma and Gompertz models appeared to generate the best visual fits to the observed data, albeit with the Gompertz model appearing to overpredict the tail and generating a likely unrealistic plateau due to a statistical artefact of the parametric fitting where a gamma parameter <0 was estimated. All other models overpredicted most of the initial half of the KM curve, and then considerably underpredicted the tail, with the exponential model producing a particularly poor visual fit to the data.

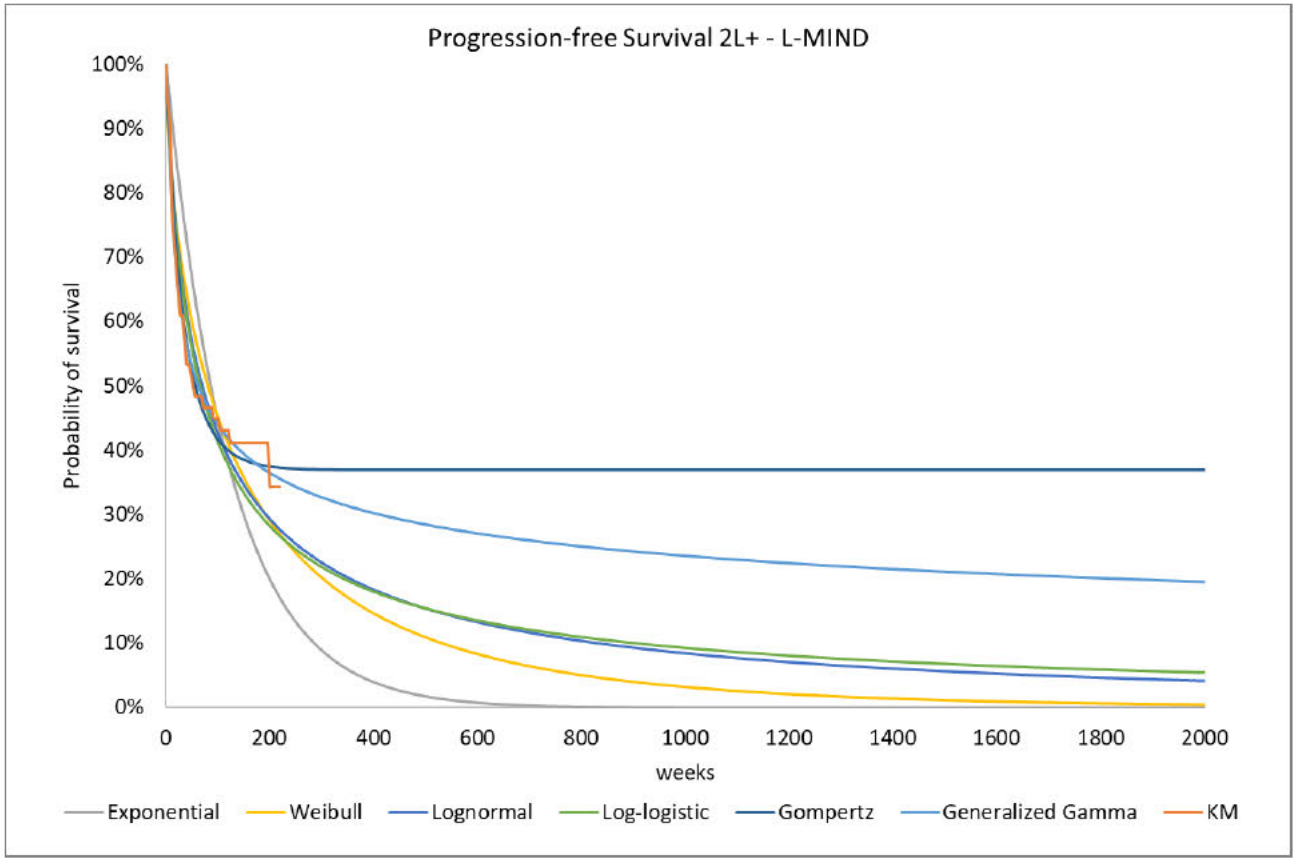

Figure 22. PFS Extrapolations: Parametric Fits for Tafasitamab and Lenalidomide

Abbreviation: 2L+ = second line or more; PFS = progression-free survival

Table 29 details the median progression-free months for all distributions, along with the percentage of those who were progression-free at two, five, and ten years. Gompertz model data are shown for completeness, although as noted above this model appears to have generated an unrealistic plateau in the data (with very similar OS predictions at 5 and 10 years).

Table 29. PFS: Median and Percentage Survived for Tafasitamab and Lenalidomide

	Median (months)	2-year PFS	5-year PFS	10-year PFS
Exponential	19.8	43%	12%	2%
Weibull	18.5	44%	23%	10%
Log-logistic	15.1	40%	24%	15%
Lognormal	16.0	42%	25%	15%
Generalised gamma	14.3	44%	34%	28%
Gompertz	14.0	41%	37%	37%

Abbreviations: PFS = progression-free survival

Figure 23 shows the smoothed hazard plots for tafasitamab and lenalidomide over the first 15 years. The Weibull, log-logistic, lognormal, and Gompertz models produced decreasing rates of progression or death per four weeks over time. The generalised gamma models produced short-term increasing hazards (for the first two model cycles) followed by long-term decreasing hazards. The exponential model (by definition) generated a constant rate of death or progression. However, further clinical validation may be required to assess the plausibility of hazard profiles for PFS.

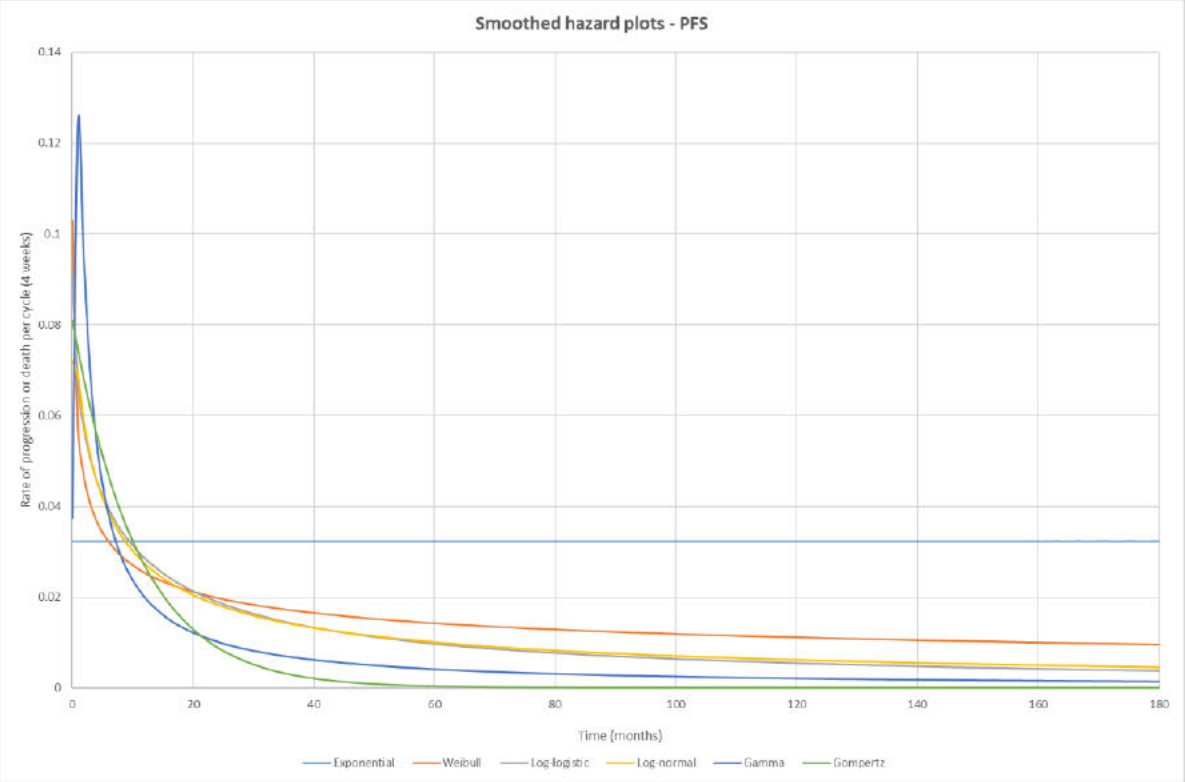

Figure 23. PFS Parametric Model Smoothed Hazard Plots for Tafasitamab plus Lenalidomide for the 2L+ L-MIND Population

Abbreviation: 2L+ = second line or more; PFS = progression-free survival

For the base-case analysis, the generalised gamma distribution was selected to model PFS, as this distribution clearly produced the best statistical fit and visual fit to the observed data. According to clinical experts in the NICE submission,

it may be assumed that patients who have survived 10 years likely have not progressed and should therefore have a distribution similar to OS. [93]. While the Gompertz model produced the next best statistical fit and also appeared to produce a relatively good visual fit to the observed data, this model generated an unrealistic plateau after the end of the KM curve. Although the lognormal and log-logistic models produced good relative statistical fits according to AIC and reasonable relative statistical fits in terms of BIC, these models produced fairly poor visual fits to the observed KM data with overpredictions of the early to middle section of the KM curve and clear underpredictions of the tail. The Weibull and exponential models both generated worse statistical fits and visual fits, with the exponential model producing a particularly poor visual fit.

8.3.2.2 R-GemOx

For the RE-MIND2 comparison of tafasitamab and lenalidomide against R-GemOx for PFS, similar to OS, proportional hazards were assessed by a visual inspection of the log cumulative hazard plots (Figure 24) and Schoenfeld residuals test (Figure 25). The log cumulative hazard plots were clearly non-parallel with some initial convergence in the curves before diverging over time, which suggested that the proportional hazards assumption was not appropriate for this comparison. Visual inspection of the Schoenfeld residual plot showed a downward trend in the residuals over time, which was non-parallel to the 0 line. This was further confirmed from the global test of proportionality from the Schoenfeld residuals test, which generated a pvalue of 0.0013 indicating the PH assumption did not hold. Therefore, independent parametric models were fitted to the R-GemOx PFS KM curve from RE-MIND2.

Figure 24. Log Cumulative Hazard Plot for RE-MIND2: PFS plots for Tafasitamab and Lenalidomide vs R-GemOx

Abbreviations: LEN = lenalidomide; PFS = progression-free survival; R-GemOx = rituximab + gemcitabine and oxaliplatin; TAFA = tafasitamab

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Figure 25. Schoenfeld residuals plot for RE-MIND2: PFS plots for Tafasitamab and lenalidomide vs R-GemOx

Abbreviation: CI = confidence interval; PFS = progression-free survival; R-GemOx = rituximab + gemcitabine and oxaliplatin

As mentioned in section 8.3.1.2, for the RE-MIND2 comparison against R-GemOx, 74 out of the original 80 tafasitamab and lenalidomide patients from L-MIND were matched 1:1 with R-GemOx patients and were therefore fairly representative of the original L-MIND population. An overlay of the unmatched total L-MIND population PFS KM curves for tafasitamab and lenalidomide with the matched tafasitamab and lenalidomide curves for RE-MIND2 versus R-GemOx are shown in Figure 26. Similar to the OS curves, as there was substantial overlap between the unmatched and matched tafasitamab and lenalidomide curves, adjustment factors were therefore not applied to the independent parametric fits for R-GemOx PFS.

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Figure 26. Overlaid Plots of Unmatched Tafasitamab and Lenalidomide PFS KM Curves from L-MIND with 1:1 Matched Curves from RE-MIND2 for Comparisons against R-GemOx

Abbreviations: 2L = second line; KM = Kaplan-Meier; LEN = lenalidomide; PFS = progression-free survival; R-GemOx = rituximab + gemcitabine and oxaliplatin; TAFA = tafasitamab

AIC and BIC estimates for the parametric models are shown in Table 30, with relative statistical fit classifications based on modified Burnham/Anderson and Kass/Raftery rules shown in Table 31.

The exponential model produced the lowest AICC and BIC indicating the best statistical fit. However, based on modified Burnham/Anderson rules applied to AICC and Kass/Raftery rules for BIC, most models produced good relative statistical fits in terms of AICC (0- to 4-point difference) and all produced a reasonable relative statistic fits for BIC (0- to 10-point difference) compared to the lognormal model. For AICC, the lognormal model produced a neutral goodness of fit (4- to 7-point difference) in comparison to the exponential model.

Table 30. Statistical Fit for RE-MIND2: PFS 2L+ R-GemOx

Distribution	AICC	AICC rank	BIC	BIC rank	Sum of AICC and BIC
Weibull	361.797	3	366.236	3	728.033
Lognormal	364.489	6	368.928	5	733.417
Log-logistic	363.727	5	368.166	4	731.893
Exponential	359.765	1	362.014	1	721.779
Generalised gamma	362.891	4	369.46	6	732.351
Gompertz	361.723	2	366.162	2	727.885

Abbreviations: 2L+ = second line or more; AICC = corrected Akaike Information Criterion; BIC = Bayesian Information Criterion; PFS = progression-free survival; R-GemOx = rituximab + gemcitabine and oxaliplatin

Table 31. Statistical fit for RE-MIND2: PFS 2L+ R-GemOx relative statistic fit classifications

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Distribution	Difference from lowest AICC	AICC relative goodness-of-fit classification	Difference from lowest BIC	BIC relative goodness-of-fit classification
Weibull	2.032	Good (0-4 difference)	4.222	Reasonable (0-10 difference)
Lognormal	4.724	Neutral (4-7 difference)	6.914	Reasonable (0-10 difference)
Log-logistic	3.962	Good (0-4 difference)	6.152	Reasonable (0-10 difference)
Exponential	Lowest AICC	Reference	Lowest BIC	Reference
Generalised gamma	3.126	Good (0-4 difference)	7.446	Reasonable (0-10 difference)
Gompertz	1.958	Good (0-4 difference)	4.148	Reasonable (0-10 difference)

Abbreviations: 2L+ = second line or more; AICC = corrected Akaike Information Criterion; BIC = Bayesian Information Criterion; PFS = progression-free survival; R-GemOx = rituximab + gemcitabine and oxaliplatin

Parametric fits for R-GemOx are shown in Figure 27. All models produced similar visual fits to most of the observed KM data, with good visual fits to the KM curve up to approximately 15 months, after which the parametric models began to diverge with the lognormal and log-logistic models predicting a greater rate of survival than the other parametric models. Between approximately 15 months and 30 months, the lognormal and log-logistic models produced better visual fits to the data, but after 30 months the KM curve drops to 0% survival with the other parametric models generating a closer fit to the tail.

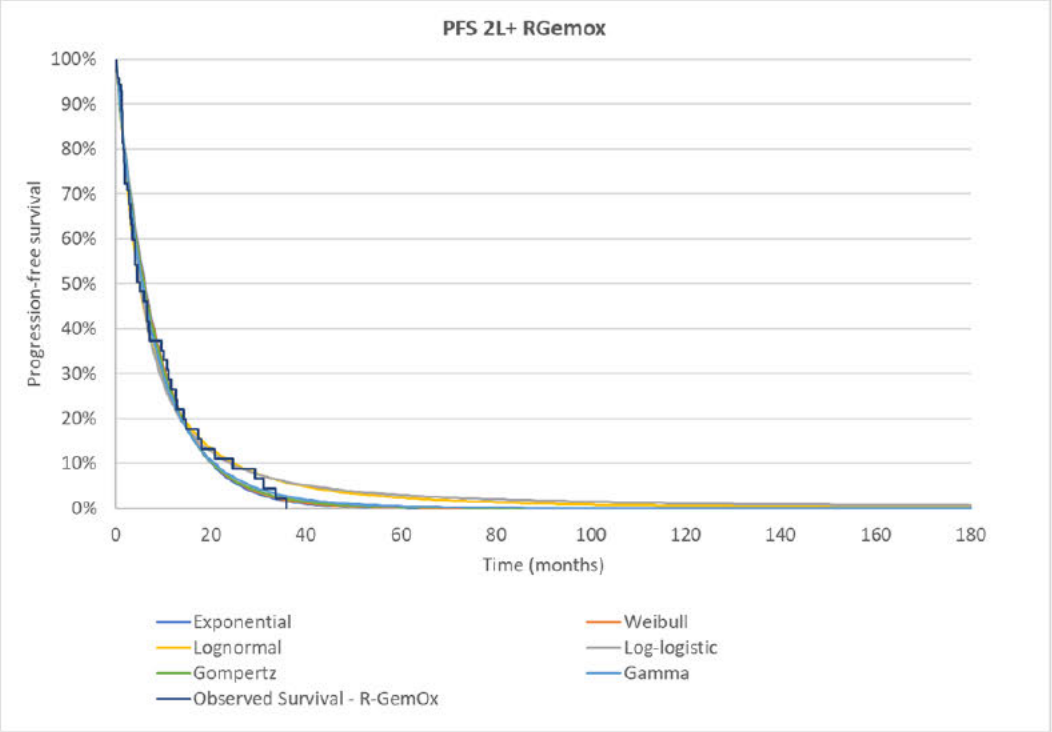

Figure 27. Parametric Survival Fits for RE-MIND2: PFS 2L+ for R-GemOx

Abbreviations: 2L+ = second line or more; PFS = progression-free survival; R-GemOx = rituximab + gemcitabine and oxaliplatin

PFS predictions at 2, 5, and 10 years from each of the parametric models are shown in Table 32. The lognormal and log-logistic curves generated the most optimistic predictions at all three time points with 10% to 11% surviving at two years, 2% to 3% surviving at five years and 1% being progression-free at 10-years. The Weibull, exponential, gamma and Gompertz models generated more pessimistic predictions at all three time-points with 6% to 8% being progression-free at two years and 0% by five years.

Table 32. Expected PFS per Distribution for RE-MIND2: PFS 2L+ for R-GemOx

Distribution	2-year PFS prediction	5-year PFS prediction	10-year PFS prediction
Weibull	7%	0%	0%
Lognormal	11%	2%	1%
Log-logistic	10%	3%	1%
Exponential	6%	0%	0%
Generalised gamma	8%	0%	0%
Gompertz	7%	0%	0%

Abbreviations: 2L+ = second line or more; PFS = progression-free survival; R-GemOx = rituximab + gemcitabine and oxaliplatin

Smoothed hazard plots for each parametric model are shown in Figure 28. The lognormal, log-logistic and generalised gamma models each produced short-term increasing then long-term decreasing mortality rates, although the lognormal and log-logistic models generated sharper short-term increases followed by sharper long-term declines in the risk of death or progression. The Weibull model produced a short decrease and then an almost constant risk of death or progression, with the Gompertz model producing a relative linear decreasing hazard profile. By definition, the exponential model generated a constant hazard over time.

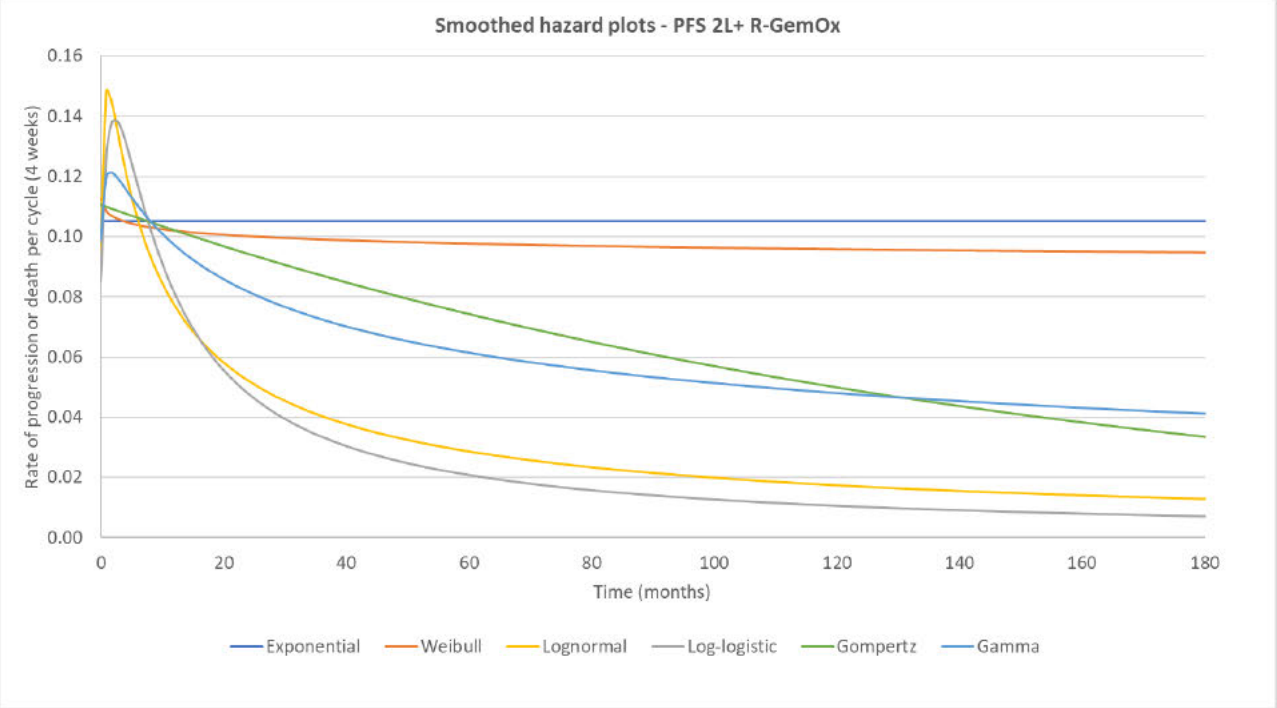

Figure 28. Smoothed Hazard Plots for RE-MIND2: PFS 2L+ for R-GemOx

Abbreviations: 2L+ = second line or more; PFS = progression-free survival; R-GemOx = rituximab + gemcitabine and oxaliplatin

In terms of available external data, estimates from the RE-MIND2 parametric models were compared against two- and five-year PFS estimates from the clinical trial data for R-GemOx (Mounier 2013) [65]. A screenshot of the PFS plot from Mounier 2013 is shown in Figure 29. The PFS curve indicated two-year and five-year PFS of approximately 19% and 13%, respectively. The parametric models appeared to potentially underpredict two-year PFS (6% to 11%) and five-year PFS (0% to 3%), with the lognormal and log-logistic models producing the closest fits although still substantially underpredicting five-year PFS.

Again, it is important to note that potential differences in the underlying characteristics of the real-world 2L+ R-GemOx population from RE-MIND2 and Meunier 2013 trial population may have limited the ability to directly compare outcomes from the two studies.

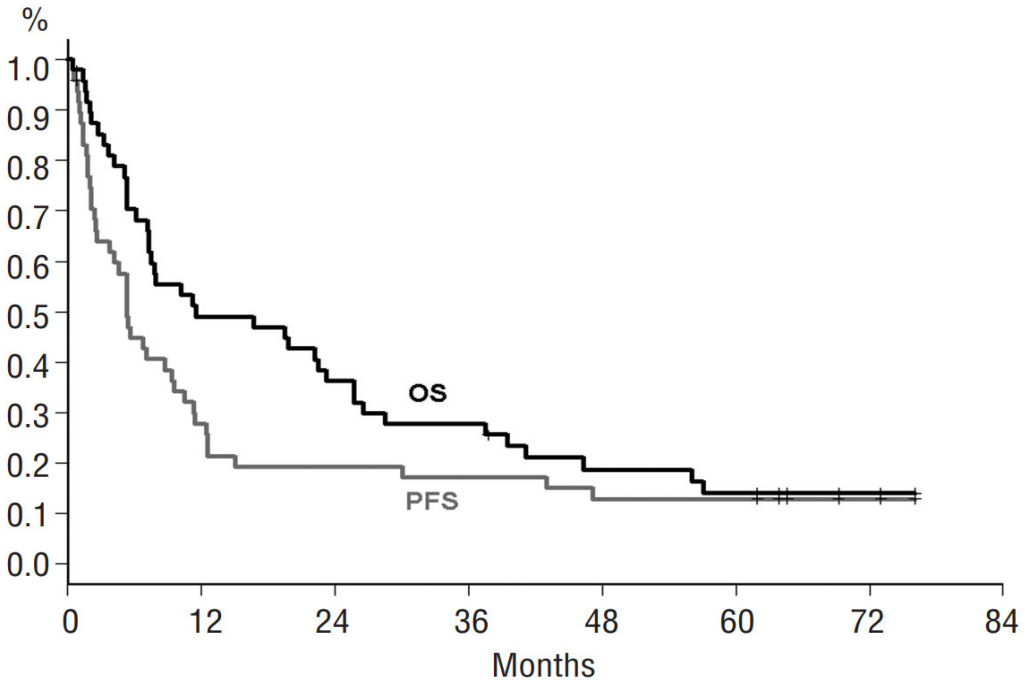

Figure 29. PFS Curve for R-GemOx from Mounier 2013

Abbreviations: OS = overall survival; PFS = progression-free survival; R-GemOx = rituximab + gemcitabine and oxaliplatin

For the base-case analysis, the exponential was selected as this had the best statistical and joint best visual fit to the observed data (where it drops to 0% at approximately 36 months). However, the parametric models appeared to have broadly underestimated PFS when compared with the Mounier 2013 study with the lognormal and log-logistic models providing the most optimistic estimates of survival, despite these models producing clear overestimates at the tail the observed data from RE-MIND2. Of these two models the log-logistic provided a better statistical fit and was therefore explored in scenario analysis.

8.3.3 TTD

Time to treatment discontinuation (TTD) is a key driver of costs and, thus, cost effectiveness. If patients stop receiving a treatment, they stop accruing treatment-related costs (e.g., drug, administration, and monitoring costs). Therefore, it is important that the model is flexible enough to realistically project the average time on treatment for each comparator. There is a high positive correlation between treatment discontinuation and efficacy outcomes, especially for PFS. Treatment duration was modelled independently from efficacy; however, the input parameters of the PFS and treatment discontinuation curves remain naturally correlated. The model also includes the option to model treatments as treat-to-progression, where treatment discontinuation is directly linked to PFS. In the model, stopping treatment affects only cost outcomes, and not efficacy outcomes, which are determined by PFS/OS. It should also be noted that where treatments are fixed duration, the model caps treatment discontinuation at the maximum fixed duration; although, it is possible for patients to discontinue treatment before the fixed duration.

8.3.3.1 Tafasitamab+LEN

The time on treatment for tafasitamab and lenalidomide for patients treated in the 2L+ settings in the L-MIND population is shown in Figure 30. Time on treatment was defined post-hoc among patients who received at least one dose of tafasitamab + lenalidomide as the date of treatment discontinuation or death, whichever occurs first, minus the date of treatment initiation, plus one day. Different treatment schedules were used for lenalidomide and tafasitamab:

lenalidomide was given for up to 12 cycles, while tafasitamab could have been given up to treatment progression. Therefore, time on lenalidomide and tafasitamab were studied separately.

Figure 30. KM Curves for Time on Treatment: Tafasitamab and Lenalidomide

Abbreviations: 2L+ = second line or more; KM = Kaplan-Meier; PFS = progression-free survival; LEN = lenalidomide; TAFA = tafasitamab; TTD = time-to-treatment discontinuation

The long-term extrapolations for the time to tafasitamab discontinuation or death are shown in Figure 31 among patients who were treated in the 2L+ setting. As lenalidomide was given for a fixed duration, no parametric survival analyses were conducted, and KM estimates were used directly in the CEM. The exponential model was a poor visual fit to the data, with the Weibull model also underpredicting most of the early to middle section of the curve before underpredicting the tail. The Gompertz model produced the closest fit to the tail, but slightly underpredicted most of the middle to late section of the KM curve and showed an unrealistic plateau in the data. The lognormal, log-logistic and generalised gamma models produced similar underpredictions to the tail, although the generalised gamma model produced a marginally better visual fit to the tail than the lognormal model, which in turn showed a slightly improvement over the log-logistic model.

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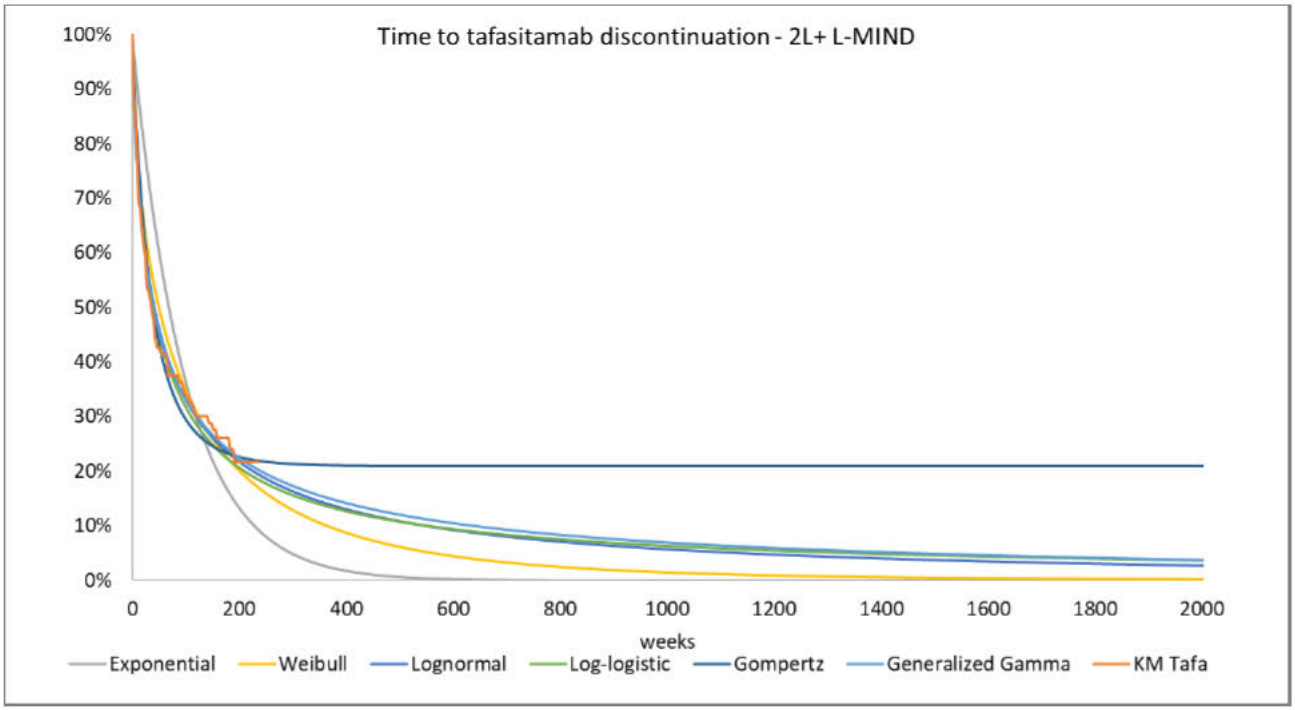

Figure 31. Time to Tafasitamab Discontinuation or Death (Months): Long-term Extrapolations

Abbreviation: 2L+ = second line or more

Table 33 presents the predicted median time to tafasitamab discontinuation or death in cycles using each of the parametric distributions, along with the predicted percentage of patients who are still on treatment at two, five, and ten years among patients treated in the 2L setting.

Similar to PFS and OS, the Gompertz distribution led to an unrealistic plateau due to a statistical artefact of the parametric fitting where a gamma parameter <0 is estimated, suggesting this distribution is likely implausible. However, results are shown for completeness in the table below.

Table 33. Percentage Discontinued

	Median (months)	2-year TTDD prediction	5-year TTDD prediction	10-year TTDD prediction
Exponential	20.0	38%	9%	1%
Weibull	17.3	36%	17%	7%
Log-logistic	14.4	33%	18%	11%
Lognormal	15.0	34%	19%	10%
Generalised gamma	12.5	34%	20%	12%
Gompertz	13.5	30%	22%	21%

Abbreviations: TTDD= Time to Treatment Discontinuation or Death

The parameters and fit statistics of each distribution are shown in Table 34. The lognormal model produced the best statistical fit to the observed data, with log-logistic, generalised gamma and Gompertz models generating good relative statistical fits (0- to 4-point difference) in terms of AICC and reasonable relative fits (0- to 10-point difference) according to BIC. The Weibull model represented an inferior relative fit based on AICC (7- to 10-point difference) and a reasonable

relative fit based on BIC (0- to 10-difference), while the exponential model was a poor statistical fit according to both AIC and BIC.

Table 34. TTDD Parametric Distribution Fit Statistics for Tafasitamab and Lenalidomide

Distribution	Parameter 1		Parameter 2		Parameter 3		Parameter 4		AICC	BIC
	Intercept	SE	Scale	SE	Shape	SE	Gamma	SE		
Weibull	3.1329	0.2110	1.6478	0.1777	0.6069	0.0654			491.369	495.977
Lognormal	2.3420	0.2345	2.0142	0.1933					484.146	488.754
Log-logistic	2.3127	0.2334	1.1849	0.1259					485.024	489.632
Exponential	3.2119	0.1280	1.0000	0.0000	1.0000	0.0000			515.903	518.233
Generalised gamma	2.1859	0.4242	2.0556	0.2120	-0.1819	0.4041			486.107	492.937
Gompertz	2.3547	0.1809					-0.0607	0.0128	487.538	492.146

Abbreviations: AICC = corrected Akaike Information Criterion; BIC = Bayesian Information Criterion; SE = standard error; TTDD= Time to Treatment Discontinuation or Death

For TTD, while lognormal and generalised gamma both produced reasonably similar statistical fits and visual fits to the tail, the lognormal model was selected for the base case analysis based on having a slightly better statistical fit than the generalised gamma model.

8.3.3.2 R-GemOx

The model includes two options to model TTD for R-GemOx. The first option, which is used in the base case analysis, applies TTD data from RE-MIND2. Complete KM data were available and used to model TTD for R-GemOx. The observed KM curves used for R-GemOx (and other comparators which are not relevant for this submission) is shown in Figure 32. Patients discontinued treatment at a relatively similar rate for the first 3-4 months, before the R-GemOx curve declined more quickly down to 0% on treatment with patients stopping treatment on R-GemOx at 6 months.

There is also an option to use median treatment duration to determine TTD based on published clinical trial data or prior NICE technology appraisals (presented in Appendix G).

Figure 32. Time to Treatment Discontinuation or Death for R-GemOx

Abbreviations: R-GemOx = rituximab + gemcitabine and oxaliplatin

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

8.4.1 Overview of health state utility values (HSUV)

8.4.1.1 Utility values per health state

Since HRQoL data was not collected in the L-MIND study, the health state utility values used in the model originate from Pola-BR's STA from NICE [79]. According to the technology appraisal guidance, HRQoL was not measured in polatuzumab's clinical trial GO29365, so the base case utility values were estimated from the ZUMA-1 trial using EQ-5D-5L [79]. NICE's Evidence Review Group (ERG) had identified alternative utility sources but they were tested in scenario analyses and the conclusion was that the base case values produced more conservative ICER estimates and they were not major drivers of the model results [79]. Therefore, the alternative utilities were not considered to be better than the ones assumed for polatuzumab [79]. A similar conclusion was reached by TLV on Pola-BR's assessment for Sweden, in which they considered that the choice of utility weights would not drive the estimation of cost per QALY gain [94].

ZUMA-1 was the pivotal trial for axicabtagene ciloleucel (Yescarta). HRQoL data were collected using EQ-5D-5L in a safety management cohort of ZUMA-1 with 34 patients with relapsed or refractory large B cell lymphoma who were treated with axicabtagene ciloleucel and the results are summarised in Table 35 [95]. The EQ-5D-5L questionnaire was administered at patient screening, and subsequently at week 4, and months 3 and 6 post– axicabtagene ciloleucel infusion, to a total of 33, 27, 20, and 7 patients at each time point, respectively [95]. Patient scores on the questionnaire were converted to EQ-5D indices to evaluate QoL [95]. Since the study was conducted in the United States (US) and the US valuation algorithm (by Shaw et al 2005) is based on EQ-5D-3L, the 5L scores were first mapped onto 3L and then the valuation algorithm was applied to convert EQ-5D-3L scores to EQ-5D index with US population based health utility values [95]. Grouping by health states, mean index scores were 0.80 for the progression free (PF) state and 0.72 for the PD state [95].

Table 35. Utility scores from ZUMA-1 safety management cohort in the US population, by health state

Study	Objective	Region	Treatment/ Comparator	Population	Results
Lin et al. 2019 [95]	To report the EQ-5D-5L ad hoc analysis results from a phase 2 SMS of axi-cel for treatment of adult patients with R/R LBCL	US	Axi-cel/NA	Adult patients with R/R LBCL • Median (range) age: 51 (21–74) years • Male: 56% • ECOG performance status of 1: 56% • International Prognostic Index (IPI) score ≥3: 32%	**EQ-5D-5L index, mean by health state (SD)** • PF: 0.80 (0.14) • PD: 0.72 (0.17)

For NICE's STA of Yescarta, a crosswalk algorithm (by van Hout et al. 2012) was used to convert EQ-5D-5L to EQ-5D-3L and then a UK valuation algorithm was applied to convert EQ-5D-3L descriptive scores to the EQ-5D-3L index with UK population-based health utility values, which are the ones assumed in the health economic model for tafasitamab (Table 37) [96].

8.4.1.2 AE disutilities

The disutilities for AEs grades 3-4 that occurred in more than 5% of patients taking either tafa+LEN or R-GemOx were sourced from NICE STA for Pola-BR [79]. In its turn, Pola-BR's STA obtained the disutilities per AE from previous appraisals in lymphoma (TA306 – pixantrone for R/R NHL; TA559 – axi-cel for DLBCL and primary mediastinal B-cell lymphoma; TA478 – brentuximab vedotin in R/R systemic anaplastic large cell lymphoma) [79]. The original studies from where these appraisals obtained the AE disutilities are presented in Table 36. In Pola-BR's appraisal, NICE's ERG considered that such sources were appropriate [79]. Also, they claimed that AE disutilities and durations have a minimal impact on the ICER and therefore they are unlikely to have a substantial effect on the cost-effectiveness results [79]. This pattern was also recognized in the scenario analysis of the present health economic evaluation (section 8.7.3) that was tested without considering AE disutilities (less than 1,000 DKK difference in ICER).

Table 36. AE disutility values used in NICE's STA for Pola-BR

AE	Disutility	Standard error	Population (n)	Disease area	Method for measuring utilities	Country	Source
Anaemia	0.25		General population (100)	Metastatic renal cell carcinoma	EQ-5D-3L VAS and TTO	UK	Swinburn et al. 2010 [97]
Febrile neutropenia	0.15	NA	General population (100)	Metastatic breast cancer	EQ-5D-3L VAS and standard gamble	UK	Lloyd et al. 2006 [98]
Hypokalaemia	0.09	-	-	-	-	-	Assumed same as leukopenia
Leukopenia	0.09	-	-	-	-	-	Assumed same as neutropenia
Neutropenia	0.09	0.01543	General population (100)	Non-small cell lung cancer	EQ-5D-3L VAS and standard gamble	UK	Nafees et al. 2008 [99]
Pneumonia	0.2	0.02	General population (89)	Chronic lymphocytic leukaemia (CLL)	Standard gamble	UK	Beusterien et al. 2010 [100]
Thrombocytopenia	0.11	NA	General population (110)	Late-stage CLL patients refractory to first- and second-line treatment	EQ-5D-3L VAS and TTO	UK	Tolley et al. 2013 [101]

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The model takes into account the duration of AEs in order to estimate the length of the decrement in HRQoL. Since duration of AEs was not collected neither in L-MIND nor in Mounier et al. 2013 (for tafa+LEN and R-GemOx, respectively), this information had to be obtained from other sources. To keep consistency with the sources for AE disutilities, the AE durations were also taken from NICE's STA report for pixantrone for the treatment of adults with relapsed or refractory aggressive non-Hodgkin's lymphoma (ID414, Table 34) [87]. Data on the AE durations were taken from the clinical study report of the pivotal study PIX301, and are therefore not available on the published study.

In the study population of PIX301, DLBCL was the most common histological subtype, occurring in almost 75% of the 140 patients enrolled [102]. Similar to L-MIND, hematological events (neutropenia, leukopenia, thrombocytopenia, febrile neutropenia and anemia) of grades 3-4 were the most common AEs in PIX301 [102]. Thus, in the lack of a better source, the safety results from PIX301 can be assumed to be relevant for tafa+LEN.

8.4.2 Health state utility values used in the health economic model

Utility values were applied to each health state to capture the quality of life associated with treatment and disease outcomes. Table 37 details the utilities used within the model for PFS, cure and PPS. The utility value for cured patients was conservatively assumed to be same as in the PFS state, as the interviewed KOLs believed the R/R DLBCL patients cannot have a utility equivalent to general population even if they are deemed to be cured. This assumption was tested in scenario analyses.

Table 37. Utilities

Health state	Estimate	SE	Sources/Notes
PFS	0.72	0.03 [78]	NICE's single technology appraisal for Polivy (ID1576) [79]
Long-term disease free	0.72	0.03	Conservatively assumed same as the progression-free survival
PPS	0.65	0.06 [78]	NICE's single technology appraisal for Polivy (ID1576) [79]

Abbreviations: PFS = progression-free survival; PPS= post-progression survival; SE = standard error

Compared to the L-MIND population, the safety management cohort of ZUMA-1 was generally younger (median age 51 vs 72 years) and had a better prognosis (32% had IPI score ≥3 against 51% in L-MIND) [70, 95]. On the other hand, both studies had 56% of patient with ECOG performance status of 1 and a similar gender distribution (56% male patients in ZUMA-1 vs 54% in L-MIND) [70, 95]. Thus, due to these differences in baseline characteristics, it is expected that the utility values obtained with the ZUMA-1 cohort are higher than what would be expected for patients in L-MIND.

Since Incyte does not have access to the individual patient data from the original trial, it was not possible to calculate utility values using the Danish preference weights. However, results from a cross-country comparison of EQ-5D utilities for the general population show that Danish values are higher than for the British, as shown in Table 38 [103]. Hence, a possible valuation of the ZUMA-1 utilities to the Danish population would result in higher values than for the UK. Therefore, it is likely that the lower values expected for the L-MIND population would to some extent be compensated by the higher Danish utilities or that the difference in utilities would not lead to major changes in ICER, as anticipated by NICE and TLV [79, 94]. In order to test these changes, scenario analyses were conducted with the utility values from two other STAs (TA306, PFS = 0.76 and PD = 0.68; and from TA567, PFS = 0.83 and PD = 0.71) to assess how much the different utilities would affect the ICER (results presented in section 8.7.3).

Table 38. EQ-5D-3L index value population norms for Denmark and UK by age group (country-specific TTO and VAS value sets)

Age group	Denmark	UK
55-64	0.870	0.799
65-74	0.847	0.778
75+	0.794	0.726

Source: Janssen et al. 2019 [103].

The AE disutilities used in the model and their corresponding durations are presented in Table 39.

Table 39. AE disutilities and corresponding durations used in the model

AE	Disutility	Disutility Duration (Days)
Anaemia	0.25	16
Febrile neutropenia	0.15	7.1
Hypokalaemia	0.09	72
Leukopenia	0.09	14
Neutropenia	0.09	15.1
Pneumonia	0.20	14.9
Thrombocytopenia	0.11	23.2

8.5 Resource use and costs

Disease- and treatment-related costs are applied to each health state and event in the model. Cost categories included: drug and administration costs applied for the duration of active treatment (determined by dosing regimen and treatment duration); routine follow-up care costs; unplanned event costs, such as AE, progression, and terminal care costs; and direct non-medical costs for transportation.

8.5.1 Price of Minjuvi (tafasitamab)

The suggested price for tafasitamab in Denmark is [redacted] DKK (AIP) per package (see Table 40). This corresponds to an average monthly pharmaceutical cost of [redacted] DKK for tafasitamab. Note that the monthly pharmaceutical cost of tafasitamab depends on the patients' weight and dosing scheme.

8.5.2 Drug Acquisition Costs

Drug costs for the treatment options included in the model including second-line treatments are shown in Table 40. An option for considering confidential price agreements (patient access schemes, PAS) has also been included in the model. Even though there is a price agreement in place for Revlimid (lenalidomide) in Denmark, the final drug price after discount remains confidential. Hence, no PAS was considered for any drug in the base case.

Next to the PAS option, the model contains an option to consider the impact of lenalidomide becoming generic in a more elaborated manner. The user can select the date of lenalidomide losing exclusivity and a percent reduction in price that would be applied. The model requires the user to set the reference date (i.e., the current date) to calculate the duration of full price lenalidomide. This should be updated when running the model. It must be noted that if this option is being used, no discount must be entered for lenalidomide in the PAS inputs (otherwise the discount will be applied twice).

Bristol-Myers Squibb Pharma EEIG, the MAH of Revlimid in Denmark, lost patent of Revlimid in the beginning in 2022. Usually, in countries with exchange system in place for generic competition (as for example Denmark and Sweden) prices are expected to drop rather quickly after the introduction of generic drugs [105]. Until April 2022, prices have dropped approximately 15% [106]. However, several competitors are to be expected in the upcoming months, most likely resulting in a heavier price drop.

Therefore, in the base case the current list price (shown in Table 40) is assumed for lenalidomide, on top of which a 90% discount is applied from 01 January 2022. In scenario analysis, it is assumed that lenalidomide loses exclusivity on 1 January 2022 and a 50% reduction in price is applied for the remainder of the model time horizon.

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Table 40. Drug Acquisition Costs

Treatment	Pack #1			Pack #2			Pack #3			Pack #4			Source
	Strength per Unit (mg)	# Units per Pack	Price (DKK)	Strength per Unit (mg)	# Units per Pack	Price (DKK)	Strength per Unit (mg)	# Units per Pack	Price (DKK)	Strength per Unit (mg)	# Units per Pack	Price (DKK)	
Intervention and comparator													
Tafasitamab	200	1	[redacted]										
Lenalidomide	5	21	31,866	10	21	33,636	15	21	35,407	20	21	37,118	Medicinpriser.dk [106]
Rituximab	500	1	6,687	100	2	2,676							
Gemcitabine	40	25	1,000	40	50	1,200							
Oxaliplatin	5	20	69	5	40	128	5	10	41				
Subsequent therapies													
Polatuzumab	140	1	72,724	30	1	15,584							
Bendamustine	25	5	367	100	5	1,174							
Tisagenlecleucel	1	1	2,133,418										
Dexamethasone	4	100	219	4	20	78	1	100	519	1.0	20	133.00	
Cytarabine	100	10	100	100	20	150							
Cisplatin	1	50	100	1	100	200							
Etoposide (IV)	20	5	71	20	25	279							
Pixantrone	29	1	5,010										
Radiotherapy													Costs of radiotherapy are assumed to be reflected in the radiotherapy administration costs
Cyclophosphamide (IV)	200	1	62	500	1	154	1000	1	308				
Doxorubicine	2	25	120	2	5	150	2	100	360				
Doxorubicine hydrochloride	2	25	120	2	5	150	2	100	360				
Fludarabine Phospate	25	2	1,310										
Methotrexate	2.5	100	35										
Prednisolone	5	100	38										
Ifosfamide	1000	1	308										
Carboplatin	10	15	84	10	45	203							
Cyclophosphamide (PO)	50	100	907										
Etoposide (PO)	mg	20	1,690										

Abbreviations: DKK, Danish Kronor; IV, intravenous; PO, orally.

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8.5.3 Administration Costs

The administration of IV and subcutaneous (SC) treatments require an outpatient visit that may include additional nursing and pharmacist preparation time. Therefore, administration costs for IV/SC treatments were programmed into the model. As the first and subsequent instances had different costs, these were implemented separately in the model. In Denmark there is no difference between the first and subsequent administration costs, so these items were assigned with the same cost. In order to avoid over complicating in the model, the IV/SC administration cost was assumed to be that of the subsequent attendance for subsequent treatments. An option for adding costs for oral administration of the drug is also included in the model, currently set to zero. Radiotherapy administration cost is also included as some patients receive radiotherapy in the subsequent line of treatment. The costs per mode of administration are shown in Table 41.

Table 41. Administration Costs

Mode of Administration	Unit Cost	Reference:
IV/SC admin: first attendance	3,225.00 DKK	DRG taktser 2022 [107]
IV/SC admin: subsequent	3,225.00 DKK	
Oral administration	0 DKK	Assumed same as for previous NICE submission
Radiotherapy	2,864.00 DKK	DRG taktser 2022 [107]

Abbreviations: DRG, diagnosis-related group; IV = intravenous; SC = subcutaneous

8.5.4 Monitoring Costs

Costs related to monitoring the treatment and the progression status of the patient were included in the model. These resources are used by patients up to the progression point. The list of disease monitoring resource items was selected based on the previous NICE submissions in R/R DLBCL [78-80, 108]. The types and frequencies of healthcare resource and laboratory tests included for tafasitamab and lenalidomide were based on those used in the L-MIND trial [78, 79, 81, 108]. Table 42 presents the unit costs for each monitoring test included in the model.

Table 42. Unit Costs for Monitoring Tests

Monitoring Test	Unit Cost	Reference
Anti-MOR00208 antibodies	86 DKK	1) DRG taktser 2022 [107]
B-, T- and NK cell flow cytometry (blood)	2,264 DKK	2) Laboratoriemedicinsk vejledning (LMV) – Region Sjælland [109]
B-cell and T-cell test	2,264 DKK	
Blood sampling	16 DKK	
Bone marrow aspirate	3,168 DKK	
Bone marrow biopsy	3,168 DKK	
Calcium phosphate	16 DKK	
Chemistry panel (including liver function test)	106 DKK	
Coagulation panel	65 DKK	
CSF	464 DKK	
CT scan	1,979 DKK	
CT scan with IV contrast	2,411 DKK	
ECG: electrocardiogram	213 DKK	
Echocardiogram	213 DKK	
Full blood counts	302 DKK	
Haematology panel	302 DKK	
Immunoglobulin	16 DKK	
Lactate dehydrogenase	16 DKK	
Liver function test	106 DKK	
MRI	2,057 DKK	
MUGA (multiple-gated acquisition) scan	2,416 DKK	
PET/CT	1,979 DKK	

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Monitoring Test	Unit Cost	Reference
Pregnancy test (serum and urine)	106 DKK	
Renal function	106 DKK	
Serology parameters (Hepatitis B: HbsAg, anti-HBc; anti-HBs; HBV-DNA)	1,152 DKK	
Serum test	16 DKK	
Urinalysis	72 DKK	
Comprehensive metabolic panel	72 DKK	
Uric acid	72 DKK	
Serum lactate dehydrogenase	16 DKK	

Abbreviations: CSF = cerebrospinal fluid; CT = computed tomography; ECG = electrocardiogram; HBc = hepatitis B core; HBs = hepatitis B surface antibody; HbsAg = hepatitis B surface antigen; HBV-DNA = hepatitis B virus deoxyribonucleic acid; IV = intravenous; MRI = magnetic resonance imaging; MUGA = multiple-gated acquisition; PET = positron emission tomography.

As mentioned in section 8.1.11, the level of resource use by patients could depend on the time spent in progression-free survival. Given a cut-off point of two years was selected for assuming reduced resource use in the mode, monitoring frequencies uses were separated by this cut-off (i.e., ≤2 years and >2 years). Frequencies and costs per cycle for these two time periods are provided in the following sections.

8.5.4.1 Monitoring Costs ≤2 Years PFS

Table 43 presents the frequency of each monitoring test for each comparator, for patients with ≤2 years of PFS.

The schedule of assessments within the clinical study report (CSR) for the L-MIND trial was used to inform model assumptions regarding monitoring test frequency for tafasitamab and lenalidomide. The model assumptions regarding monitoring test frequency for R-GemOx was based on input from a Danish clinical expert [89].

Table 43. Monitoring Tests: Frequency of Use for Patients with ≤2 Years in PFS (per model cycle)

Monitoring Test	Tafasitamab and Lenalidomide	R-GemOx
Anti-MOR00208 antibodies	[redacted]	
Blood sampling	[redacted]	1.33
Bone marrow biopsy	[redacted]	
Chemistry panel (including liver function test)		1.33
CT scan	[redacted]	
Haematology panel		1.33
MRI	[redacted]	
Pregnancy test (serum and urine)	[redacted]	
Serology parameters (Hepatitis B: HbsAg, anti-HBc; anti-HBs; HBV-DNA)	[redacted]	
Urinalysis	[redacted]	
Uric acid		1.33
Serum lactate dehydrogenase		1.33
Source	L-MIND CSR [81]	Based on Danish clinical expert [89]

Abbreviations: CSR = clinical study report; CT = computed tomography; HBc = hepatitis B core; HBs = hepatitis B surface antibody; HbsAg = hepatitis B surface antigen; HBV-DNA = hepatitis B virus deoxyribonucleic acid; IV = intravenous; MRI = magnetic resonance imaging; PFS = progression-free survival; R-GemOx = rituximab + gemcitabine and oxaliplatin

In addition to the per cycle monitoring costs, a one-off monitoring cost was also applied for some of the comparators. This is to ensure that the resources which are used for a limited period of time are not accounted for to the whole duration of PFS. Table 44 details the one-off costs used within the model.

For tafasitamab and lenalidomide, three examples of the reported resource use from the L-MIND trial did not continue up to two years. These exams included B, T and NK cell flow cytometry (up to cycle 8), electrocardiogram (ECG [up to

cycle 12]) and positron emission tomography (PET) computed tomography (CT [occurred only once at cycle 12]). Therefore, these were included as a one-off cost by multiplying their frequency with the cost of each exam and summing these.

For R-GemOx the resource use from months 1 through 5 was captured in a one-off monitoring cost, which was equivalent to the cost of one consultant visit.

Table 44. One-off Monitoring Cost

Comparator	One-off Monitoring Costs	Source
Tafasitamab and lenalidomide	[redacted]	Laboratoriemedicinsk vejledning (LMV) – Region Sjælland [109]
R-GemOx	[redacted]	DRG taktser 2022 [107]

Abbreviations: DRG, diagnosis-related group; R-GemOx = rituximab + gemcitabine and oxaliplatin

Table 45 summarises monitoring cost for each comparator that is applied per cycle for patients with ≤2 years in PFS.

Table 45. Monitoring Cost per Cycle (≤ 2 years in PFS)

Treatment	Cost per Model Cycle (patients with ≤2 years in PFS)
Tafasitamab and lenalidomide	[redacted]
R-GemOx	[redacted]

Abbreviations: R-GemOx = rituximab + gemcitabine and oxaliplatin

8.5.4.2 Monitoring Costs >2 Years of PFS

Table 46 presents the frequency of each monitoring test for each comparator, for patients with >2 years of PFS. The frequencies are based on input from a Danish clinical expert [89].

Table 46. Monitoring Costs: Frequency of Use per Model Cycle (patients with >2 years PFS)

Monitoring test	Frequency per cycle (Year 1)	Frequency per cycle (Year 2)	Frequency per cycle (Year 3)	Frequency per cycle (Year 4)	Frequency per cycle (Year +5)
CT scan	0	0	--	--	--
Full blood counts	0.166	0.166	--	--	--
Source	Based on Danish clinical expert [89]	Based on Danish clinical expert [89]	--	--	--

Abbreviation: CT = computed tomography; PFS = progression-free survival

In lack of inputs for R/R DLBCL, the indications provided in guidelines for DLBCL are used as a source for resource use in patients with >2 years PFS [24]. Table 47 summarises monitoring cost per cycle that is applied each year for patients with >2 years of PFS.

Table 47. Monitoring Cost per Cycle (>2 years in PFS)

Cost per cycle (patients with >2 years in PFS)	
Year 1	[redacted]
Year 2	[redacted]
Year 3	[redacted]
Year 4	[redacted]
Year 5	[redacted]

Abbreviation: PFS = progression-free survival

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8.5.5 Disease Management Cost

Costs related to disease management are included in the model. These resources are used by patients on or off the initial treatment, regardless of health states (i.e., PF or PD). The list of disease management resources is based on the previous NICE submissions in R/R DLBCL [78-80, 108] but are assumed to be also reflect Danish clinical practice. Table 48 lists the unit costs for each of the possible disease management resource use items.

Table 48. Disease Management Resource Unit Cost

Disease Management Resource	Unit Cost	Source
Consultant visit	3,225 DKK	DRG takster 2022 [107]
Day care	3,058 DKK	
District nurse (visit)	2,910 DKK	
GP (visit)	3,225 DKK	
Haematologist (visit)	3,225 DKK	
Home care (day)	4,531 DKK	
Hospice (day)	2,387 DKK	
Hospitalisation	8,555 DKK	
Inpatient (day)	8,555 DKK	
Nurse (visit)	10,475 DKK	
Oncologist (visit)	2,910 DKK	
Palliative care team	3,225 DKK	
Radiologist (visit)	19,330 DKK	
Specialist nurse (visit)	2,864 DKK	
Terminal care cost	2,387 DKK	

Abbreviations: GP = general practitioner.

The level of resource use for disease management could depend on the time spent in the PFS state, which is the same as for the monitoring costs. Given a cut-off point of two years for assuming reduced resource use in the model (Section 8.1.11), disease management frequencies were separated by this cut-off point (i.e., ≤2 years and >2 years). Frequencies and costs per cycle for these two time periods are provided in the following sections.

8.5.5.1 Disease Management Costs ≤2 Years of PFS

Table 49 presents the frequency of use for each disease management resource for each comparator for patients who have had ≤2 years of PFS.
The assessments schedule within the CSR for the L-MIND trial was used to inform the model assumptions regarding disease management resource frequency for tafasitamab and lenalidomide.

Table 49. Disease Management: Frequency of Use (≤2 Years of PFS)

Disease Management Resource	Tafasitamab and Lenalidomide	R-GemOx
Consultant visit	[redacted]	0.4
District nurse (visit)	[redacted]	
Source:	L-MIND CSR[81]	ID1166 [80]

Abbreviations: CSR = clinical study report; R-GemOx = rituximab + gemcitabine and oxaliplatin

Table 50 summarises the disease management costs for each comparator that were applied per cycle for patients who have had ≤2 years of PFS.

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Table 50. Disease Management Cost per Cycle (≤2 Years of PFS)

Treatment	Cost per Model Cycle for (progression-free ≤2 years)
Tafasitamab and lenalidomide	[redacted]
R-GemOx	[redacted]

Abbreviations: PFS = progression-free survival; R-GemOx = rituximab + gemcitabine and oxaliplatin

8.5.5.2 Disease Management Costs >2 Years of PFS

Table 51 presents the frequency of each disease management resource for each comparator, for patients with >2 years of PFS.

Table 51. Disease Management: Frequency of Use (>2 Years of PFS)

Disease Management Resource	Year 1	Year 2	Year 3	Year 4	Year 5+
Consultant visit	0.33	0.17	0.17	0.08	0.08
Source	Tilly et al 2015[24]				

Abbreviation: PFS = progression-free survival

In lack of inputs for R/R DLBCL, the indications provided in guidelines for DLBCL are currently used as a source for disease management frequencies in patients with >2 years PFS [24].

Table 52 summarises disease management resource cost per cycle that is applied each year for patients with >2 years of PFS.

Table 52. Disease Management Cost per Cycle (>2 Years of PFS)

Cost per Year (patients with >2 years of PFS)	
Year 1	[redacted]
Year 2	[redacted]
Year 3	[redacted]
Year 4	[redacted]
Year 5	[redacted]

Abbreviation: PFS = progression-free survival

8.5.5.3 Disease Management Costs: Post-progression

The L-MIND CSR did not capture the disease management frequency for progression. Therefore, the resource use for all comparators was assumed to have been the same as that which was reported in the polatuzumab NICE submission, which were derived from clinical expert opinion [78]. Table 53 presents the frequency of use for each disease management resource for patients who have progressed.

Table 53. Disease Management: Frequency of Use (Progressed)

Disease Management Resource	Frequency of use
Day care	1.9
District nurse (visit)	4.0
GP (visit)	3.3
Haematologist (visit)	1.2
Home care (day)	9.3
Hospice (day)	0.9
Inpatient (day)	0.2

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Nurse (visit)	0.2
Oncologist (visit)	0.4
Radiologist (visit)	0.0
Specialist nurse (visit)	2.5
Source	Assumption to be the same as Pola-BR [78]

The total post-progression disease management cost for both tafasitamab+LEN and R-GemOx is displayed in Table 54.

Table 54. Disease Management Cost per Cycle: Post Progression

Treatment	Cost
Total Disease Management Cost per Cycle: Post Progression	[redacted]

8.5.5.4 One-off Disease Management Costs

Table 55 details the one-off costs applied within the model. The annual frequency of palliative care team use was taken from the Polatuzumab NICE submission (17.3), adjusted by the cycle length and then multiplied by the cost of the Specialized Palliative Care, Large, Home visit, DRG 26HJ01 (18.683 DKK) to give a one-off cost for progression [110].

In addition, a one-off cost for mortality was also applied. The cost was based on the DRG tariff for Medium Specialized Palliative Care, DRG 26MP46 (43.687 DKK), therefore it was assumed this value would be applied as a one-off cost in our model.

Table 55. One-off Costs

Event	Cost per Model Cycle
Progression	[redacted]
Mortality	[redacted]

8.5.6 Subsequent Treatments

Drug costs for subsequent treatment options after progression are included in the model. These post-progression costs are a combination of possible SCT and other anti-cancer drug costs, including their administration costs. The proportions of patients receiving different subsequent treatments upon progression on each induction treatment are listed in Table 56 and were based on data from the RE-MIND2 study [111]. According to a Danish clinical expert, it is difficult to assess 3L treatment since many patients do not get any treatment at all [89]. Since this information is in line with the data presented below (i.e., nearly 30% of R-GemOx patients moved to a subsequent treatment), the RE-MIND2 data was preferred for use in the model.

Table 56. Subsequent Treatment Distributions

	Patient Proportions per Initial Line of Treatment	
	Tafasitamab and Lenalidomide	R-GemOx
R-GemOx	[redacted]	[redacted]
R2	[redacted]	[redacted]
Pixantrone	[redacted]	[redacted]
Lenalidomide	[redacted]	[redacted]
Pola-BR	[redacted]	[redacted]
BR	[redacted]	[redacted]
Rituximab	[redacted]	[redacted]
Carboplatin, Etoposide, Ifosfamide & Rituximab	[redacted]	[redacted]
Cyclophosphamide, Etoposide, Prednisone & Procarbazine	[redacted]	[redacted]

	Patient Proportions per Initial Line of Treatment	
	Tafasitamab and Lenalidomide	R-GemOx
Cyclophosphamide, Doxorubicin hydroxyl & Rituximab	[redacted]	[redacted]
Rituximab, Dexamethasone, Cytarabine & Oxaliplatin	[redacted]	[redacted]
R-DHAP	[redacted]	[redacted]
CAR-T	[redacted]	[redacted]
Cyclophosphamide, Fludarabine Phosphate & Other Antineoplastic agents	[redacted]	[redacted]
Methotrexate	[redacted]	[redacted]
GemOx	[redacted]	[redacted]
Radiotherapy	[redacted]	
Notes		[redacted]
Reference	RE-MIND2[111]	RE-MIND2[111]

Abbreviations: CAR-T = chimeric antigen receptor T-cell; GemOx = gemcitabine and oxaliplatin; Pola-BR = polatuzumab + bendamustine + rituximab; R2 = lenalidomide + rituximab; R-DHAP = rituximab, dexamethasone, cytarabine, and cisplatin; R-GemOx = rituximab + gemcitabine and oxaliplatin; SCT = stem cell transplant

Subsequent treatment costs for CAR-T, R-DHAP, and R2 were all calculated based on a weighted average of SCT use (12.5%, 12.5 % and 22.2% respectively) [80, 108]. For the other anti-cancer treatments listed in Table 56, Appendix K shows an overview of dosing schedule and summary costs. The total subsequent treatment costs for both comparators are listed in Table 57.

Table 57. Total Subsequent Treatment Costs

Treatments	Total Cost	Sources
Tafasitamab and lenalidomide	[redacted]	RE-MIND2
R-GemOx	[redacted]	RE-MIND2

Abbreviations: R-GemOx = rituximab + gemcitabine and oxaliplatin

8.5.7 Co-medications

Table 58 details the drug dosing and cost calculation for the co-medication costs for each of the treatments. In the L-MIND study, co-medications for patients who did not experience any infusion related reactions to tafasitamab during the first three infusions (doses) was optional for subsequent infusions at the discretion of the investigator [81]. Otherwise, the co-medication was continued for subsequent administrations. In lack of a clear input on the proportion of the patients who receive the co-medications, an average percentage 70% was assumed for patients who require co-medications in tafasitamab and lenalidomide treatment strategy.

Table 58. Co-medication Drug Dosing and Cost Calculation

Treatment	Dependency	Dose	Cost per dose	# of admin per Tx cycle	Cost per Tx cycle	# of weeks per Tx cycle	Cost per model cycle
Tafasitamab and Lenalidomide co-meds (induction):							
[redacted]							
[redacted]							
[redacted]							
Tafasitamab and Lenalidomide co-meds (maintenance):							

[redacted]							
[redacted]							
[redacted]							
Rituximab, Gemcitabine & Oxaliplatin co-meds:							
[redacted]							
[redacted]							

Abbreviations: DKK = Danish Krone; R-GemOx = rituximab + gemcitabine and oxaliplatin; NA = not applicable; Tx = treatment

Table 59 details the administration costs per cycle associated with the co-medication costs. Only those co-medications that are IV infusions require administration. The cost is based on the cost of one hospitalization day for a patient with tumours on lymphatic and blood-forming tissues (DRG 17MA98) [107].

Table 59. Administration Dosing for Co-medications

Treatment	# of Administration per Treatment Cycle	Administration Route
Tafasitamab and Lenalidomide co-meds (induction):		
Acetaminophen (paracetamol)	4	PO
Diphenhydramine	4	IV
Methylprednisolone	4	IV
Tafasitamab and Lenalidomide co-meds (maintenance):		
Acetaminophen (paracetamol)	2	PO
Diphenhydramine	2	IV
Methylprednisolone	2	IV
Rituximab, Gemcitabine & Oxaliplatin co-meds:		
Methylprednisolone	2	IV
Acetaminophen	2	PO
Dexchlorpheniramine	2	PO

Abbreviations: IV = intravenous; NA = not available; PO = per oral

Table 60 displays the total co-medication costs for each of the treatments used within the model.

Table 60. Co-medication Costs

Treatment	Co-medication Cost per Model Cycle (Induction)	Co-medication Cost per Model Cycle (Maintenance)
Tafasitamab and lenalidomide	[redacted]	[redacted]
R-GemOx	[redacted]	[redacted]

Abbreviations: DKK = Danish Krone, R-GemOx = rituximab + gemcitabine and oxaliplatin.

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8.5.8 AE Costs

The costs of managing the AEs that were considered in the model are presented in Table 61 below. The costs are based on DRG tariffs from the Danish Health Data Authority [107].

Table 61. Cost of Managing AEs per Event

AE	Cost per Event	Comment	Source
Anaemia	6,450.00 DKK	Assumption: 2 heamatologist visits, DRG: 17MA98	DRG takster 2022 [107]
Febrile neutropenia	22,419.00 DKK	DRG: 16MA10	
Hypokalaemia	3,225.00 DKK	DRG: 17MA98	
Leukopenia	22,419.00 DKK	DRG: 16MA10	
Neutropenia	22,419.00 DKK	DRG: 16MA10	
Pneumonia	2,180.00 DKK	DRG: 04MA98	
Thrombocytopenia	38,408.00 DKK	DRG: 16MA03	

Abbreviations: AE = adverse event; DKK = Danish Krone

Total AE management costs per treatment used in the model are displayed in Table 62 below.

Table 62. AE Management Costs per Treatment

Treatment	AE cost per model cycle
Tafasitamab and lenalidomide	[redacted]
R-GemOx	[redacted]

Abbreviations: AE = adverse event; DKK = Danish Krone; R-GemOx = rituximab + gemcitabine and oxaliplatin

8.5.9 Non-medical direct costs

The model allows the inclusion of non-medical direct costs, which includes transportation costs and time spent by patients and relatives. For transportation costs, an average cost of 200 DKK per treatment cycle was considered for both the intervention and comparator. For time spent by patients and relatives, it was assumed that 2 hours were spent per cycle, with a cost of 181 DKK/hour [112].

Table 63. Patient costs used in the model

Costs	**Cost** (per **treatment cycle**)
Transportation costs	200 DKK
Time spent by patients and relatives	362 DKK

8.6 Results

8.6.1 Base case overview

An overview of the main base case inputs and their corresponding justifications is presented in Table 64.

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Table 64. Base case overview and justifications

	Setting	Base Case	Justification
Main Settings	Perspective	Limited societal	Standard setting as per DMC guideline
	Time horizon	35 years	Covering a lifetime for patients in the target population
	Discount rate for health and cost outcomes	3.5%	Discount rate according to Denmark's Ministry of Finance [82]
	Population	R/R DLBCL; patients receiving more than two lines of treatment (2L+)	Current focus population for tafasitamab
	Switch timepoint for prolonged progression-free state	2 years	Based on KOL recommendation
	Proportion of progression-free patients reaching prolonged progression-free state	[redacted]	Assumed as rate of CR among 2 years PFS- based on KOL recommendation
	Switch timepoint for considering long-term disease freedom	2 years	Based on KOL recommendation
	Proportion of progression-free patients disease free after the switch point	[redacted]	Assumed as rate of CR among 2 years PFS- based on KOL recommendation
	Consider disease free patients as off treatment	Yes	Based on KOL recommendation
	Baseline age	69 years	L-MIND[81]
	Males	54.3%	L-MIND[81]
	BSA	1.91	L-MIND[81]
Efficacy	OS approach: tafasitamab and lenalidomide	Parametric Single Fit; lognormal	Best statical fit and relatively good visual fit to the data
	PFS approach: tafasitamab and lenalidomide	Parametric single fit; generalised Gamma	Best statical fit and visual fit to the data
	OS approach (RE-MIND2): R-GemOx	Lognormal	Best statistical fit of models with most plausible long-term extrapolations in relation to external data
	PFS approach (RE-MIND2): R-GemOx	Exponential	Best statistical fit and joint best visual fit to observed data
	Mortality within PFS	[redacted]	Constant ratio of death and progression. In lack of specific inputs, assumed all comparators are the same as tafasitamab and lenalidomide
	Treatment discontinuation rule: tafasitamab	Treatment discontinuation curve; lognormal	Second best statistical fit; aligned with PFS assumptions
	Treatment discontinuation rule: lenalidomide	Treatment discontinuation curve; KM curve	Lenalidomide has a fixed duration thus no extrapolations were needed
	Treatment discontinuation rule: R-GemOx (RE-MIND2)	KM curves from RE-MIND2	Best available source

	Setting	Base Case	Justification
Cost Settings	Tafasitamab price	[redacted]	Incyte
	Lenalidomide price	Price of generic lenalidomide from Apr-2022	Best available source
	Monitoring for tafasitamab and lenalidomide; PFS ≤ 2 years	Frequencies reported in L-MIND [81]	Best available source
	Monitoring for tafasitamab and lenalidomide; PFS > 2 years	Frequencies reported in ESMO guidelines for DLBCL [24]	Best available source
	Disease management tafasitamab and lenalidomide; PFS ≤ 2years	Frequencies reported in L-MIND [81]	Best available source
	Disease management tafasitamab and lenalidomide; PFS > 2years	Frequencies reported in ESMO guidelines for DLBCL [24]	Best available source
	Disease management tafasitamab and lenalidomide; post-progression	Assumed same as Pola-BR	Assumption made in lack of inputs for tafasitamab and lenalidomide
	Co-medications	Assumed [redacted] tafasitamab and lenalidomide patients receive co-medications	Assumption in lack of specific inputs
	Transportations costs	200 DKK per cycle	Assumption based on average treatment administration with tafasitamab and lenalidomide
	Time spent by patients and relatives	362 DKK per cycle	Assumption based on estimated time spent by patients and relatives for treatment administration with tafasitamab and lenalidomide
Utility Settings	Utility approach	Utilities sourced from polatuzumab NICE submission [79]	Best available source
	AE disutility	Include	Best practice

Abbreviations: AE = adverse event; BR = bendamustine + rituximab; BSA = body surface area; CAR-T = chimeric antigen receptor T-cell; CR = complete response; DLBCL = diffuse large B-cell lymphoma; ESMO = European Society for Medical Oncology; HR = hazard ratio; KM = Kaplan-Meier; KOL = key opinion leader; NICE = National Institute of Health and Care Excellence; OS = overall survival; PFS = progression-free survival; Pola-BR = polatuzumab + bendamustine + rituximab; R/R = relapsed/refractory; R-GemOx = rituximab + gemcitabine and oxaliplatin.

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8.6.2 Base case results

Tafasitamab+LEN provided a gain of [redacted] LYs and [redacted] QALYs over a lifetime horizon (35 years), when compared to R-GemOx. The treatment with tafasitamab+LEN was also associated with higher costs (appr. [redacted] DKK more than R-GemOx), leading to an ICER of [redacted] per QALY. A detailed description of the base case results is presented in Table 65.

Table 65. Base case results

Per patient	Tafasitamab+LEN	R-GemOx	Difference
Life years gained			
Total life years gained	[redacted]	[redacted]	[redacted]
Life years gained (Progression-free health state)	[redacted]	[redacted]	[redacted]
Life years gained (Post-progression health state)	[redacted]	[redacted]	[redacted]
Life years gained (Cured)	[redacted]	[redacted]	[redacted]
Life years gained (On treatment time)	[redacted]	[redacted]	[redacted]
Life years gained (Off treatment time)	[redacted]	[redacted]	[redacted]
QALYs			
Total QALYs	[redacted]	[redacted]	[redacted]
QALYs (Progression-free state)	[redacted]	[redacted]	[redacted]
QALYs (Post-progression state)	[redacted]	[redacted]	[redacted]
QALYs (Long-term disease free)	[redacted]	[redacted]	[redacted]
QALYs (adverse reactions)	[redacted]	[redacted]	[redacted]
Costs			
Total costs	[redacted]	[redacted]	[redacted]
Drug costs - Induction	[redacted]	[redacted]	[redacted]
Drug costs - Maintenance	[redacted]	[redacted]	[redacted]
Admin costs - Induction	[redacted]	[redacted]	[redacted]
Admin costs - Maintenance	[redacted]	[redacted]	[redacted]
Co-medication costs- Induction	[redacted]	[redacted]	[redacted]
Co-medication costs- Maintenance	[redacted]	[redacted]	[redacted]
Monitoring costs	[redacted]	[redacted]	[redacted]
Adverse event management costs	[redacted]	[redacted]	[redacted]
Disease management costs - Pre-progression	[redacted]	[redacted]	[redacted]
Disease management costs - Post-progression	[redacted]	[redacted]	[redacted]
Disease management costs - One-off - Progression	[redacted]	[redacted]	[redacted]
Disease management costs - One-off - Death	[redacted]	[redacted]	[redacted]
Subsequent treatment costs	[redacted]	[redacted]	[redacted]
Transportation costs and time spent by patients and relatives - Pre-progression	[redacted]	[redacted]	[redacted]
Transportation costs and time spent by patients and relatives - Post-progression	[redacted]	[redacted]	[redacted]
Incremental results		Tafasitamab+LEN vs. R-GemOx	
ICER (per QALY)		[redacted]	

8.7 Sensitivity analyses

The uncertainty of the model results was assessed with deterministic sensitivity analyses (DSA) and a probabilistic sensitivity analysis. These are further presented in sections 8.7.1 and 8.7.2, respectively. Scenario analyses (section 8.7.3) were also performed to test the impact of alternative values on selected model inputs.

8.7.1 DSA

All major model variables were tested through a one-way DSA to identify the model drivers and examine key areas of sensitivity. During these analyses, each variable was systematically increased and decreased with results generated for the higher and lower values. The higher and lower values were based on the CIs or published ranges. If such data were absent, the higher and lower values were calculated as ±20% of the mean base-case value. The higher and lower values used in the DSA are listed in Appendix L. The DSA results in ICERs (DKK per QALY) are shown in Table 66.

Table 66. DSA results (ICERs in DKK/QALY)

Scenario	Lower Value (DKK/QALY)	Upper Value (DKK/QALY)	Difference (DKK/QALY)
Starting Age	[redacted]	[redacted]	[redacted]
Efficacy: OS Single Parametric Fit - Parameter 1 (2L+): Tafasitamab & Lenalidomide	[redacted]	[redacted]	[redacted]
Efficacy: PFS Single Parametric Fit - Parameter 1 (2L+): R-GemOx	[redacted]	[redacted]	[redacted]
Efficacy: PFS Single Parametric Fit - Parameter 2 (2L+): Tafasitamab & Lenalidomide	[redacted]	[redacted]	[redacted]
Efficacy: PFS Single Parametric Fit - Parameter 3 (2L+): Tafasitamab & Lenalidomide	[redacted]	[redacted]	[redacted]
Efficacy: OS Single Parametric Fit - Parameter 1 (2L+): R-GemOx	[redacted]	[redacted]	[redacted]
Efficacy: OS Single Parametric Fit - Parameter 2 (2L+): Tafasitamab & Lenalidomide	[redacted]	[redacted]	[redacted]
Health states utility: Long-term disease free	[redacted]	[redacted]	[redacted]
Efficacy: OS Single Parametric Fit - Parameter 2 (2L+): R-GemOx	[redacted]	[redacted]	[redacted]
Efficacy: Tx Disc Single Parametric Fit - Parameter 1 (2L+): Tafasitamab	[redacted]	[redacted]	[redacted]

Once the results were generated, these were ranked by their impact on the incremental outcomes in a tornado diagram (Figure 33). The impact was determined by the absolute difference between the outcome values with lowest and highest parameter values. The tornado diagram included the most impactful parameters (10 in number). Starting age was the input with the higher uncertainty, followed by the efficacy parametric fits for OS and PFS for both tafasitamab+LEN and R-GemOx.

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Figure 33. Tornado diagram - DSA results

An additional analysis was conducted to determine how variations in the drug price for tafasitamab impact the ICER by applying different discounts to tafasitamab's target price. The results are presented in Figure 34

Figure 34. ICER estimations with different prices for tafasitamab

8.7.2 PSA

The PSA was performed to assess the impact on the model outputs of uncertainty in the parameter estimates. The probability distributions used to model uncertainty in the CEM are [113]:

- Beta distributions (confined by the interval zero to one and typically used for inputs like proportions and health state utility values)
- Gamma distributions (confined by the interval zero to ∞ and typically used for costs)

- Lognormal distributions (typically used if the logarithm of the parameter's error distribution is normally distributed, like with relative risks, odds ratios, and HRs)
- Normal/Cholesky distributions (generalisation of the univariate normal distribution to higher dimensions, and typically used for time-to-event parameters)

The parameters tested in the PSA along with their selected distributions are listed below:

- Cost inputs (administration, monitoring, terminal care, and AEs, which used Generalised gamma distributions)
- OS, PFS, and TTD constant HRs (Normal distributions)
- OS, PFS, and TTD parameters for parametric fitting (Normal/Cholesky)
- Utility inputs (health states, disutilities, AEs, and proportions, which used Beta distributions)

The model also included Cholesky decomposition matrix calculation fields for modelling pairs of input parameters for which the covariance structure between two variables was known. For example, all survival curve function parameters (OS, PFS, and TTD) were varied using this method to account for the correlation between the estimated parameters of the survival functions. Distributions and parameter values used for the PSA are listed in Appendix J.

Five hundred iterations of the model were performed for PSA and the incremental costs and incremental QALYs recorded for each PSA iteration. Table 67 shows the PSA results and the comparison with the base-case analysis.

Table 67. PSA results

	Base Case Results	PSA Results
Incremental Costs (DKK)	[redacted]	[redacted]
Incremental Benefits QALYs	[redacted]	[redacted]
ICER (DKK/QALYs)	[redacted]	[redacted]

The scatter plot with the PSA results (Figure 35) shows that the base case result (Mean) seems stable in comparison to the 500 simulations. Also, the cost-effectiveness acceptability curve (CEAC, Figure 36) shows that tafasitamab+LEN is more likely to become cost-effective from a WTP threshold of approximately [redacted]

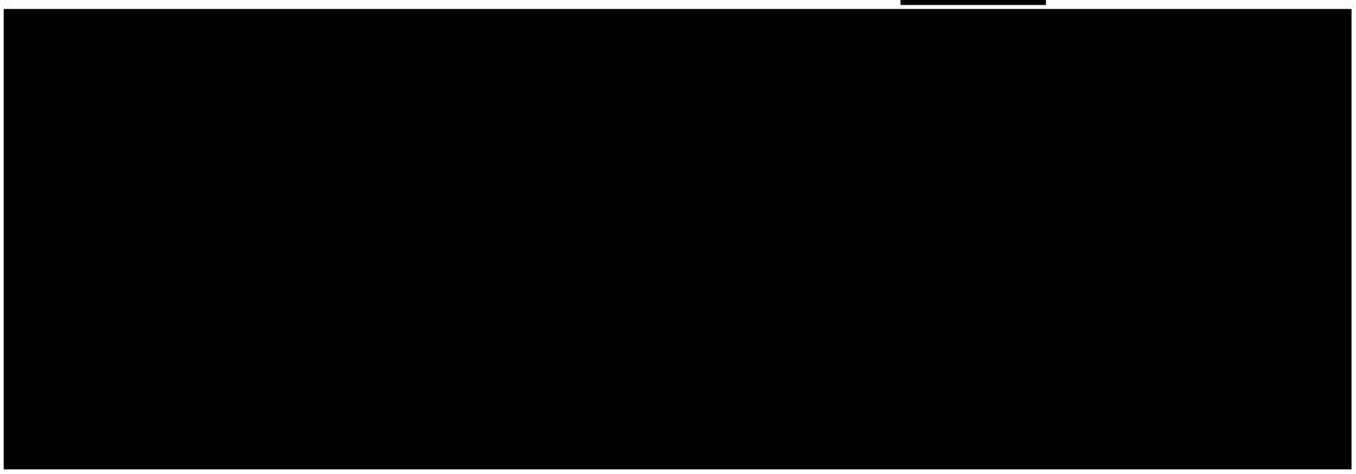

Figure 35. Scatter plot with PSA results

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Figure 36. Cost-effectiveness acceptability curve (CEAC). Tafasitamab+LEN vs. R-GemOx

8.7.3 Scenario Analyses

The model can run scenario analyses. The scenarios tested as part of this analysis and the corresponding ICERs obtained for each scenario are detailed in Table 68 below. The ICER varied between approximately [redacted] DKK per QALY and [redacted] DKK per QALY. The lower value was obtained when the disease management costs for tafasitamab+LEN patients in the progressed state was set to 50% of the base-case input, while the higher value was the consequence of using a zero proportion of progression-free patients to be disease free after the switch point. Removal of patient costs, such as transportation cost to hospital, had almost no impact on the results (ICER of [redacted] DKK/QALY). This was an expected outcome, patients with R/R DLBCL have high pharmaceutical as well as disease management costs, the patient costs are inessential in comparison.

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Table 68. Scenario Analyses and Justifications

Input Category	Input/Assumption	Base-case Assumption	Scenario Assumption	Scenario Justification	ICER (DKK/QALY)	QALY gain
Base case					[redacted]	[redacted]
Main Settings	Model population used to inform efficacy parameters	2L+ population	2L	In line with the assumptions on safety and treatment duration for tafasitamab and in line with the population for polatuzumab NICE submission	[redacted]	[redacted]
	Mean age at diagnosis	69 years	67 years	To test the outcomes when the mean age at diagnosis in Denmark is considered	[redacted]	[redacted]
	Time horizon	35 years	10 years	To analyse the outcomes in shorter term	[redacted]	[redacted]
	Discount rate for health and cost outcomes	3.50%	0%	To analyse the impact of discounting	[redacted]	[redacted]
	Switch timepoint for a prolonged progression-free state	2 years	4 years	To test a conservative assumption	[redacted]	[redacted]
	Proportion of progression-free patients reaching a prolonged progression-free state	78.60%	30%	Based on an expert opinion that anticipated that approximately 70% of alive, progression-free patients after two years would require ongoing monitoring and follow-up visits	[redacted]	[redacted]
			0%	To test a worst-case scenario	[redacted]	[redacted]
	Switch timepoint for considering a long-term disease freedom	2 years	4 years	To test a conservative assumption	[redacted]	[redacted]
	Proportion of progression-free patients disease free after the switch point	78.60%	30%	In line with the prolonged PFS scenario	[redacted]	[redacted]
			0%	To test a worst-case scenario	[redacted]	[redacted]
	Consider disease free patients as off treatment	Yes	No	To test a conservative assumption	[redacted]	[redacted]
Efficacy (tafasitamab and lenalidomide)	OS approach	Lognormal parametric fit	Generalised gamma parametric fit	Generalised gamma: only marginally worse statistical fit, slightly better visual fit to tail of KM curve	[redacted]	[redacted]

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Input Category	Input/Assumption	Base-case Assumption	Scenario Assumption	Scenario Justification	ICER (DKK/QALY)	QALY gain
			Log-logistic parametric fit	Log-logistic: second best statistical fit, only slightly worse visual fit to tail of KM curve	[redacted]	[redacted]
	PFS approach	Generalised Gamma parametric fit	Gompertz	Other models had consistently poor relative statistical fits and visual fits to observed data except Gompertz, which more reasonable statistical fit but had implausible plateau	[redacted]	[redacted]
Efficacy (R-GemOx)	OS approach	Lognormal	Log-logistic	Log-logistic: similar to lognormal with only slightly worse statistical fit	[redacted]	[redacted]
			Generalised gamma	Generalised gamma: similar to lognormal with only slightly worse statistical fit	[redacted]	[redacted]
	PFS approach	Exponential	Log-logistic	Potentially more plausible in relation to external data, good relative statistical fit	[redacted]	[redacted]
Treatment Duration	Treatment duration: Tafasitamab and lenalidomide	Lognormal parametric fit	Tx duration tafasitamab and lenalidomide: Treat to progression	Consistent with tafasitamab targeted label	[redacted]	[redacted]
			Log-logistic parametric fit	Second best fit for TTD	[redacted]	[redacted]
Death within PFS	Constant ratio	10%	5% (-50%) 15% (+50%)	To explore the effect of uncertainty in the assumption of a constant death ratio	[redacted] [redacted]	[redacted] [redacted]
Utilities	AE disutilities	Health state utilities sourced from Polatuzumab NICE submission. Disutility for adverse events sourced from different literature sources.	No disutility for AEs	To explore the effect of uncertainty AE assumptions and duration on the results	[redacted]	[redacted]

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Input Category	Input/Assumption	Base-case Assumption	Scenario Assumption	Scenario Justification	ICER (DKK/QALY)	QALY gain
	Health state utility values	PFS = 0.72 PD = 0.65	PFS = 0.76 PD = 0.68	Test utility values from other source (NICE STA TA306)	[redacted]	[redacted]
			PFS = 0.83 PD = 0.71	Test utility values from other source (NICE STA TA567)	[redacted]	[redacted]
Costs and Resource Use	Lenalidomide generic price	Assuming discounted price for lenalidomide (90% drop in the price) as of 1/1/2022	Assuming discounted price for lenalidomide (50% drop in the price) as of 1/1/2022	To consider the impact of lenalidomide becoming generic	[redacted]	[redacted]
	Subsequent treatment costs	It is currently sourced from different literature sources for each comparator. Data gaps exist and simplifying assumptions has been employed.	Assume zero subsequent treatment costs (thus all patients only receive palliative care upon progression).	To test the impact of subsequent treatments basket variations among comparators	[redacted]	[redacted]
	Vial sharing	No vial sharing assumed (wastage)	Vial sharing (All drugs)	To test the possibility of vial sharing for all drugs and its impact on costs	[redacted]	[redacted]
			Vial sharing (Tafasitamab)	To test the possibility of vial sharing for tafasitamab and its impact on costs	[redacted]	[redacted]
	Disease management costs: Tafasitamab and lenalidomide (progressed)	Assumed same frequency of resource use as Pola-BR	Reduce to 50% base-case frequencies	As the tafasitamab and lenalidomide treatment is associated with relatively longer survival rates, the post-progression stage is longer for this treatment and, therefore, the frequency of resources used per cycle for disease management is an important input that impacts the costs. In absence of reliable sources for the scenario analysis, it is assumed that patients need half of the frequency of resources needed for Pola-BR.	[redacted]	[redacted]

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Input Category	Input/Assumption	Base-case Assumption	Scenario Assumption	Scenario Justification	ICER (DKK/QALY)	QALY gain
	Transportation costs	200 DKK per treatment cycle	0 DKK	To test the impact of including transportation costs	[redacted]	[redacted]

Abbreviations: 2L+ = second line or more; 2L = second line; AE = adverse event; BR = bendamustine + rituximab; CAR-T = chimeric antigen receptor T-cell; HR = hazard ratio;;OS = overall survival; PFS = progression-free survival; Pola-BR = polatuzumab + bendamustine + rituximab; R2 = lenalidomide + rituximab; R-GemOx = rituximab + gemcitabine and oxaliplatin; TTD = time to discontinuation; Tx = treatment

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9 Budget impact analysis

9.1 Model Description

The budget impact model (BIM) was developed in Microsoft Excel® to assess the budgetary impact of introducing tafasitamab vs. existing comparators for the treatment of patients with R/R DLBCL who are ineligible for receiving transplants. The BIM uses a traditional structure in which a scenario reflecting the current market situation without tafasitamab and lenalidomide is compared to a scenario with a market including an estimated uptake of tafasitamab and lenalidomide over time. To capture the costs relevant to different health states of the patients, a survival partition approach was selected given it is recognised as one of the most commonly adopted model structures for oncology treatments [114].

9.1.1 BIM Structure

Figure 37 shows a funnel style diagram which represents the order of calculation to estimate the eligible population for the model. First, the number of incident DLBCL patients is calculated based on epidemiological data, including the total population for Denmark and the incidence of DLBCL. The number of incident DLBCL patients is then multiplied by the proportion that are relapsed/refractory (R/R). This number is then multiplied by the proportion that are transplant ineligible. Finally, the eligible population is calculated by multiplying the number of transplant ineligible R/R DLBCL patient by the proportion receiving 2L treatment.

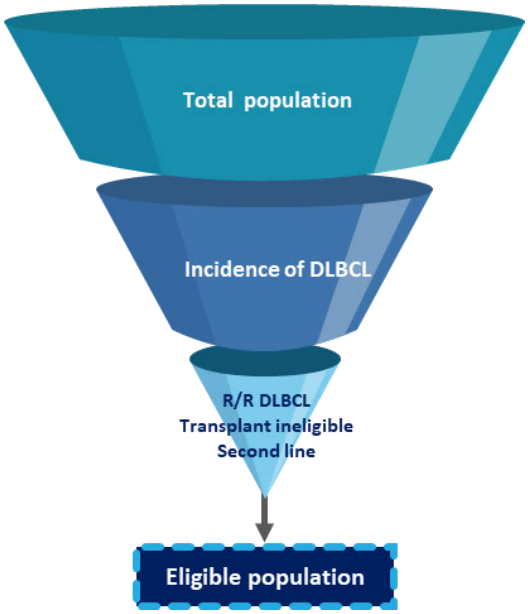

Figure 37. Eligible population

Abbreviations: DLBCL = diffuse large B-cell lymphoma; R/R = relapsed/refractory

Figure 38 describes the BIM structure. The total budget was calculated for a world without tafasitamab and lenalidomide (Comparators) and a world with tafasitamab and lenalidomide. Each year, patients with R/R DLBCL who were ineligible for a transplant were allocated the 2L treatments available in the two market scenarios. Patients could stop receiving 2L treatment based on the median treatment duration of each treatment. However, patients do not switch to further lines of treatment unless they progress. Patients who remain on 2L treatment accrue treatment related costs (drug costs and administration costs) over the time if they are receiving treatment. Pre-progression monitoring associated costs are accrued for as long as patients remain progression-free. Patients receiving treatment are at risk of experiencing

treatment-related AEs and accrue AE-related management costs. For details on costs and resource use calculations, see section 8.5. At the end of the time horizon, the costs accrued over time during pre- and post-progression in each scenario (i.e., without and with tafasitamab and lenalidomide) are accumulated. The total cost for each scenario is estimated separately, and the net budget impact is calculated by subtracting the total costs of the reference scenario (without tafasitamab) from the total cost of the alternative scenario (with tafasitamab).

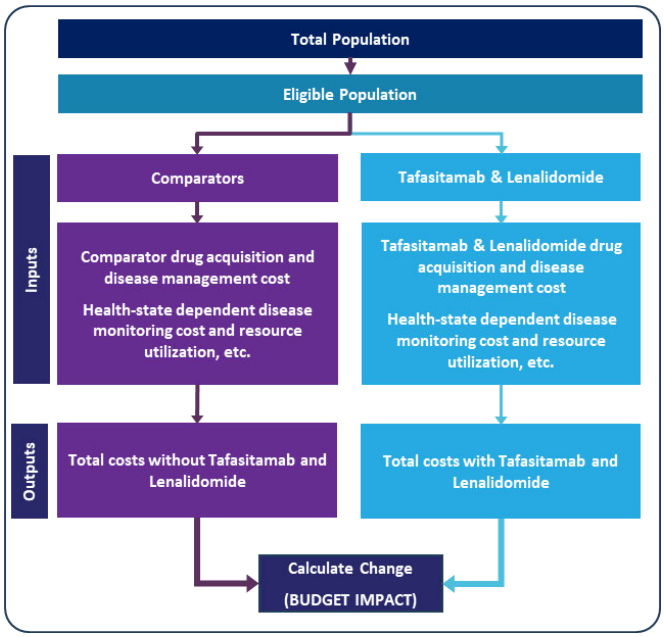

Figure 38. BIM Structure

9.1.2 Target population

Similar to C-CEM, see section 8.1.2

9.1.3 Perspective

Similar to C-CEM, see section 8.1.3.

9.1.4 Cycle length

Similar to C-CEM, see section 8.1.4

9.1.5 Time horizon

The time horizon for this model is flexible with up to a maximum of five years. The time horizon in a BIM is rarely more than five years, and often one year [115]. The model reports the budget impact for all five possible time horizons (i.e., one, two, three, four, and five years).

9.1.6 Comparator

Similar to C-CEM, see section 8.1.6.

9.1.7 Model inputs

Similar to C-CEM, see section 8.1.7. The only difference in the BIM is that it takes only medical costs into account, i.e., non-medical direct costs (transportation costs and time spent by patients and relatives) are not included.

9.1.8 Model outputs

The model aggregates the costs for each scenario and reports the budget impact by:

- The total budget impact by treatment (total costs for tafasitamab and lenalidomide, and other treatments)
- The total budget impact by year (total costs for tafasitamab and lenalidomide, and other treatments)
- Total, induction and maintenance drug, administration, co-medication monitoring, AE management, disease management, and subsequent treatment costs

Deterministic sensitivity analyses (DSA) was used to test the influence of the uncertainty of the model parameters on the results.

9.1.9 Mortality within PFS

Similar to C-CEM, see section 8.1.9

9.1.10 Long-term disease freedom

Similar to C-CEM, see section 8.1.10

9.1.11 Prolonged PFS

Similar to C-CEM, see section 8.1.11

9.1.12 Market shares

The market shares of the 2L+ treatments considered for Denmark in absence of tafasitamab were provided by Incyte. The market shares are based on the treatments that are currently used for R/R DLBCL in Denmark, i.e. R-GemOx, and therefore have market shares first in year 2024. For the settings with tafasitamab in the market, a hypothetical market share peak of almost [redacted] In this setting the market shares of other comparators were reduced proportionate to their original shares, so that the sum of market shares is 100%. Table 69 presents the shares used within the model.

Table 69. Market shares in Denmark with and without tafasitamab

Parameter	Without Tafasitamab					With Tafasitamab				
	2022	2023	2024	2025	2026	2022	2023	2024	2025	2026
Tafasitamab and lenalidomide	-	-	-	-	-	[redacted]				
R-GemOx	100.0%	100.0%	100.0%	100.0%	100.0%	[redacted]				

9.1.13 Population Estimates

The data inputs used to calculate the number of patients with R/R DLBCL who were ineligible for transplantation and eligible for 2L+ treatment with tafasitamab and lenalidomide are based on the epidemiology presented in Table 70.

The number of incident cases of DLBCL is calculated from the number of incident cases of NHL in Denmark (Table 3) [18]. Afterwards, the percentage of patients who are relapsed/refractory within DLBCL is applied to the number of DLBCL patients. In the same way, proportions of patients undergoing treatment or enrolled in clinical trials were taken into consideration. Finally, the proportion of transplant-ineligible patients and in 2L were applied to calculate the final incidence for the population of interest.

DLBCL accounts for approximately 37% of all NHL newly diagnosed cases [3-5]. The proportion of patients who were R/R was calculated based on the proportions of drug-treatable population per line of treatment [116]. It is estimated that 80% of patients in 2L and 63% in 3L+ are receiving some kind of treatment [116]. From those, 15% and 10% are likely to be enrolled in a clinical trial, respectively [116]. Hence, the remaining patients are expected to receive a commercially-available treatment. The proportion of R/R DLBCL patients who are transplant ineligible (60%) was calculated based on the PARMA trial study, where it is assumed that transplant salvages approximately 40% of patients

with R/R DLBCL [42]. The estimated number of patients eligible for treatment with tafasitamab+LEN is presented in Table 4.

Table 70. Target Population Characteristics at the Baseline

Description	Value	Sources
Danish incidence of DLBCL	See Table 3	Swerdlow et al, Armitage et al, Smith et al, NORDCAN [3-5, 20]
Drug-treatable population	1L: 62%, 2L: 23%, 3L+: 15%	Decision Resources Group [116]
Treatment rate	2L: 80%, 3L+: 63%	
Clinical trial patients	2L: 15%, 3L+: 10%	
Proportion of 2L patients who are transplant ineligible	60%	Raut, 2014 [42]

Abbreviations: 2L = second line; 3L+, third line or more; DLBCL = diffuse large B-cell lymphoma; NORDCAN, Association of the Nordic Cancer Registries.

The model allows the user to directly input the number of patients with R/R DLBCL who are ineligible for transplant on 2L treatment. The relevant calculations were conducted separately and are presented in a separate sheet in the model.

The expected number of patients to be treated over the next five years in the scenarios with and without the introduction of tafasitamab+Len in Denmark are shown in Table 71.

Table 71. Expected number of patients in Denmark with and without tafasitamab

Treatment	Without Tafasitamab					With Tafasitamab				
	2022	2023	2024	2025	2026	2022	2023	2024	2025	2026
Tafasitamab and lenalidomide	-	-	-	-	-	[redacted]				
R-GemOx	149	148	150	135	115	[redacted]				

9.1.14 Model validation

Similar to C-CEM, see section 8.1.12.

9.2 Relative efficacy inputs

The efficacy inputs for tafasitamab+LEN and R-GemOx used in the BIM were similar to the inputs used in the C-CEM (described in sections 0 and 8.3).

9.3 Resource use and costs

Healthcare resource utilization and the corresponding costs used in the BIM were similar to the inputs used in the C-CEM (described in section 8.5).

9.4 Results

The budget impact analysis was conducted using the model specifications listed in Table 72 below. The breakdown of expected direct medical costs for the scenarios without and with tafasitamab are presented in Table 73 and Table 74, respectively.

The budget impact of having tafasitamab reimbursed in Denmark (Table 75) is estimated to be approximately [redacted] over the first five years of its introduction into the market.

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Table 72. Base-case Setting and Justifications

	Setting	Base Case	Justification
Main Settings	Perspective	Limited societal	Standard setting as per DMC guideline
	Time horizon	5 years	Maximum standard time horizon considered for BIMs[115]
	Population	R/R DLBCL; 2L+	Indication of tafasitamab
	Switch timepoint for prolonged progression-free state	2 years	Based on KOL recommendation
	Proportion of progression-free patients reaching prolonged progression-free state	[redacted]	Assumed as rate of CR among 2 years PFS- based on KOL recommendation
	Switch timepoint for considering long-term disease freedom	2 years	Based on KOL recommendation
	Proportion of progression-free patients long-term disease freedomafter the switch point	[redacted]	Assumed as rate of CR among 2 years PFS- based on KOL recommendation
	Consider long-term disease freepatients as off treatment	Yes	Based on KOL recommendation
	Baseline age	69 years	L-MIND[81]
	Males	54.3%	L-MIND[81]
	BSA	1.91	L-MIND[81]
Efficacy	OS approach: tafasitamab and lenalidomide	Parametric Single Fit; lognormal	Second best statistical fit; based on KOL recommendations
	PFS approach: tafasitamab and lenalidomide	Parametric single fit; generalised Gamma	Second best statistical fit; based on KOL recommendations
	OS approach: R-GemOx (RE-MIND2)	Log-logistic	Good statistical fit, reasonable visual fit, appropriate hazard profile and plausible long-term extrapolations
	PFS approach: R-GemOx (RE-MIND2)	Lognormal	Relatively good statistical fit, reasonable visual fit, clinically plausible hazard profile and one of the most appropriate/conservative long-term extrapolations compared to external data
	Mortality within PFS	[redacted]	Constant ratio of death and progression. In lack of specific inputs, assumed all comparators are the same as tafasitamab and lenalidomide

	Setting	Base Case	Justification
	Treatment discontinuation rule: tafasitamab	Treatment discontinuation curve; lognormal	Second best statistical fit; aligned with PFS assumptions
	Treatment discontinuation rule: lenalidomide	Treatment discontinuation curve; KM curve	Lenalidomide has a fixed duration thus no extrapolations were needed
	Treatment discontinuation rule: R-GemOx (RE-MIND2)	KM curves from RE-MIND2	Best available source
Cost Settings	Tafasitamab price	[redacted]	Assumption advised by Incyte
	Lenalidomide price	90% discount on the list price from 01 Jan 2022	Assumption of generic price for lenalidomide from 01 Jan 2022
	Monitoring for tafasitamab and lenalidomide; PFS≤ 2years	Frequencies reported in L-MIND[81]	Best available source
	Monitoring for tafasitamab and lenalidomide; PFS> 2years	Frequencies reported in ESMO guidelines for DLBCL[24]	Best available source
	Disease management tafasitamab and lenalidomide; PFS≤ 2years	Frequencies reported in L-MIND[81]	Best available source
	Disease management tafasitamab and lenalidomide; PFS> 2years	Frequencies reported in ESMO guidelines for DLBCL[24]	Best available source
	Disease management tafasitamab and lenalidomide; post-progression	Assumed same as Pola-BR	Assumption made in lack of inputs for tafasitamab and lenalidomide
	Co-medications	Assumed 70% tafasitamab and lenalidomide patients receive co-medications	Assumption in lack of specific inputs

Abbreviations: AE = adverse event; BSA = body surface area; CR = complete response; DLBCL = diffuse large B-cell lymphoma; ESMO = European Society for Medical Oncology; HR = hazard ratio; KM = Kaplan-Meier; KOL = key opinion leader; OS = overall survival; PFS = progression-free survival; Pola-BR = polatuzumab + bendamustine + rituximab; R/R = relapsed/refractory; R-GemOx = rituximab + gemcitabine and oxaliplatin.

Table 73. Expected costs without tafasitamab

Cost Outcomes	R-GemOx (DKK)	TOTAL (DKK)
Direct Medical Costs	[redacted]	[redacted]
Drug costs - Induction	[redacted]	[redacted]

Cost Outcomes	R-GemOx (DKK)	TOTAL (DKK)
Drug costs - Maintenance	[redacted]	[redacted]
Admin costs - Induction	[redacted]	[redacted]
Admin costs - Maintenance	[redacted]	[redacted]
Co-medication costs- Induction	[redacted]	[redacted]
Co-medication costs- Maintenance	[redacted]	[redacted]
Monitoring costs	[redacted]	[redacted]
Adverse event management costs	[redacted]	[redacted]
Disease management costs - Pre-progression	[redacted]	[redacted]
Disease management costs - Post-progression	[redacted]	[redacted]
Disease management costs - One-off - Progression	[redacted]	[redacted]
Disease management costs - One-off - Death	[redacted]	[redacted]
Subsequent treatment costs	[redacted]	[redacted]

Table 74. Expected costs with tafasitamab

Cost Outcomes	Tafasitamab & Lenalidomide (DKK)	R-GemOx (DKK)	TOTAL (DKK)
Direct Medical Costs	[redacted]	[redacted]	[redacted]
Drug costs - Induction	[redacted]	[redacted]	[redacted]
Drug costs - Maintenance	[redacted]	[redacted]	[redacted]
Admin costs - Induction	[redacted]	[redacted]	[redacted]
Admin costs - Maintenance	[redacted]	[redacted]	[redacted]
Co-medication costs- Induction	[redacted]	[redacted]	[redacted]
Co-medication costs- Maintenance	[redacted]	[redacted]	[redacted]
Monitoring costs	[redacted]	[redacted]	[redacted]
Adverse event management costs	[redacted]	[redacted]	[redacted]
Disease management costs - Pre-progression	[redacted]	[redacted]	[redacted]

Cost Outcomes	Tafasitamab & Lenalidomide (DKK)	R-GemOx (DKK)	TOTAL (DKK)
Disease management costs - Post-progression	[redacted]	[redacted]	[redacted]
Disease management costs - One-off - Progression	[redacted]	[redacted]	[redacted]
Disease management costs - One-off - Death	[redacted]	[redacted]	[redacted]
Subsequent treatment costs	[redacted]	[redacted]	[redacted]

Table 75. Budget impact with and without tafasitamab

	Without Tafasitamab on market (DKK)	With Tafasitamab on market (DKK)	Budget Impact (DKK)
Budget Share of Tafasitamab & Lenalidomide		[redacted]	
Total costs for Tafasitamab & Lenalidomide	[redacted]	[redacted]	[redacted]
Total costs for other available treatments	[redacted]	[redacted]	[redacted]
Total costs	[redacted]	[redacted]	[redacted]

10 Discussion on the submitted documentation

DLBCL is a cancer of the lymphatic system that causes serious complications. Despite numerous treatment options and the recent launch of novel therapies, such as CAR-T, there remains an unmet need among patients with R/R DLBCL who are ineligible for or who choose not to receive salvage HDCT and/or SCT. This report highlighted the need for new treatment options that will delay progression and prolong survival, while improving or maintaining the patients' quality of life (QoL).

Tafasitamab is Incyte's investigational, Fc-enhanced, humanised anti-CD19 monoclonal antibody that has demonstrated pre-clinical activity, including in patients with R/R B-cell malignancies. Pre-clinical data suggest that the combination of tafasitamab and lenalidomide has synergistic potential [81].

A phase II trial evaluating tafasitamab and lenalidomide for the treatment of patients with R/R DLBCL (L-MIND) is ongoing [81]. To produce comparative efficacy data, the RE-MIND2 study was conducted to compare the L-MIND population to matching real-world cohorts of patients receiving standard of care treatments.

Results from the October 2020 data cut of the L-MIND trial (full analysis set [n=80] and with a median follow-up period of 33.9 months) showed a median PFS of 11.6 (95% CI: 6.3, 45.7) months [91]. With a median follow-up period of 42.7 months, the median for OS was 33.5 (95% CI: 18.3, NR) [81]. The L-MIND study demonstrated that the combination of tafasitamab and lenalidomide is an effective, well-tolerated, chemotherapy-free option for the treatment of patients with R/R DLBCL who are ineligible for ASCT [81]. When comparing to the real-world standard of care treatments, RE-MIND2 showed that tafasitamab and lenalidomide combination results in statistically significantly improved PFS and OS compared with e.g R-GemOx.

Incyte is seeking HTA approval in Denmark for tafasitamab, in combination with lenalidomide, for use in the treatment of patients with R/R DLBCL who are ineligible for ASCT. To assess whether the clinical benefits associated with tafasitamab and lenalidomide treatment can be achieved at reasonable costs, a cost-effectiveness analysis using a lifetime survival partition modelling approach was performed to estimate ICERs of tafasitamab and lenalidomide vs. relevant comparators in the treatment of R/R DLBCL patients who are ineligible for ASCT. Also, a budget impact analysis using a traditional BIM approach combined with a survival partition modelling approach was performed to assess whether the budgetary impact of introducing tafasitamab and lenalidomide to the market.

In the health economic model, the base-case scenario, which was consistent with the clinical trial findings, showed that the tafasitamab and lenalidomide combination yielded longer PFS and OS and was associated with the highest QALYs. The health and QoL gains associated with tafasitamab and lenalidomide came with a higher lifetime total cost compared with R-GemOx.

Patient's age when entering the model, cured state utility, and efficacy settings had a great impact on the results when considering the health outcomes. Since survival curves are always capped with the survival of the general population, increase/decreasing the age at baseline would mean getting farther/closer to the maximum possible surviving age. Given the cure assumptions are implemented in the base case, the impact of the starting age becomes even more important: cured patients would live as long as a patient of the same age in the general population; thus, if the age changes, survival could also significantly change. The utility assigned to the cured health state was also important in all comparisons as it defined the QALYs calculated for this state.

Both CEM and BIM was designed after careful consideration of the clinical and treatment pathways for patients with R/R DLBCL to ensure that key aspects of the disease and treatment practices were captured in the model. After

researching previous models, reviewing critiques from HTAs, and investigating different outcomes, the model was designed to provide extensive flexibility on how to estimate clinical benefits of tafasitamab and lenalidomide.

10.1 Limitations and Considerations for Model Updates

To provide an estimate of the economic value of this combination therapy, it is necessary to extrapolate PFS and OS to a lifetime time horizon by fitting the observed data with selected parametric models. The choice of the parametric models represents an important and challenging exercise in these types of analyses to accurately predict the long-term treatment effects. Curve selection included careful consideration and evaluation of the goodness of fit of the models to the observed data using AIC and BIC, as well as visual inspection of the fitted curves to actual data. In some cases, while the best fit based on the AIC and BIC was the exponential curve, was not selected for the base-case analysis given its unrealistic constant hazard profile over time. This choice was validated by the clinical experts interviewed in the UK ad board.

While resource use was based on the best available sources, several assumptions and simplifications were needed as data were not available for all comparators. For instance, there was limited availability of utility values used to estimate HRQoL in R/R DLBCL. The best available sources were previous NICE submissions which were based on UK utility values. Due to the unavailability of individual patient data, it was not possible to apply the DMC's methodology to the Danish context. Furthermore, the post-progression resource use for tafasitamab and lenalidomide and R-GemOX were not available and hence the same frequencies as Pola-BR were assumed.

11 List of experts

[redacted]

On July 6, 2021, an advisory board was conducted in the UK. The objective was to;

- Collect expert feedback on the robustness and credibility of the data package for tafasitamab in R/R DLBCL (L-MIND-study, Re-MIND study, RE-MIND2 study)
- Validate the structure, design, inputs, and key assumptions of the economic model to be used in the UK setting where these data are implemented

Participant	Role
Clinical advisors	
[redacted]	[redacted]
Health Economics Advisors	
[redacted]	[redacted]

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

An extensive systematic literature review (and an update) was conducted to investigate publications on efficacy and safety of treatments for R/R DLBCL. A summary of the SLRs is provided below. Further details are provided in the documents attached to the application:

- 9_SLR DLBCL Clinical v3.pdf
- 10_SLR DLBCL Clinical Update Final 3.0.pdf

This appendix concerns the clinical SLR, where the main objective was to identify, compile, and summarize evidence regarding the efficacy and safety of currently available pharmacologic interventions for transplant-ineligible patients with R/R DLBCL. The SLR aimed to answer two research questions:

1. What is the efficacy and effectiveness of treatments for R/R DLBCL?
2. What are the AEs associated with treatments in R/R DLBCL?

Bibliographic databases were searched using predefined search strategies (presented in Appendix A of the attached documents) which were developed for the purposes of this SLR The databases in which the searches were conducted are presented in [redacted] All searches were conducted 4 February 2021, with update searches performed on the 28 and 29 June 2021.

A search of the grey literature was conducted, including a search for conference abstracts on Embase, as well as select regulatory and health technology assessment (HTA) websites including NICE, the Scottish Medicines Consortium (SMC), the All Wales Medicines Strategy Group (AWMSG), the Canadian Agency for Drugs and Technologies in Health (CADTH), the IQWiG, the Haute Autorité de Santé (HAS), the Institute for Clinical and Economic Review, and the Pharmaceutical Benefits Advisory Committee (PBAC). The HTA websites included in the literature search are presented in [redacted]

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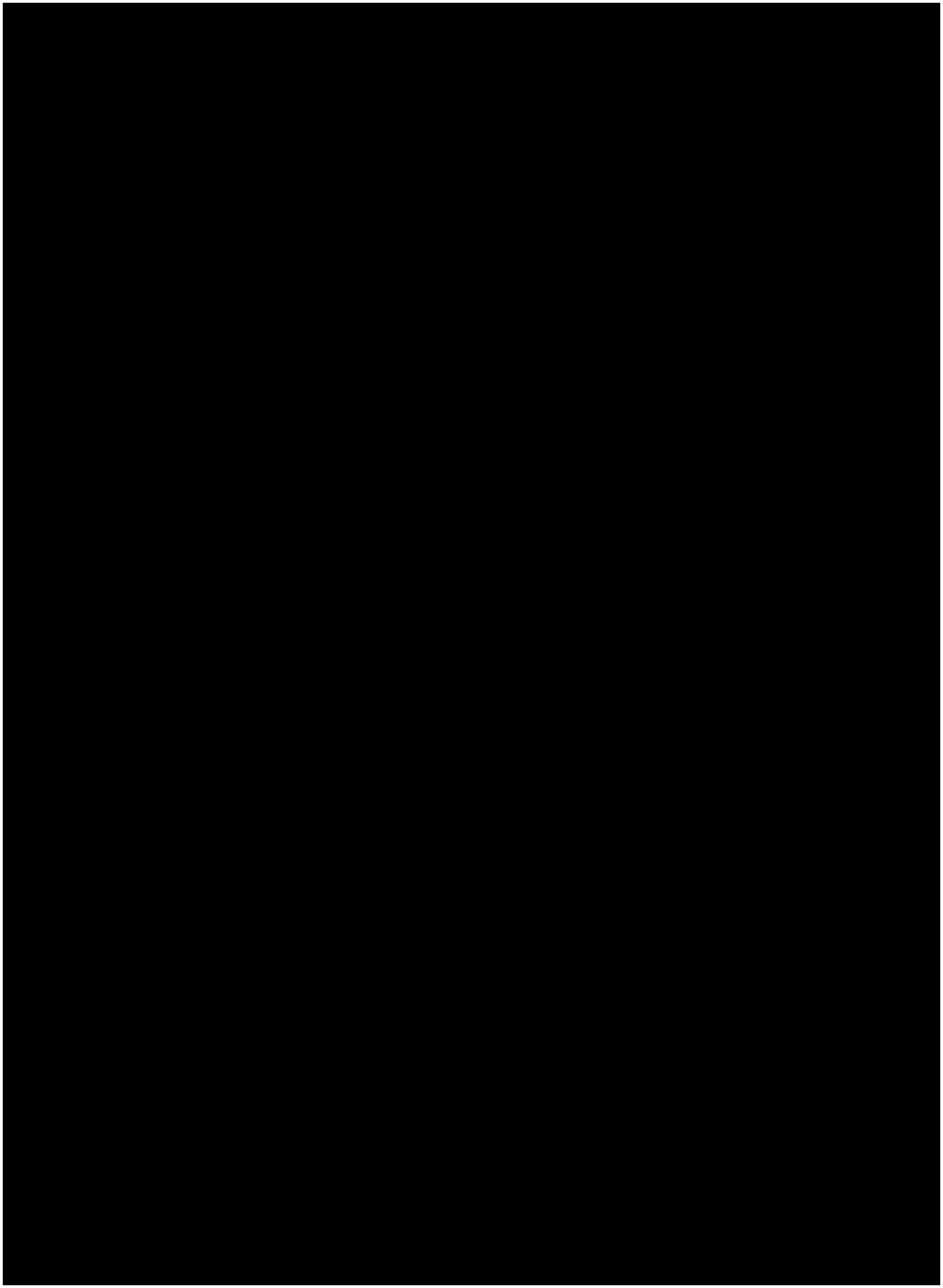
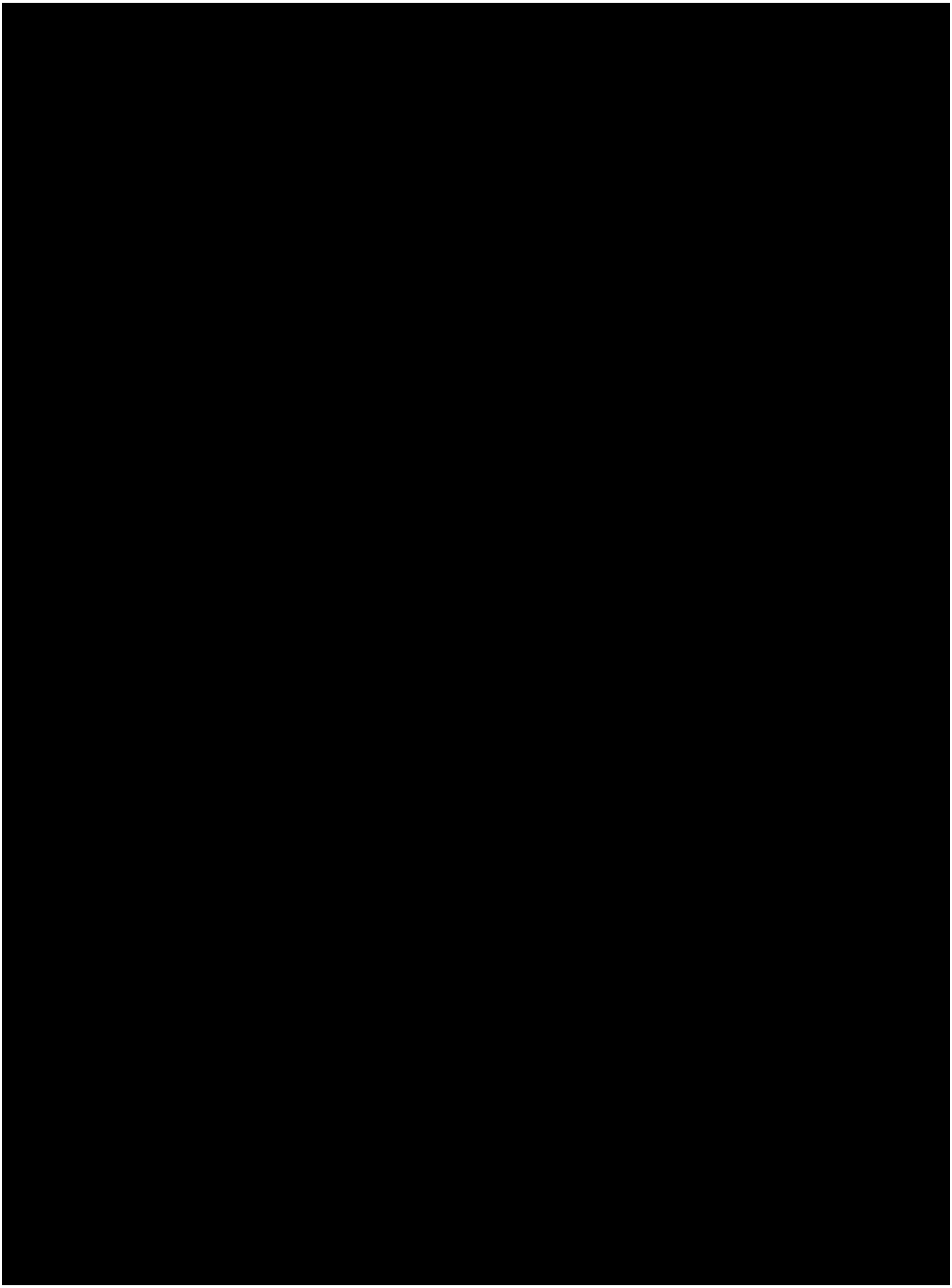
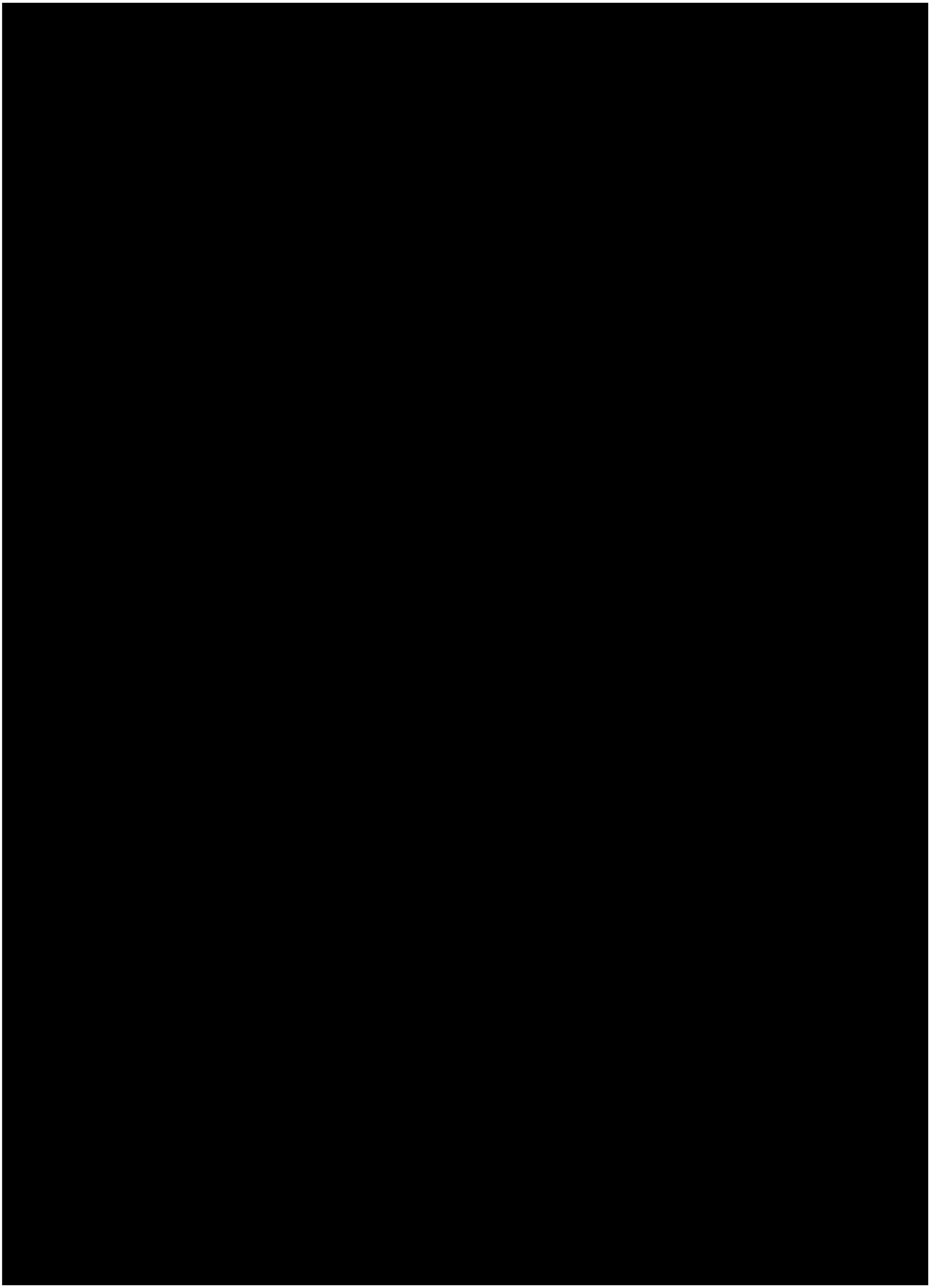
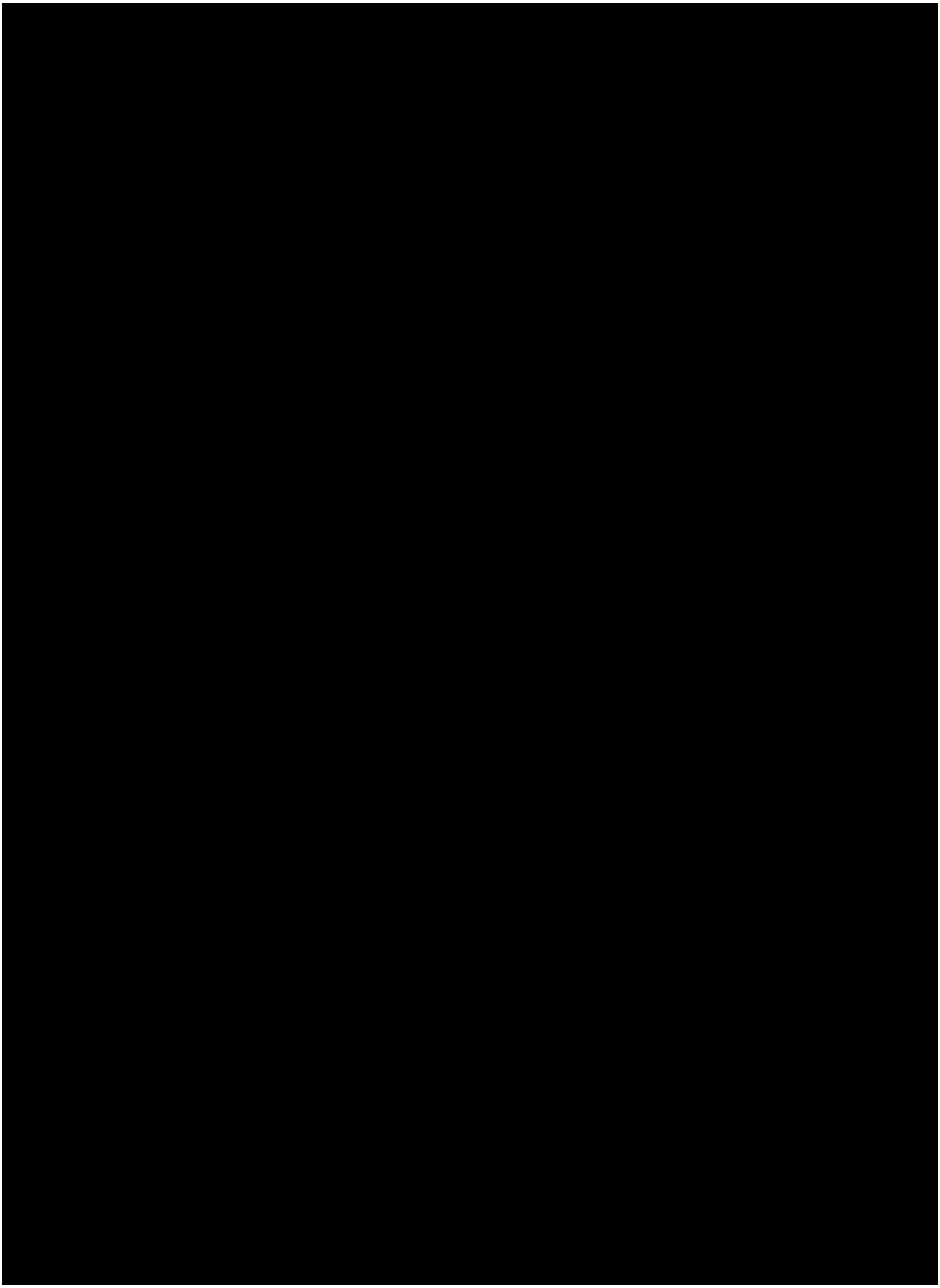
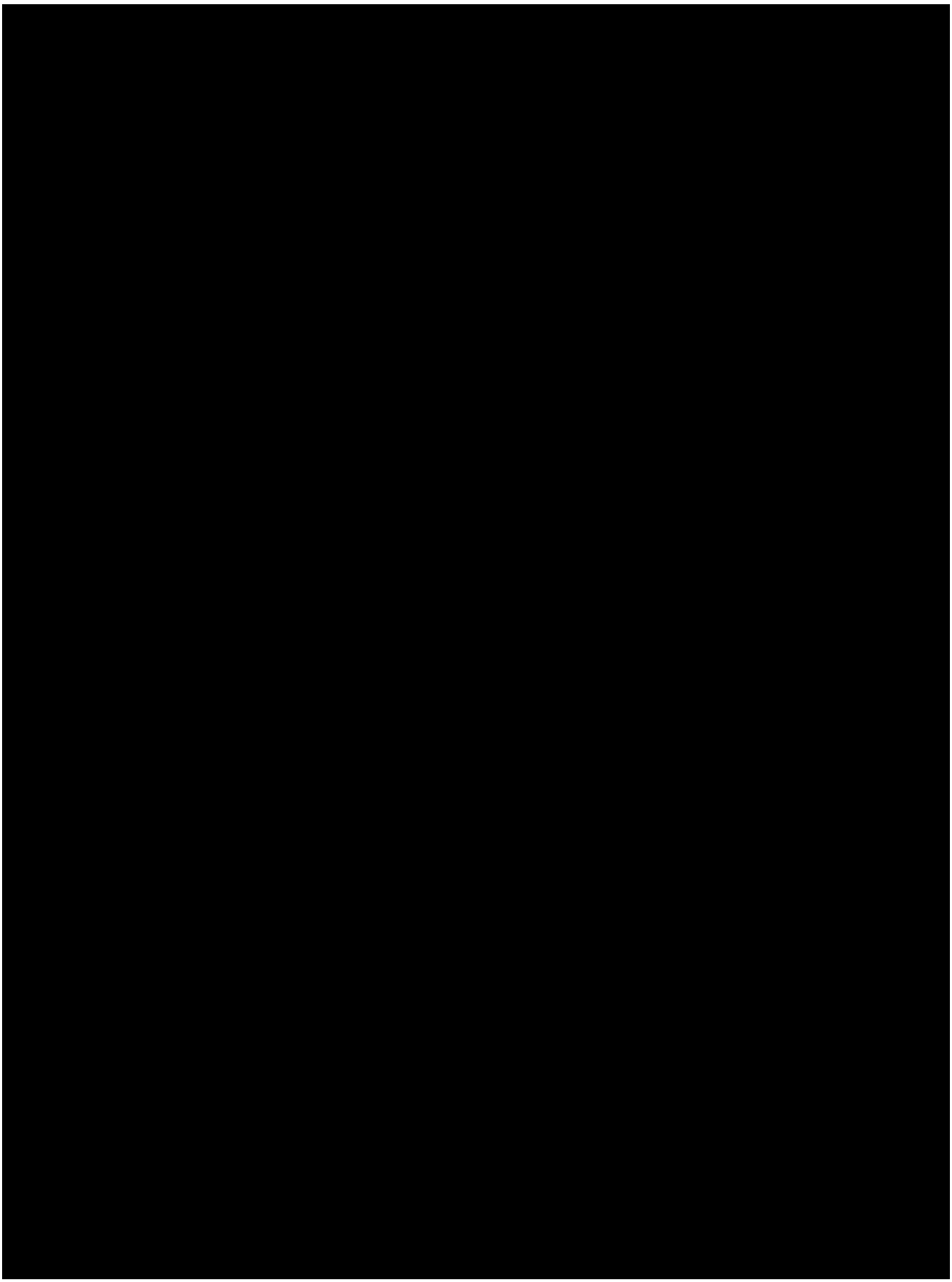
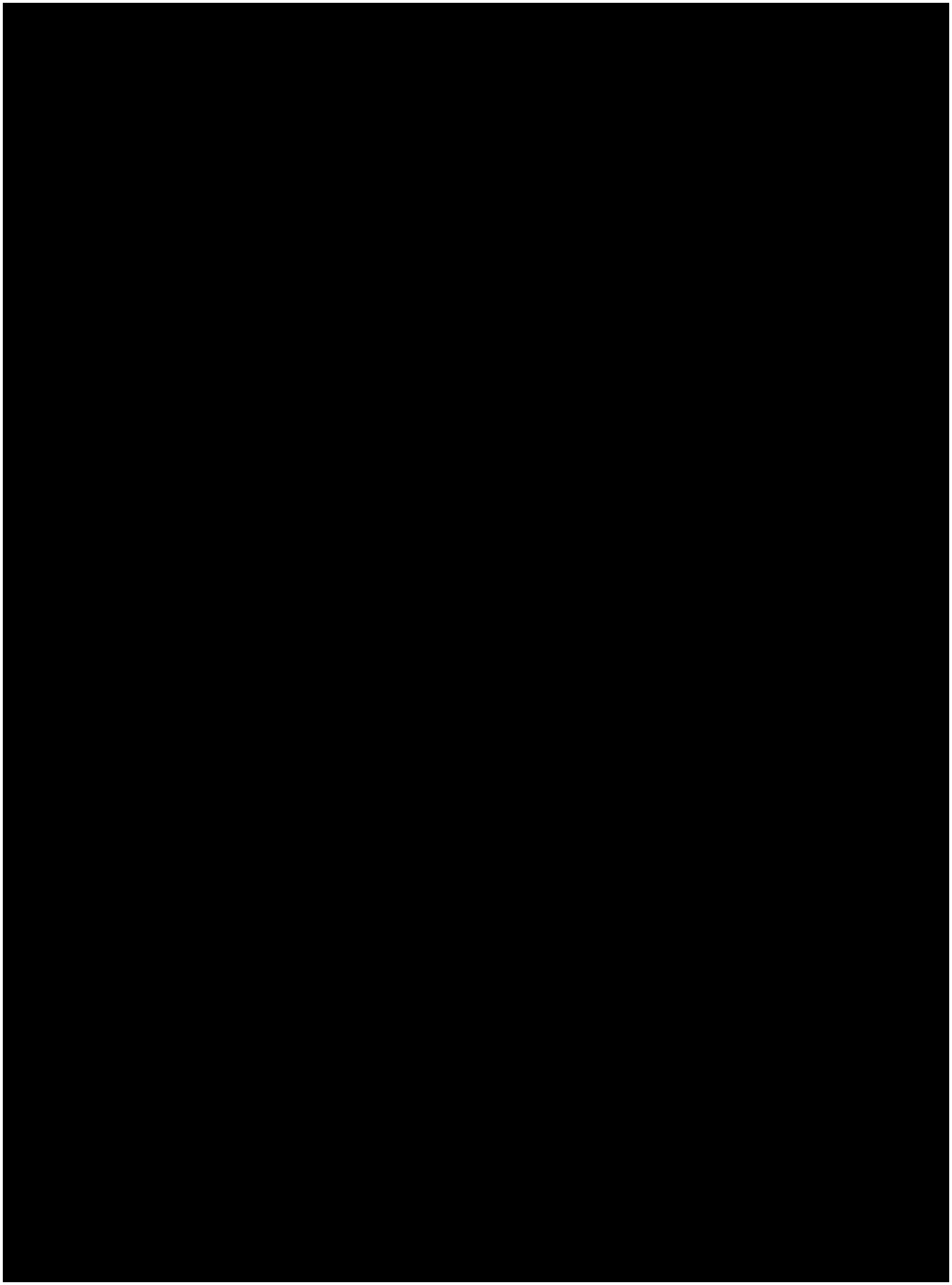


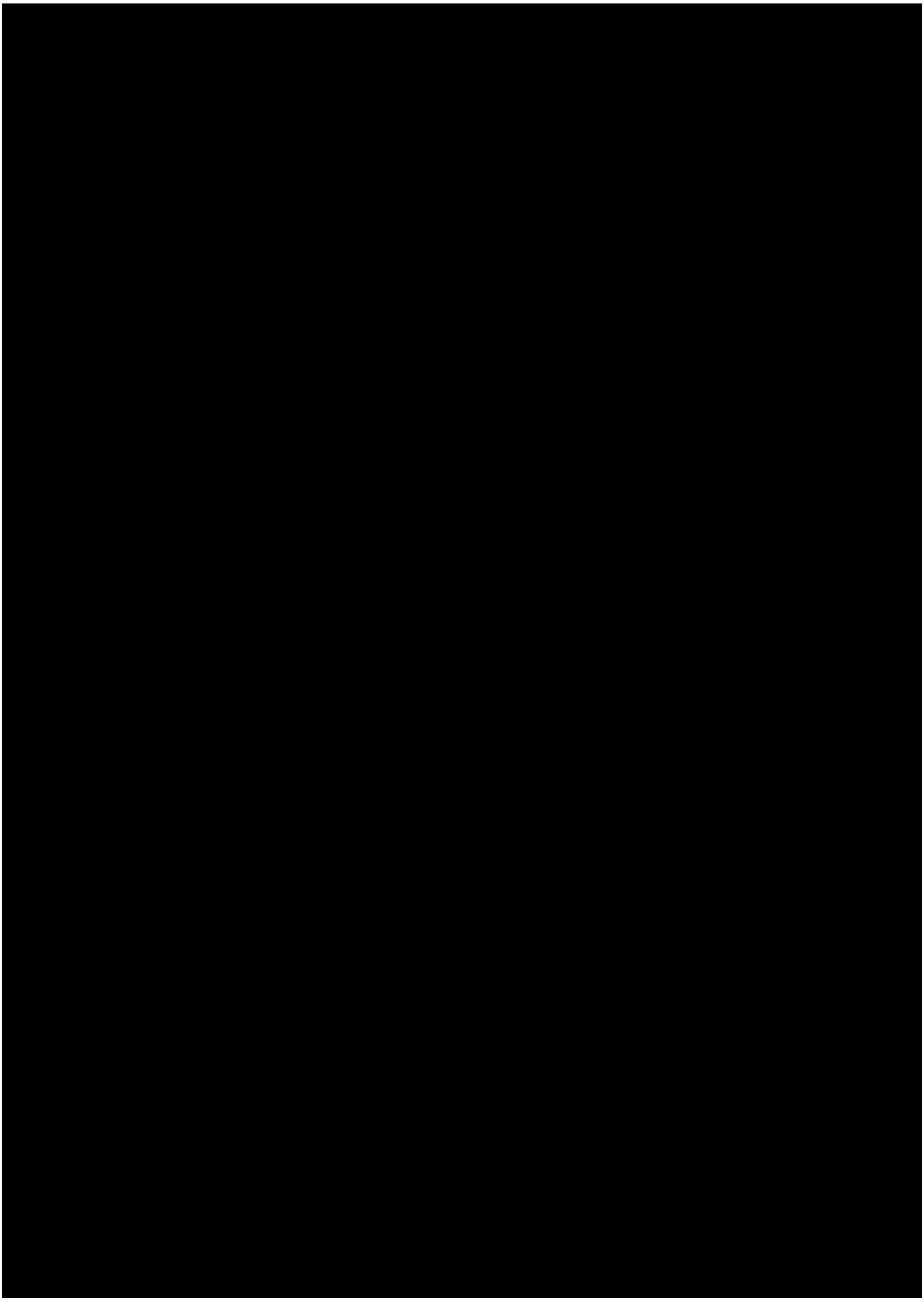


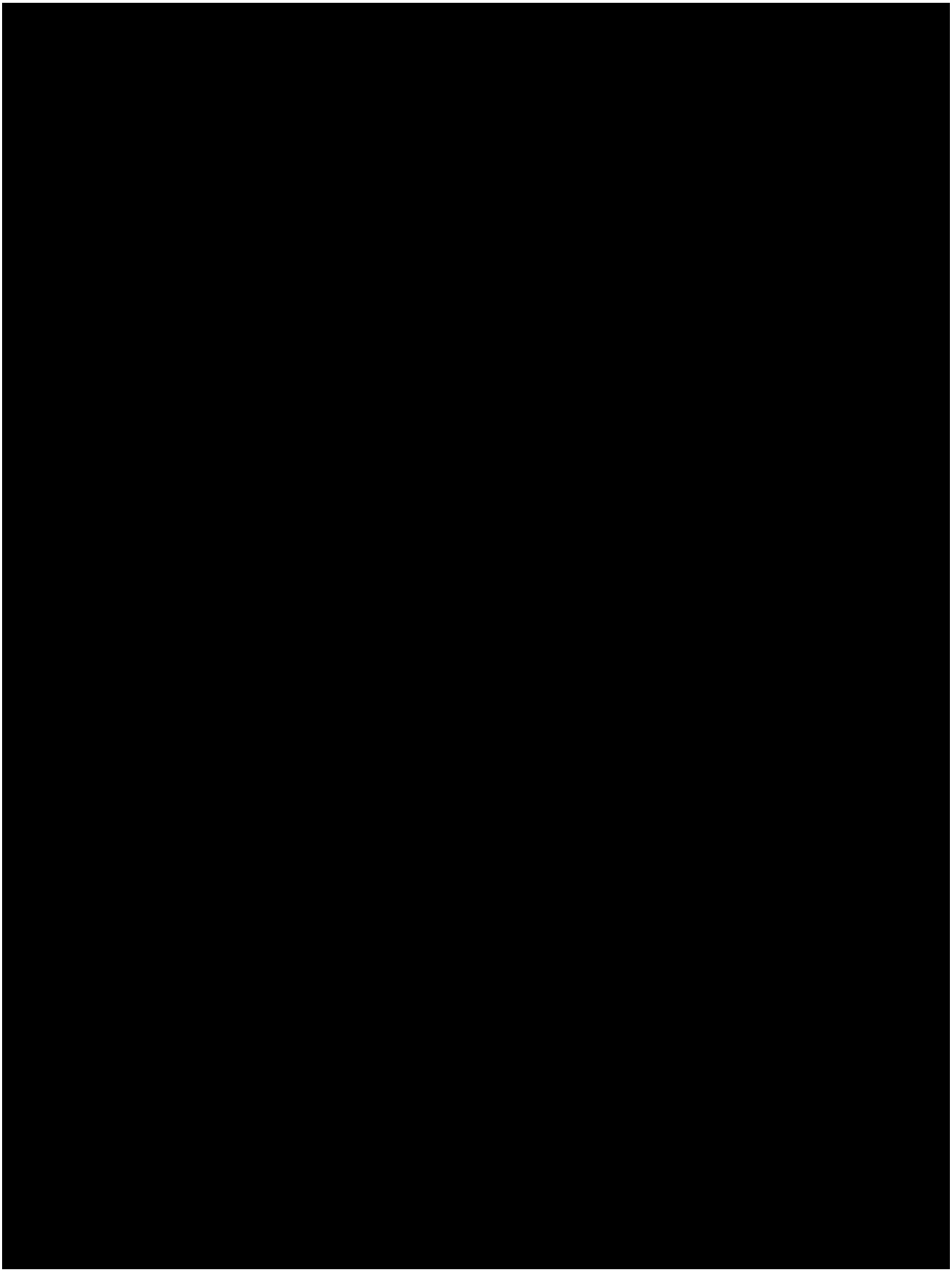


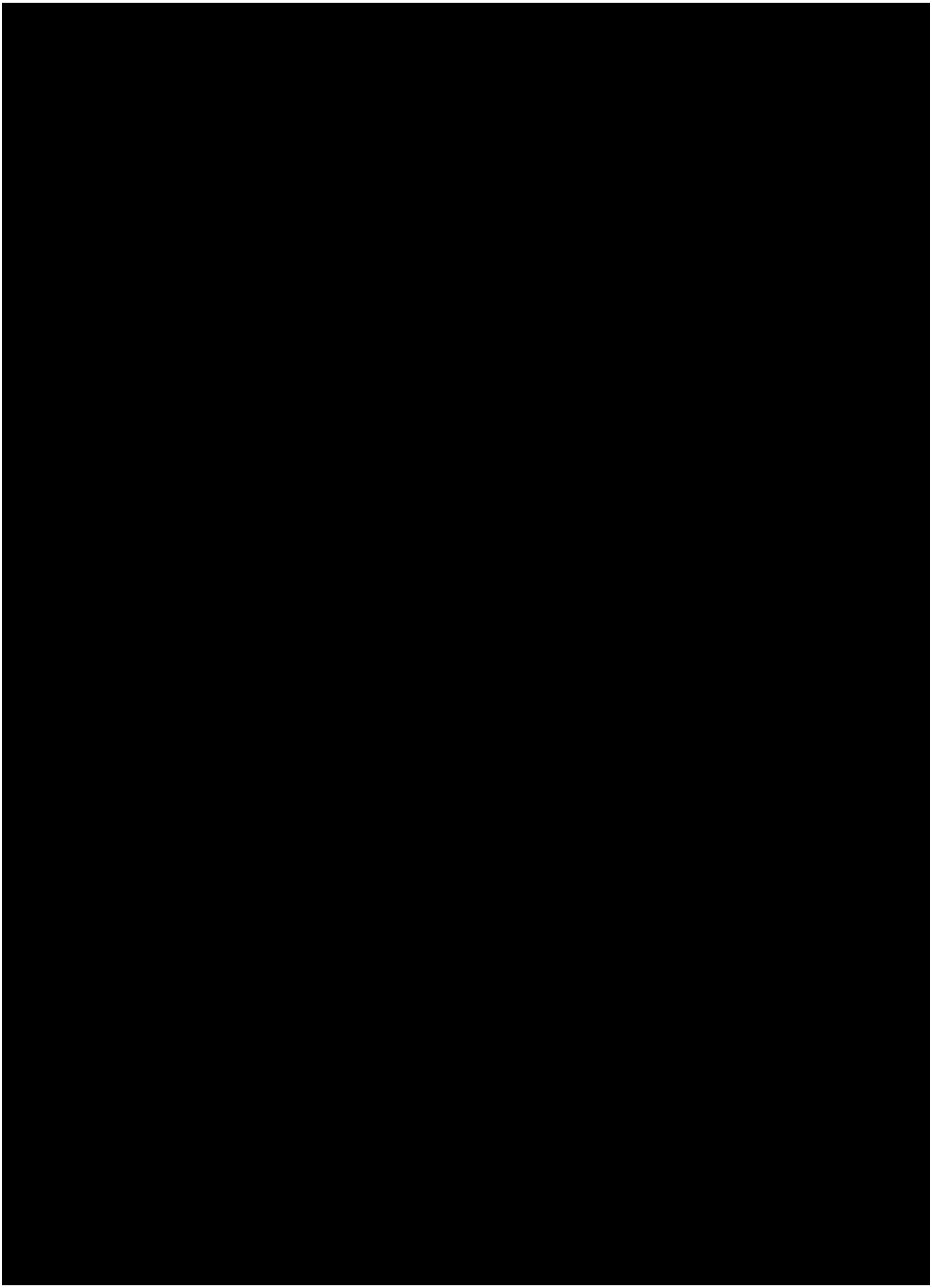


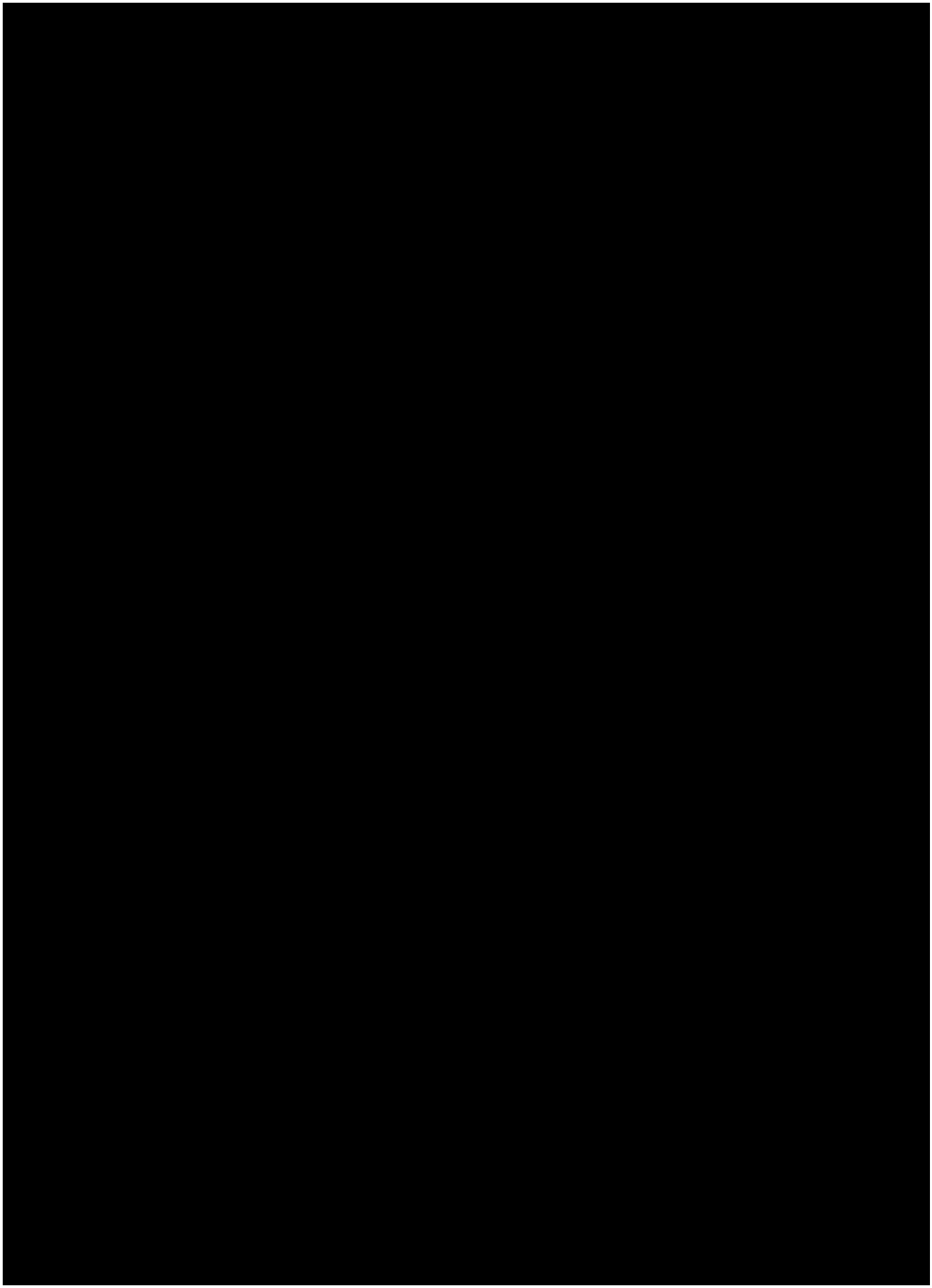


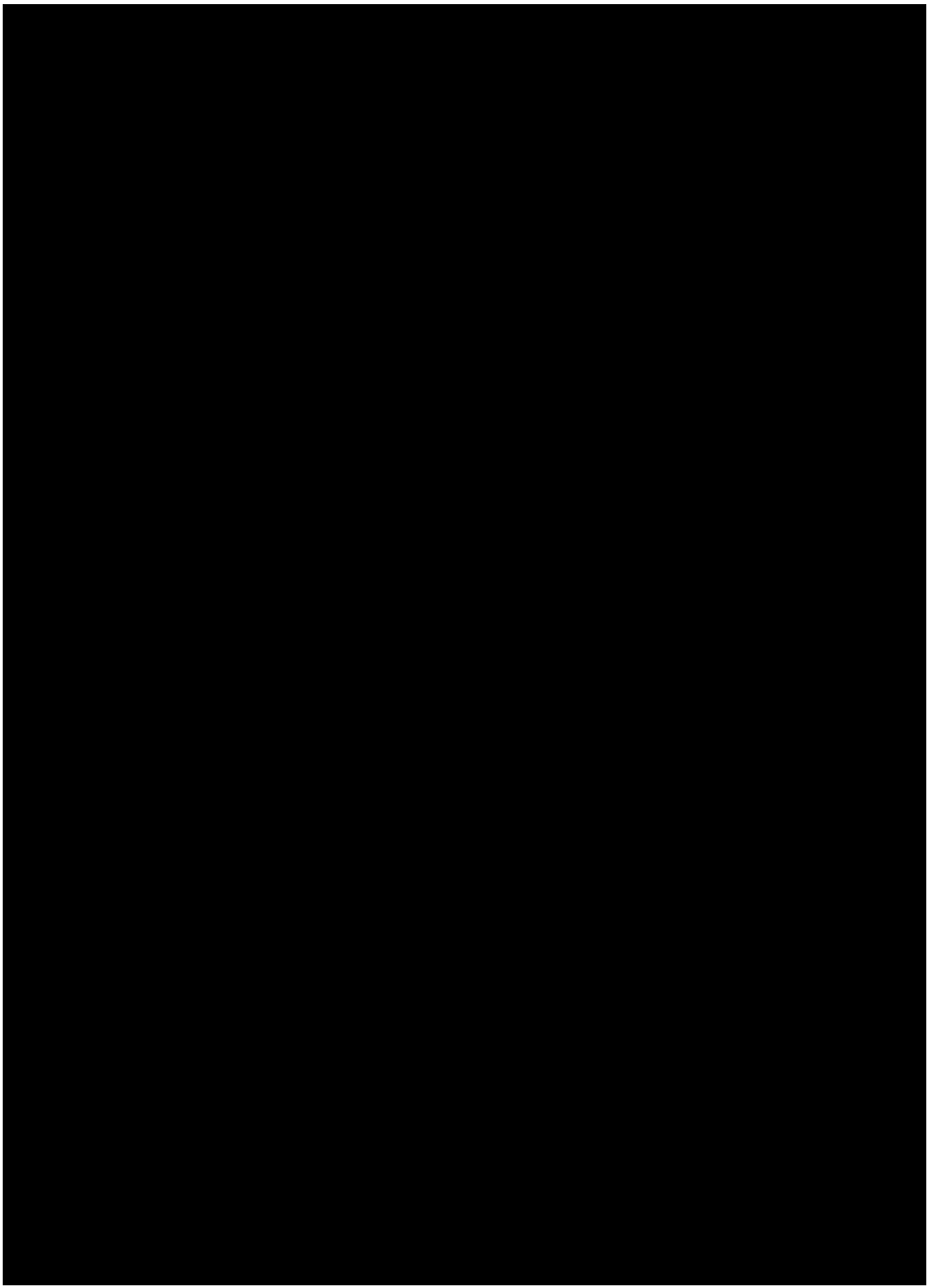


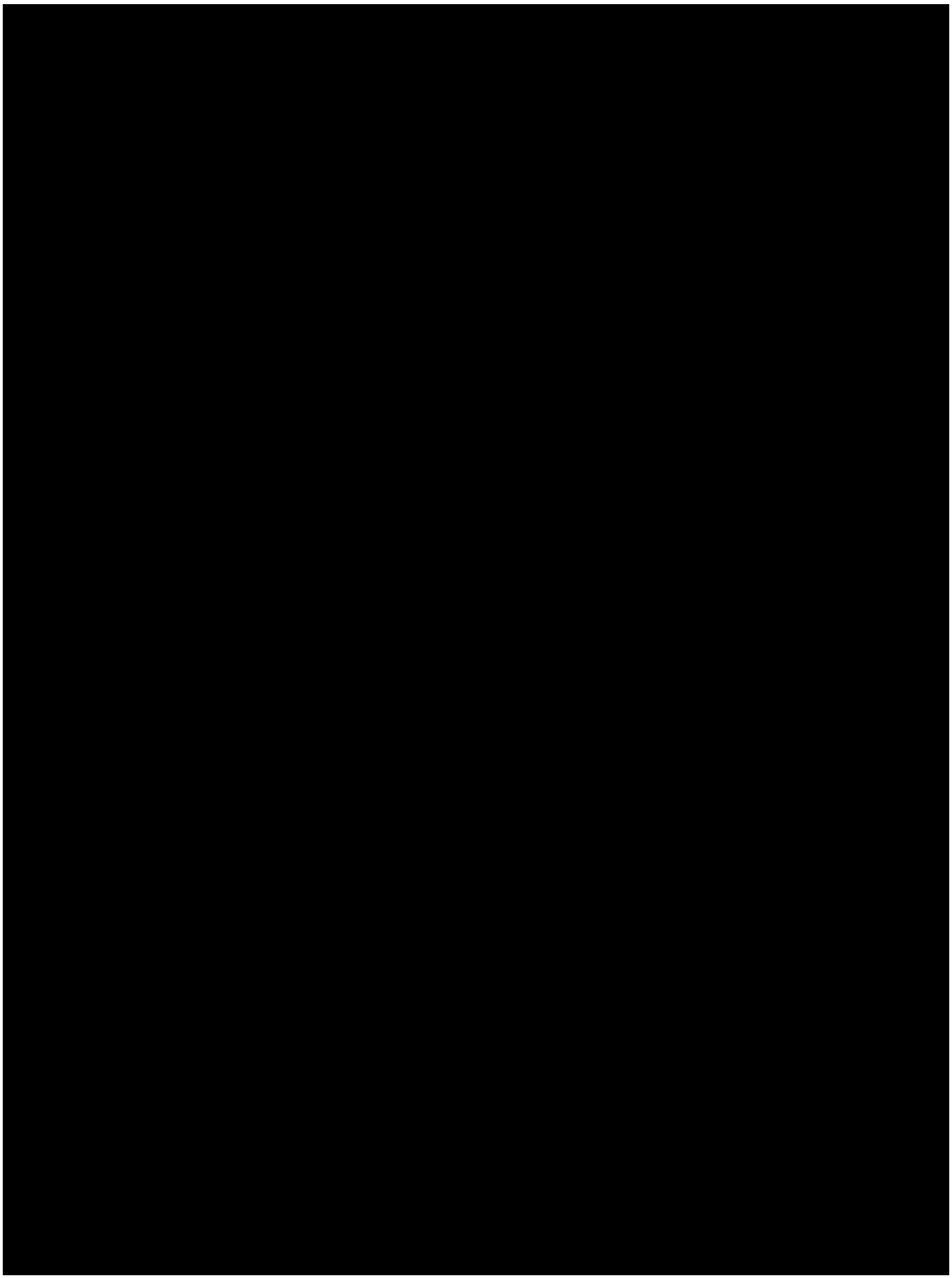


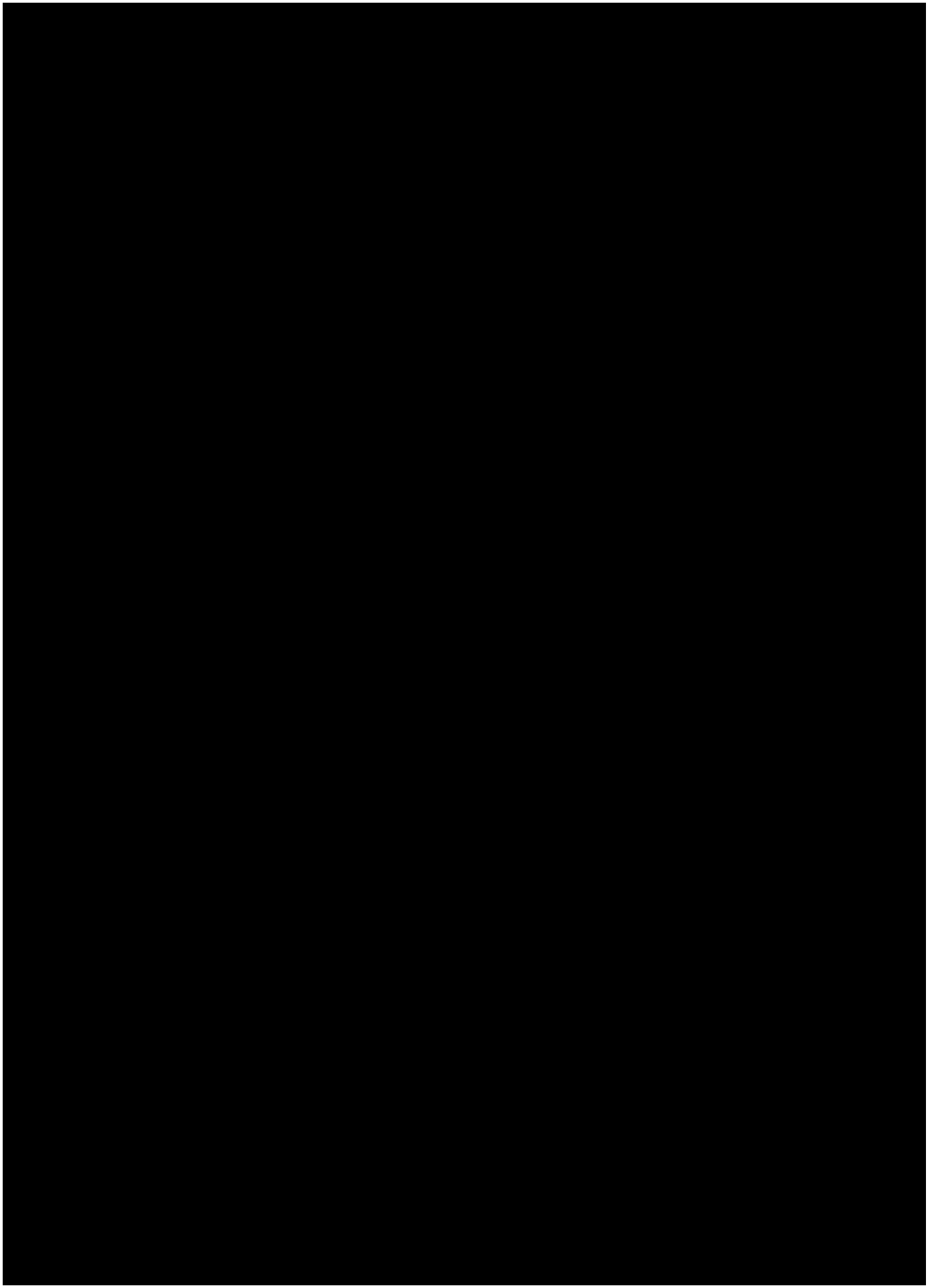


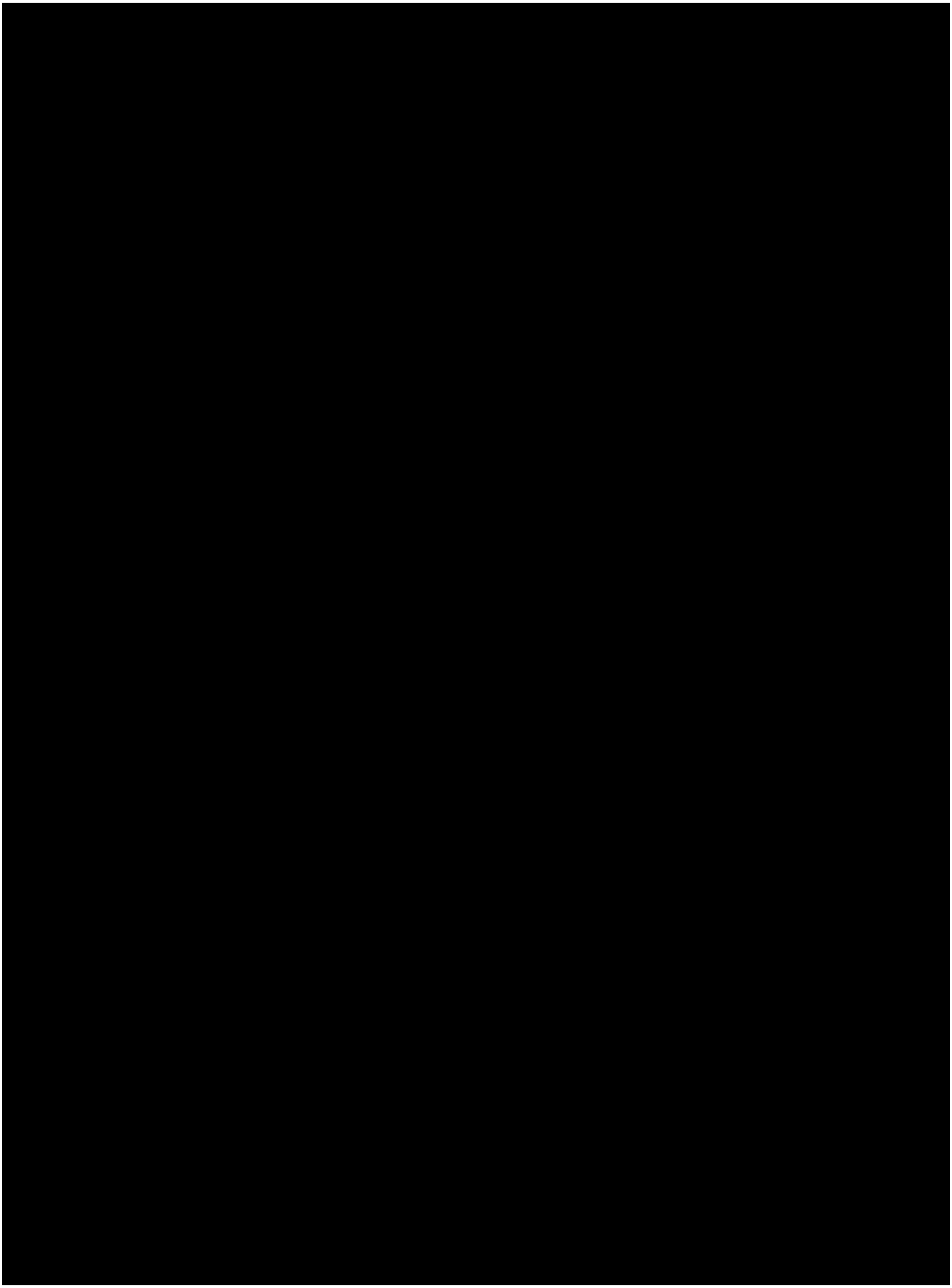


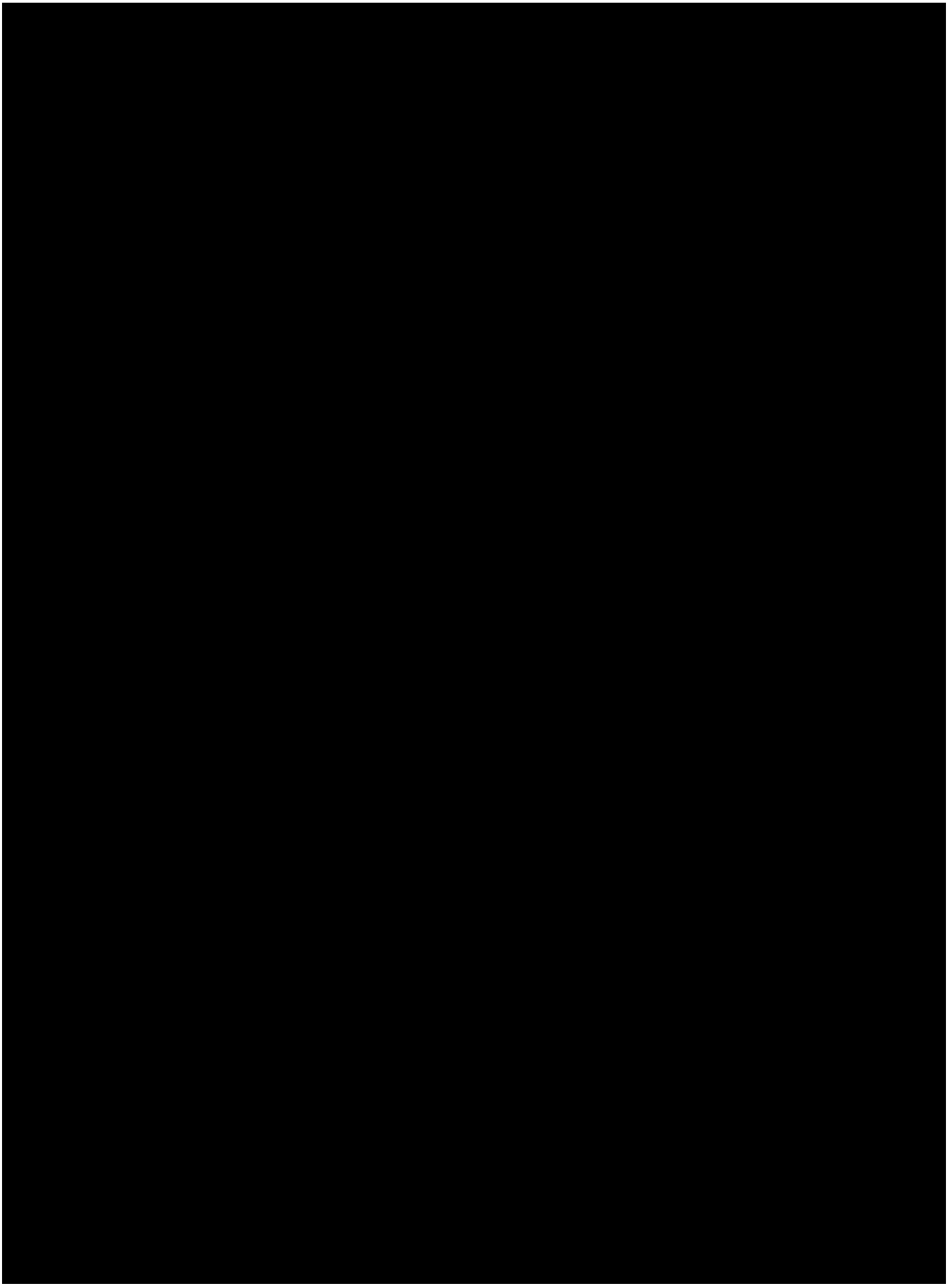


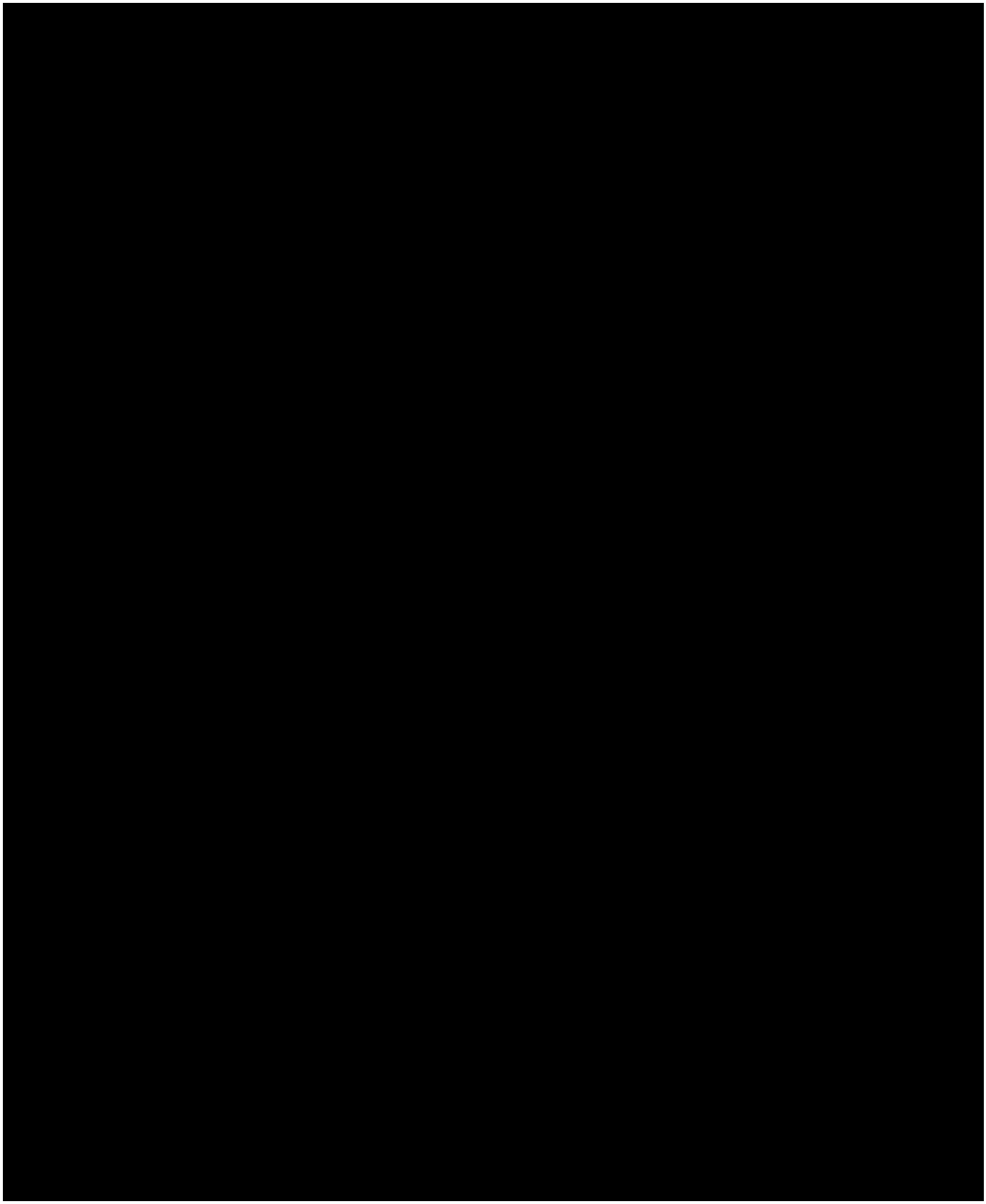












Systematic selection of studies

The PRISMA flow diagram for evidence in the SLR of clinical evidence in R/R DLBCL is presented in Figure 39. The PRISMA flow diagram for the updated search is presented in Figure 40. For the Danish context, the comparator in question is R-GemOX, Figure 41 present the PRISMA flow diagram relevant for this assessment, taking into account the original and updated SLR. The diagram also presents the reason for exclusion.

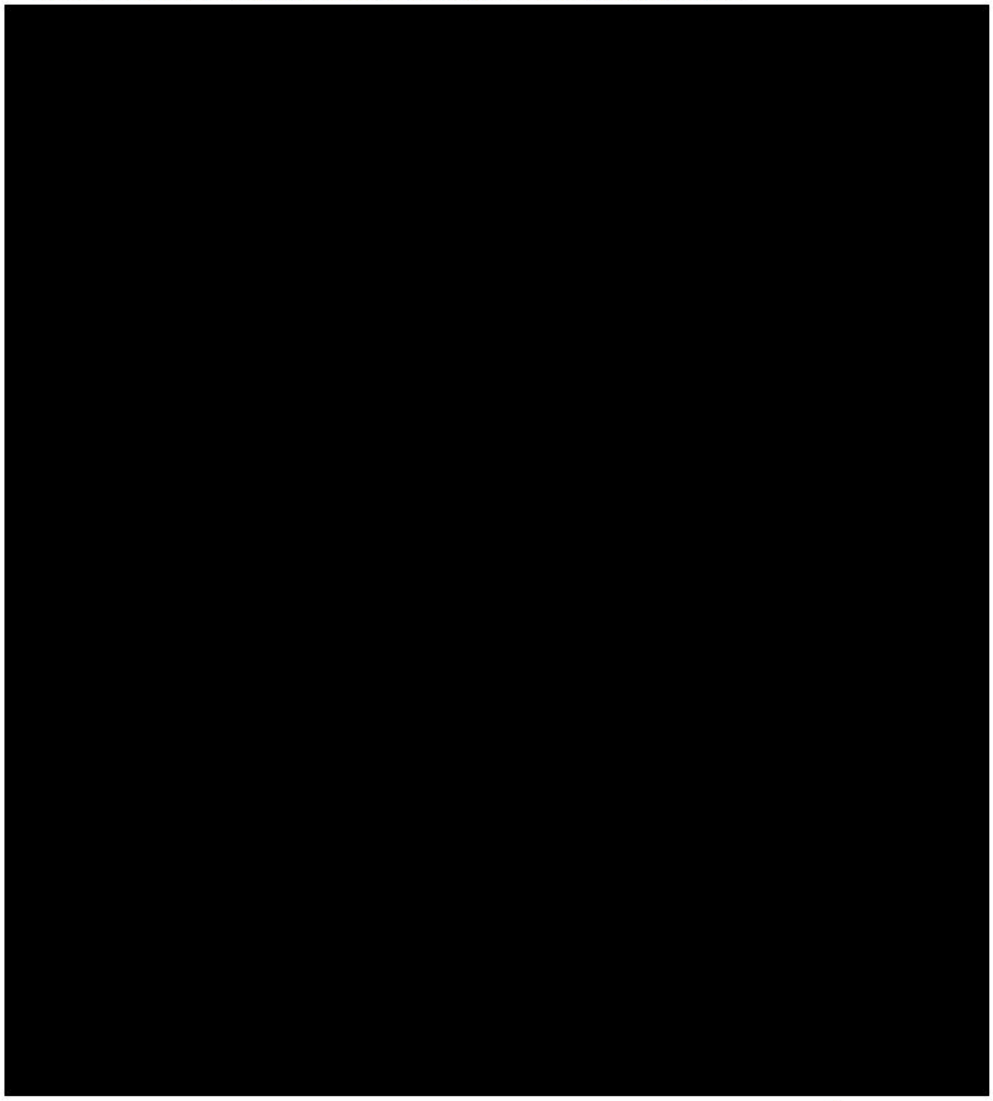


Figure 39. PRISMA flow diagram for evidence in the SLR of clinical evidence in R/R DLBCL

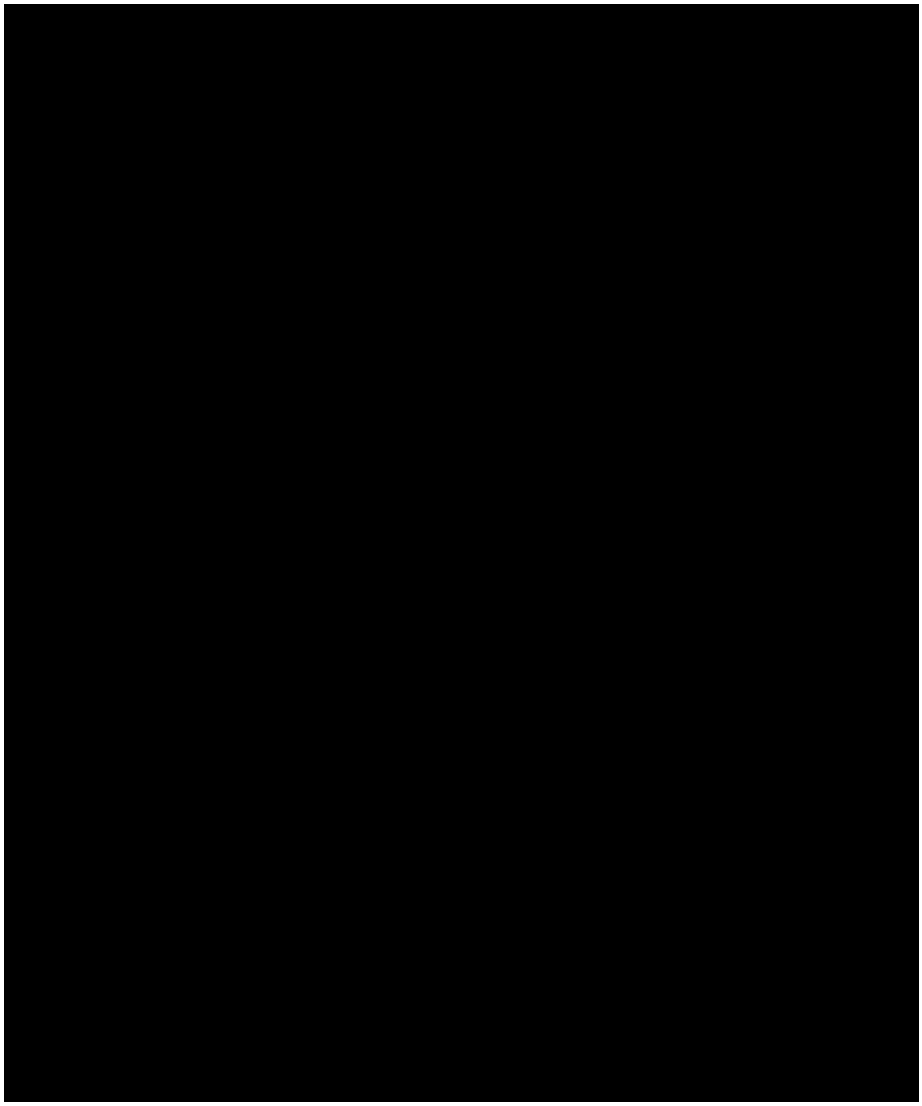


Figure 40. PRISMA flow diagram for the updated SLR of clinical evidence in R/R DLBCL

Figure 41. PRISMA flow diagram records relevant for the comparator in Danish setting

The list of excluded references is presented below and full text papers is presented in Appendix D in the attached document "9_SLR DLBCL Clinical v3.pdf" and in Appendix C in the updated SLR "10_SLR DLBCL Clinical Update Final 3.0.pdf".

Quality assessment

Quality assessments of randomised controlled trials (RCTs) and observational studies identified by the SLR were performed. For RCTs, an adapted checklist from the CRD was used (see Table 78) [117]. For observational studies, a quality assessment tool was adapted from a checklist from the Critical Appraisal Skills Programme (CASP, see Table 79) [118]. In the case of single-intervention trials and open-label extensions, the application of the adapted CRD tool would have resulted in the majority of questions having a "not applicable" response. Therefore, the adapted CASP tool was considered more informative and was used to evaluate these study designs. Only one quality assessment per unique study was performed.

Table 78. Adapted CRD checklist for quality assessment of randomised controlled trials

Study question	Response (yes/no/partially/not clear/NA)	How is question addressed in the study?
Was randomisation carried out appropriately?		

Was the concealment of treatment allocation adequate?	
Were the groups similar at the outset of the study in terms of prognostic factors (eg, disease severity)?	
Were the care providers, participants, and outcome assessors blind to treatment allocation? If any of these people were not blinded, what might be the likely impact on the risk of bias (for each outcome)?	
Were there any unexpected imbalances in dropouts between groups? If so, were they explained or adjusted for?	
Is there any evidence to suggest that the authors measured more outcomes than they reported?	
Did the analysis include an ITT analysis? If so, was this appropriate and were appropriate methods used to account for missing data?	

Abbreviations: CRD, Centre for Reviews and Dissemination; ITT, intention-to-treat; NA, not applicable.

Adapted from: "Systematic reviews: CRD's guidance for undertaking reviews in health care." York: Centre for Reviews and Dissemination, 2008.

Table 79. Adapted CASP checklist for quality assessment of observational studies

Study question	Response (yes/no/partially/not clear/NA)	How is question addressed in the study?
Was the cohort recruited in an acceptable way?		
Was the exposure accurately measured to minimise bias?		
Was the outcome accurately measured to minimise bias?		
Have the authors identified all important confounding factors?		
Have the authors taken account of the confounding factors in the design and/or analysis?		
Was the follow-up of patients complete?		
How precise (eg, in terms of CI and p values) are the results?		

Abbreviations: CASP, Critical Appraisal Skills Programme; CI, confidence interval; NA, not applicable.

Adapted from: Critical Appraisal Skills Programme (CASP): Making sense of evidence 12 questions to help you make sense of a cohort study.

Overall quality assessment and strength of evidence

The overall quality assessment is reported in Table 80 below. This table summarizes the quality assessment results based on the individual study scores from their respective quality assessment tools (presented in the respective sections for each treatment) and the risk of bias. The results must be interpreted with caution they include a qualitative assessment of bias. All studies were reviewed and assessed based on clinical trials and pharmacoepidemiological concepts, depending on the study design.

In addition to the quality assessment, a pyramid of evidence has been developed in order to visually summarize the strength of the evidence for each study in the SLR (Figure 42). All studies were classified based on their study design. The strength of the evidence was evaluated, and the bottom of the pyramid represents studies with weaker evidence, while the upper part of the pyramid represents studies with stronger evidence.

Table 80. Global quality assessment of clinical SLR studies

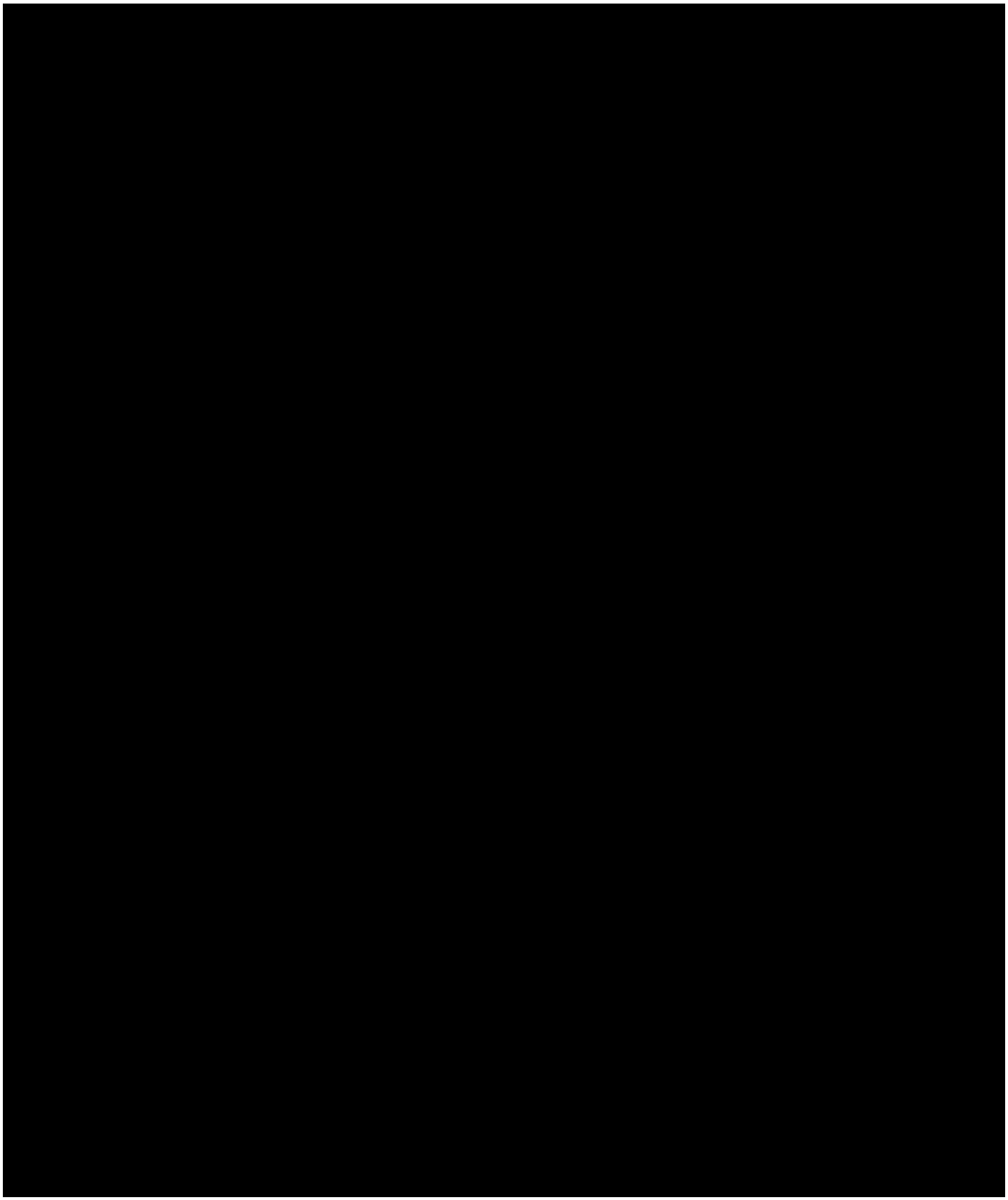
Overall assessment (Quality tool + bias assessment)	Study ID/authors
[redacted]	[redacted]

Figure 42. Pyramid of evidence

Unpublished data

N/A

List of excluded studies



Appendix B – Main characteristics of included studies

L-MIND

Trial name: L-MIND	NCT number: NCT02399085
Objective	To determine the activity of a combination of tafasitamab+lenalidomide in terms of objective response rate (ORR = complete response [CR] + partial response [PR]) in adult patients with R-R DLBCL.
Publications – title, author, journal, year	Salles G, Duell J, González Barca E, Tournilhac O, Jurczak W, Liberati AM, Nagy Z, Obr A, Gaidano G, André M, Kalakonda N, Dreyling M, Weirather J, Dirnberger-Hertweck M, Ambarkhane S, Fingerle-Rowson G, Maddocks K. Tafasitamab plus lenalidomide in relapsed or refractory diffuse large B-cell lymphoma (L-MIND): a multicentre, prospective, single-arm, phase 2 study. Lancet Oncol. 2020 Jul;21(7):978-988. doi: 10.1016/S1470-2045(20)30225-4. Epub 2020 Jun 5.
	Duell J, Maddocks KJ, González-Barca E, Jurczak W, Liberati AM, De Vos S, Nagy Z, Obr A, Gaidano G, Abrisqueta P, Kalakonda N, André M, Dreyling M, Menne T, Tournilhac O, Augustin M, Rosenwald A, Dirnberger-Hertweck M, Weirather J, Ambarkhane S, Salles G. Long-term outcomes from the Phase II L-MIND study of tafasitamab (MOR208) plus lenalidomide in patients with relapsed or refractory diffuse large B-cell lymphoma. Haematologica. 2021 Sep 1;106(9):2417-2426. doi: 10.3324/haematol.2020.275958. PMID: 34196165; PMCID: PMC8409029.
Study type and design	A phase 2, open-label, single-arm, multicentre study to evaluate the efficacy and safety of tafasitamab+lenalidomide in adult patients with R/R DLBCL who were ineligible for high-dose chemotherapy (HDCT) and autologous stem cell transplantation (ASCT).
Sample size (n)	Eighty-one patients were enrolled, of whom 80 patients received both tafasitamab and LEN, and one patient received only tafasitamab.
Main inclusion and exclusion criteria	Main inclusion criteria: Patients who: a. Age > 18 years b. Histologically confirmed diagnosis of DLBCL c. had 1-3 prior regimens d. were not eligible for HDCT and ASCT Main exclusion criteria: Patient with primary refractory DLBCL
Intervention	12 tafasitamab + LEN 28-day cycles followed by tafasitamab monotherapy (in patients with stable disease or better) until disease progression Tafasitamab was 12 mg/kg IV over ~2 hours • Cycles 1–12 o Days 1–21: LEN PO, starting with 25 mg/day • Cycles 1 o Days 1, 4, 8, 15, 22: tafasitamab • Cycles 2–3 o Days 1, 8, 15, 22: tafasitamab • Cycles 4–12 o Days 1 and 15: tafasitamab In cases of protocol-defined toxicities: LEN dose reduction (5 mg/day/step, once per cycle, without re-escalation)

Trial name: L-MIND	NCT number: NCT02399085
Comparator(s)	Not applicable
Follow-up time	35 months (Data cut-off: 30 October 2020)
Is the study used in the health economic model?	Yes
Primary, secondary and exploratory endpoints	**Primary endpoint**: ORR (ORR = CR + PR) as assessed by IRC Secondary endpoints: • DCR (DCR = ORR + SD) • DOR (duration of CRs or PRs until progression or relapse was evaluated) • PFS • Time-to-progression (TTP; first dose of study drug until time of progression or death from lymphoma only) • OS • Time-to-next-treatment (TTNT) Safety assessments: Safety and tolerability assessed by evaluating the frequency, duration, and severity of AEs Additional endpoints: • Determination and characterisation of anti-tafasitamab antibody formation • Pharmacokinetic analysis of tafasitamab • Absolute and percentage change from baseline in B-, T-, and NK cell populations • Analysis of exploratory and diagnostic biomarkers from blood and tumour tissue (eg, CD19, CD20, B-cell lymphoma-2, B-cell lymphoma-6 expression, CD 16 expression on NK cells, and ADCC capacity), GEP for cell of origin subtyping and evaluation of AEs and ORR by FcγRIIIa and FcγRIIa polymorphism
Method of analysis	The primary and secondary endpoints in L-MIND were analysed descriptively for each analysis population using appropriate statistics (counts/percentages for discrete variables, mean, median, standard deviation, minimum, maximum, number of valid observations for continuous variables). For specific variables, p-values and 95% confidence intervals (CIs) were presented. No formal statistical hypothesis testing was planned [148].
Subgroup analyses	• Number of prior therapies: ≥2 vs 1 • Primary refractory: Yes vs No • Refractory to last therapy: Yes vs No • Rituximab-refractory: Yes vs No • GCB cell of origin disease: Yes vs No Results for subgroup analysis are presented in section 7.1.2.3
Other relevant information	

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

This section contains the baseline characteristics of patients in L-MIND and RE-MIND2.

Table 81. Baseline characteristics of patients in studies included for the comparative analysis of efficacy and safety of tafasitamab+LEN compared to systemic therapies (L-MIND vs RE-MIND2)

		L-MIND	RE-MIND2 (MAS_Pool*)	
		Tafasitamab + lenalidomide (N=81, patients in safety population)	Tafasitamab + lenalidomide (N=76)	Systemic therapies pooled (N=76)
[redacted]				

Abbreviations: ANC, absolute neutrophil count; ASCT, autologous stem cell transplant; DLBCL, diffuse large B-cell lymphoma; LDH, lactate dehydrogenase; MAS, matched analysis set; R/R, relapsed or refractory; ULN, upper limit of normal.

*MAS_Pool included 1:1 matched patients from the L-MIND study and the observational cohort using baseline covariates. See Table 85 for definitions on MAS_Pool.

§Along with primary refractoriness and refractoriness to last prior therapy these were the covariates used for matching and weighing.

Notes: Percentages were calculated based on the number of patients in each cohort. The baseline characteristics were applied at the start of the respective therapy line. Index date was defined as start of R/R DLBCL treatment.

Source: Incyte, Data on file (RE-MIND2 CSR).[74]

Comparability of patients across studies

L-MIND and RE-MIND2 patient populations

[redacted]

Comparability of the study populations with Danish patients eligible for treatment

[redacted]

Appendix D – Efficacy and safety results per study

Definition, validity and clinical relevance of included outcome measures

Well defined definitions to the outcomes exists [149]. No investigation of the validity of outcome measures was done.

Results per study

This section contains the results of each of the studies included in this submission.

Table 82. Results of L-MIND (NCT02399085), see Table 9-Table 11

Outcome	Study arm	N	Result (CI)	Estimated absolute difference in effect			Estimated relative difference in effect			Description of methods used for estimation	References
				Difference	95% CI	*P* value	Difference	95% CI	*P* value		
[redacted]											
[redacted]											
[redacted]											
[redacted]											
[redacted]											

Outcome	Study arm	N	Result (CI)	Estimated absolute difference in effect			Estimated relative difference in effect			Description of methods used for estimation	References
				Difference	95% CI	*P* value	Difference	95% CI	*P* value		
[redacted]											

Abbreviations: CI, confidence interval; CR, complete response; DoR, duration of response; NR, not reported; OR, objective response; ORR, objective response rate; PR, partial response

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

L-MIND study

[redacted]

Most frequent treatment-emergent adverse events

[redacted]

TEAEs by treatment phase

[redacted]

Table 83. Summary of selected treatment-emergent adverse events by lenalidomide status (treatment phase) at event onset, System Organ Class and Preferred Term (SAF; L-MIND)

System organ class	Preferred term	Before discontinuation of lenalidomide (n=80)* n (%)/events	After discontinuation of lenalidomide (n=51)† n (%)/events
Any TEAE		[redacted]	[redacted]
Infections and infestations		[redacted]	[redacted]
	Bronchitis	[redacted]	[redacted]
	Pneumonia	[redacted]	[redacted]
	Urinary tract infection	[redacted]	[redacted]
	Respiratory tract infection	[redacted]	[redacted]
	Upper respiratory tract infection	[redacted]	[redacted]
	Lower respiratory tract infection	[redacted]	[redacted]
Blood and lymphatic disorders		[redacted]	[redacted]

Neutropaenia	[redacted]	[redacted]
Anaemia	[redacted]	[redacted]
Thrombocytopaenia	[redacted]	[redacted]
Febrile neutropaenia	[redacted]	[redacted]

Abbreviations: AE, adverse event; MedDRA, Medical Dictionary for Regulatory Activities; SAF, safety analysis set; TEAE, treatment-emergent adverse events.

Note: TEAEs before discontinuation of lenalidomide were defined as any AE reported in the following time interval (including the lower and upper limits): date of first administration of study treatment; date of last administration of lenalidomide + 7 days, or if they were considered to be related to lenalidomide. TEAEs after discontinuation of lenalidomide were defined as any AE not considered to be related to lenalidomide and reported in the following time interval (including the lower and upper limits): date of last administration of lenalidomide + 8 days, date of last administration of tafasitamab + 30 days. AEs occurring after the latter date were considered as a TEAE if they were considered to be related to tafasitamab. MedDRA (Version 21.0) coding dictionary was used.

Within the 2 subgroups the following rules were applied:

A patient with more than 1 TEAE within a preferred term was counted once for that PT.

A patient with more than 1 TEAE within a SOC was counted once for that SOC.

A patient was counted only once for the maximum toxicity under each SOC and PT but all events were presented.

Source: Incyte, Data on file (L-MIND CSR Addendum 3) [69].

[redacted]

Treatment discontinuation and deaths

[redacted]

Clinically notable adverse events

[redacted]

Naïve comparison of safety

[redacted]

Safety conclusions

[redacted]

Appendix F – Comparative analysis of efficacy and safety

Rationale for comparative evidence

Overall, the clinical evidence for tafasitamab in combination with lenalidomide followed by tafasitamab monotherapy provide an appropriate base for assessment of its clinical efficacy in R/R DLBCL patients who are not eligible for ASCT. L-MIND is a large, international clinical trial; therefore, results can be considered broadly applicable to populations worldwide. Further, its primary endpoint of ORR and key secondary endpoints of DoR, DCR, PFS, and OS are widely regarded as appropriate to assess the efficacy of anti-cancer therapy and/or are relevant to routine clinical practice.

While L-MIND is a proof-of-concept, single-arm study, there are several considerations that greatly strengthen its position as the clinical evidence base for treatment with tafasitamab in combination with lenalidomide followed by tafasitamab monotherapy. Most importantly, a new randomised trial in the same indication—performed to confirm the positive results of L-MIND—would delay the availability of the tafasitamab+lenalidomide combination for R/R DLBCL patients. It would take especially long to obtain results with the same level of maturity as the data currently available from L-MIND. This did not seem acceptable when considering the unmet need. Further, a randomised comparative study to confirm the findings of L-MIND would have come up against three main issues, as outlined below.

The absence of an appropriate control arm

In terms of clinical pharmacology, the combination of several treatments always raises the question of the specific contribution of each agent in terms of efficacy. In the specific case of two "new" treatments in the indication (ie, when neither is used as monotherapy for the indication), this implies comparing combination therapy with the use of only one of the partners to isolate the contribution of each. Therefore, a comparison of the combined therapy (tafasitamab and lenalidomide followed by tafasitamab monotherapy) against lenalidomide monotherapy was relevant. However, lenalidomide monotherapy is not a commonly used treatment in practice due to a non-optimal efficacy profile. Its use in combination with tafasitamab is based on the pharmacological rationale of a synergistic effect between the two agents and improved tolerability as lenalidomide is discontinued after 12 cycles [58].

Furthermore, as an established treatment pathway is lacking in R/R DLBCL, it was not possible to compare tafasitamab in combination with lenalidomide followed by tafasitamab monotherapy against the SoC. At present, treatment consists of different chemotherapies plus rituximab and none of the current therapies have robust supporting evidence showing superior efficacy and safety compared to the others. Additionally, as discussed previously in Section 5.2.1, up to 60% of patients may develop CD20-negative transformation after treatment with rituximab-containing chemotherapy in the 1L.[47-49, 154] The loss of CD20 antigen expression after rituximab therapy greatly reduces the options for 2L+ treatment in these patients.

Comparison to another control arm that better reflects patient management—ie, a chemotherapy of the clinician's choice—would also be relevant to evaluate the therapeutic improvement gained with tafasitamab in combination with lenalidomide followed by tafasitamab monotherapy. However, it should be stressed that the choice of treatment in R/R DLBCL is guided by the patient's profile, local practices, and the availability of treatments at national and local levels (ie, CAR T-cell treatments and Pola-BR). Thus, the "case mix" of this control arm (in terms of regimens used and with what frequency) would depend on the centres participating in the study. Hence, the control arm would never be fully representative of a highly heterogeneous, real-world practice.

The suitability of a newer, targeted therapy as a comparator for tafasitamab in combination with lenalidomide followed by tafasitamab monotherapy in a clinical trial may be considered. However, alternatives to immunochemotherapy (Pola-BR and CAR T-cell therapies) were developed in parallel to the tafasitamab+lenalidomide combination. Therefore, it was not possible to anticipate these new treatments in the development program for tafasitamab in combination with lenalidomide followed by tafasitamab monotherapy.

Currently pola-BR is approved for the treatment of R/R DLBCL patients but has not been giving a recommendation of use in Denmark in the UK, EU, and North America. It has been recommended for reimbursement by NICE in the UK, as well as in the Netherlands, Germany, Sweden, and Norway. However, notably, it received a negative final opinion by the French authority HAS due in part to a poor pivotal study design, a lack of efficacy shown for polatuzumab in relation to BR, and a historical comparison with relatively old data using different methods of evaluation .[155] As there may be issues with availability of this treatment in different regions and because it is not currently reimbursed in countries other than those mentioned above (ie, France, Italy, Spain, Belgium, Finland, Denmark, etc), it would not be suitable as a comparator for an international, randomised clinical trial. CAR T-cell therapies are only approved for DLBCL patients in the ≥3L. In practice, the administration of CAR T-cell therapy comprises only a minority of patients, both without comorbidities and with a kinetic of disease actually compatible with the manufacturing and administration time of these treatments. Real-life data with CAR T-cell therapies stress the need for an effective selection of patients that will ultimately benefit from these treatments, compared to the alternate therapies. In particular, it becomes important to identify predictive markers to exclude patients that will relapse early after the CAR T-cell therapy administration [156, 157]. Due to these limitations, CAR T-cell therapies may not be suitable for a large proportion of R/R DLBCL patients who would be candidates for treatment with tafasitamab and, therefore, they would not be suitable as a comparator in a clinical trial.

The inherent imbalance between two treatment arms when only one arm has a maintenance regimen

The EMA considers that a progression occurring under treatment may be of a different nature from a progression occurring outside treatment, and recommends that this should be taken into account in the design of comparative studies, where possible, according to the specificities of the therapeutic context [158]. Generally speaking, the comparison of a chronic treatment and a fixed-duration treatment, both given in parallel, makes it difficult to interpret the efficacy results, particularly when it comes to evaluation criteria such as DoR and PFS, which are censored at the time of progression. OS is indirectly impacted by subsequent treatments received after the experimental drug. First, it cannot be excluded that the administration scheme (maintenance, as opposed to a fixed duration) may have an impact on the effectiveness of these subsequent treatments (ie, selection of more aggressive tumours, resistance, etc). Moreover, in a trial comparing continuous and fixed treatments, the two groups of patients should have different outcomes if continuous treatment is effectively prolonged. The subsequent treatments given will also potentially be different between the two groups (since the period will be different) and so the OS may be biased in this context. Neither monitoring the lines of subsequent treatment, nor imposing following treatment are practical or ethical. Imposing the following treatment would be difficult given the highly individual and heterogenous treatment regimens in R/R DLBCL. Furthermore, keeping patients in a study also prevents them from potentially benefitting from new experimental treatments, especially if they are assigned to the control arm of a randomised clinical trial. The ESMO guidelines clearly indicate R/R DLBCL patients should be included in trials with novel therapies [24]. Finally, it should be noted that previous ASCT procedures (and now previous treatment with CAR T-cell therapies) are a source of complexity for the interpretation of survival data between two groups of patients treated for R/R DLBCL [159-162].

The potential for obsolescence of the results in the context of a rapidly evolving therapeutic strategy

Since new targeted treatments are currently entering the market,[163-165] if a randomised clinical trial were started in the same population today, there would be a high probability that none of the currently available comparators would be representative of clinical practice by the time of study completion. Chemotherapy regimens with rituximab are less effective and have poorer safety profiles than newer, targeted treatments [166]. In addition, as discussed in the previous section, some newer targeted therapies such as Pola-BR and CAR T-cell therapies may not be available in all regions and may not be suitable for all patients who could potentially receive tafasitamab. Furthermore, several trials are underway evaluating treatments already approved for R/R DLBCL in other settings (eg, evaluation of CAR T-cell therapies at earlier stages, evaluation of new 1L protocols).

The controlled collection of real-world data

As mentioned above, the launch of a new prospective study would have resulted in a statistically significant extension of the time required to obtain results with a time frame equivalent to the maturity of the L-MIND data at the time of their submission. The use of external controls has the advantage of leveraging the maturity of the data already available.

The SCHOLAR-1 study, while a large, international, pooled analysis, had a high heterogeneity that precludes relevant comparison. There were several key differences in the patient population compared to L-MIND. First, the patients in L-MIND were older with a median age of 72 years as compared to 55 years in the SCHOLAR-1 study. Second, the patients in the L-MIND study were transplant ineligible, and therefore, arguably more difficult to treat. Third, 52% of patients in L-MIND had a high-intermediate to high risk IPI score compared to 33% in the SCHOLAR-1 study, and therefore, an overall worse prognosis [2, 58]. Finally, the SCHOLAR-1 study did not record biomarkers such as cell of origin or the presence of chromosomal translocations [2].

To appropriately contextualize the data, in the absence of an randomised controlled trial, two indirect treatment comparisons using estimated propensity score (ePS) 1:1 Nearest Neighbour (NN) matching methodology were developed (RE-MIND2 and RE-MIND). These retrospective studies, which are used as external controls to the clinical data from tafasitamab in combination with lenalidomide followed by tafasitamab monotherapy collected in the L-MIND study, constitute two large, real-world cohorts of R/R DLBCL patients (RE-MIND2: N=3454 and RE-MIND: N=490). In contrast to SCHOLAR-1, the RE-MIND studies have generated data on the outcomes of several treatments, in a homogenous manner, and in a well-defined population, with patients meeting the same inclusion/exclusion criteria as for the L-MIND study.

Quality of the comparison

The use of real-world data in the evaluation of a treatment for approval (EMA) or reimbursement are only acceptable if the data generated meet the requirements of quality, reliability, and transparency [167-169]. In the RE-MIND studies, the external controls were carried out independently on the basis of study protocols. The design and objectives of the two studies were registered and the statistical analysis plans were defined prior to the start of the studies. Additionally, the study designs were developed with the input of and agreed upon by the FDA (US). Several steps were undertaken to assure the comparability of the study groups and measurements. The methodology used to create the treatment groups was state of the art and included cohort balancing (see Cohort balancing). Sensitivity analyses were carried out to test the robustness of the results and a bias analysis was conducted to rule out the effect of hidden confounding factors.

RE-MIND2 study

Study design

Selection of study population

Patients were selected from sites in North America, Europe, and the Asia Pacific region according to the inclusion and exclusion criteria outlined in this section. A total of 3454 patients were enrolled and included in the observational study database [74].

Comparability of L-MIND and RE-MIND2 patient populations

Described in Appendix C.

Treatment administered

Observational cohorts included patients who received any systemic therapy for R/R DLBCL listed in ESMO/NCCN guidelines. The pre-specified treatments received as anti-DLBCL therapy are presented as the respective cohorts (eg, BR cohort, R-GemOx cohort, etc). The following observational cohorts were included in the study:

- Systemic therapies pooled cohort
- BR cohort
- R-GemOx cohort
- Rituximab + lenalidomide (R-Len) cohort
- CAR T-cell cohort
- Pola-BR cohort
- Pixantrone monotherapy

Data from the L-MIND study database (data cut-off 30 November 2019; ie, approximately two years after the last patient was enrolled in the study) were used for comparison with the observational cohort of the RE-MIND2 study [74, 150]. In the L-MIND study, the administration of a combination of tafasitamab and lenalidomide was followed by tafasitamab monotherapy until disease progression, whereas other comparator therapies in RE-MIND2 were administered as a fixed treatment duration [150]. For patients in the observational cohort, an analysis window of 44 months was applied in place of a data cut-off date. This corresponded to the maximum follow-up time for an individual patient in the L-MIND study (44 months or 1338 days; first patient enrolled: March 2016, primary completion data cut-off date 30 November 2019) [74].

Cohort balancing

State of the art, ePS-based 1:1 Nearest Neighbour (1:1 NN) matching methodology was utilised to select "matched" patients from comparator arms to achieve the desired level of balance between the observational and L-MIND cohorts. A propensity score is the probability of a patient being assigned to a particular treatment given a set of observed covariates.[171] In RE-MIND2, the following baseline covariates were used to estimate the propensity score (Table 84).[74]

Table 84. Baseline covariates used in the estimate of the propensity score estimate (RE-MIND2)

Baseline covariates	
1	Number of prior lines of therapy (1 vs 2/3)
2	Ann Arbor Stage I/II vs III/IV
3	Age (as categorical variable with subgroups <70 vs ≥70 years of age)

4	History of primary refractoriness (Yes vs No)
5	Refractoriness to last therapy line (Yes vs No)
6	Prior ASCT (Yes vs No)
7	Elevated LDH (LDH > ULN vs LDH ≤ ULN)
8	Neutropaenia (ANC <1.5 x 10^9/L vs ANC ≥1.5 x 10^9/L)
9	Anaemia (Hb <10 g/dL vs Hb ≥10 g/dL).

Abbreviations: ANC, absolute neutrophil count; ASCT; autologous stem cell transplant; Hb, haemoglobin; LDH, lactate dehydrogenase; ULN, upper limit of normal.

Source: Incyte, Data on file (RE-MIND2 CSR).[74]

Note that the ECOG value and IPI score were not included in the covariate matching. While conducting the RE-MIND study it was noted that many ECOG values were missing. Propensity score matching requires all variable to be present, as such, adding ECOG on top of the other nine matching covariates would considerably reduce the population available for matching. Because of the already limited numbers of patients eligible for matching, reducing the pool further may have resulted in a small population size with inadequate statistical power. In an effort to balance completeness with feasibility, the decision was made to not include ECOG in the primary confirmatory analysis, but to perform a sensitivity analysis where ECOG was included.

To balance the L-MIND cohort vs systemically-administered therapies (pooled), subgroup strata were categorised based on the first of the nine covariates, number of lines of therapy (ie, two or three or four therapy lines). 1:1 (the ratio of the L-MIND cohort to the observational cohort) NN matching without replacement was performed using the remaining eight baseline covariates (Table 84) per each stratum. The final matched population for analysis was the aggregation of the matched population of each stratum.[74]

To balance the L-MIND cohort vs pre-specified treatment regimens, 1:N* NN matching for the nine baseline characteristics (Table 84) was performed. Comparative analysis with the L-MIND cohort was performed only if a certain balance of baseline characteristics had been achieved (i.e., standardized mean difference [SMD; ratio of difference in means on standard deviation] ≤0.2 for all covariates). A sensitivity analysis using a balanced weighting application of ePS ("overlap weights") was performed for the primary efficacy endpoint and all relevant secondary efficacy endpoints (see Sensitivity analyses). Matching was performed only if the number of patients eligible for matching in the pre-specified cohort was larger than the number of patients in the L-MIND cohort FAS population.

* *'1:N' denotes the ratio of the L-MIND cohort to the observational cohort with a maximum ratio of 1:4. In the interim cohort balancing, prior to the data cut-off date (13 November 2020), nearest neighbour matching was performed by stepwise increasing the matching ratio from 1:1 to 1:4 until for one or more baseline covariates a SMD of 0.2 was exceeded. The matched population with SMD ≤ 0.2 for all baseline characteristics and the highest matching ratio was selected as the primary analysis set for endpoint calculation. At the fourth interim analysis, a decision was made to use a matching ratio of 1:1 for all matched analysis sets.*

Analysis populations

The following key analysis populations were defined for the RE-MIND2 study (Table 85). More details are available in the RE-MIND2 Statistical Analysis Protocol (SAP).

Table 85. Statistical analysis populations for RE-MIND2

Analysis populations	Description
Analysis sets for the observational cohort only	
Enrolled patients (ENR)	All patients enrolled in the observational study and all patients except screen failures in the L-MIND study.
Observational Enrolled Analysis Set (Ob-ENR)	All patients enrolled in the observational study.
Observational Full Analysis Set (Ob-FAS)	All patients in Ob-ENR who: Met the inclusion/exclusion criteria Received systemic treatment for DLBCL according to ESMO/NCCN guidelines Had baseline tumour assessment Had valid index date (at least month and year available) for the given line for at least one therapy line Did not meet any of the following scenarios: Identified as a duplicate in the de-duplication medical review report Was 'Not R/R DLBCL patient' Met the 6-month follow-up rule as described in Section 2 of the SAP*
Modified Observational Full Analysis Set (mOb-FAS)	All patients in Ob-FAS. The 6-month follow-up rule* was not applied.
Key analysis sets	
Full Analysis Set (FAS)	Patients from the Ob-FAS and patients from the L-MIND study who received at least one dose of tafasitamab and one dose of LEN with a minimum of 6 months follow-up.
Modified Full Analysis Set (mFAS)	Patients from mOb-FAS and patients from the L-MIND study who received at least one dose of tafasitamab and one dose of LEN.† The 6-month follow-up rule* was not applied.
Matched Analysis Set (MAS_Pool)	A subset of the FAS who met criteria for matching as described in Section 8.3.3.5 of the SAP and included 1:1 matched patients from the L-MIND study and the observational cohort using baseline covariates§ as described in Section 8.4.5 of the SAP.
MAS for the pre-specified treatment (MAS_BR and MAS_R-GemOx)‡	Subsets of the FAS for each pre-specified treatment who met criteria for matching as described in Section 8.3.3.6 of the SAP using baseline covariates§as explained in Section 8.4.5 of the SAP and included 1:1 matched patients from the L-MIND study and each pre-specified treatment.

Abbreviations: ANC, absolute neutrophil count; ASCT, autologous stem cell transplant; BR, bendamustine + rituximab; CAR-T, CD19 CAR-T therapies; CNS, central nervous system; CR, complete response; DLBCL, diffuse large B-cell lymphoma; FAS, Full Analysis Set; Hb, hemoglobin; LDH, lactate dehydrogenase; LEN, lenalidomide; NCCN/ESMO, National Comprehensive Cancer Network/European Society for Medical Oncology; NN, Nearest Neighbour; Pola-BR, polatuzumab vedotin + bendamustine + rituximab; PIX, pixantrone monotherapy; PR, partial response; R-Len,

rituximab + lenalidomide; R-GemOx, rituximab + gemcitabine + oxaliplatin; R/R DLBCL, refractory or relapsed diffuse large B-cell lymphoma; SAP, statistical analysis plan; SMD, standardized mean difference; ULN, upper limit of normal.

*Given the observational nature of the study, there might be a bias in favor of the L-MIND cohort because of the following reasons: For patients treated in a clinical trial it is more likely that an early but short-lasting response to the treatment is adequately captured due to the precisely defined tumor assessment frequency in the protocol. For patients treated in daily practice outside of a clinical trial a short-lasting response may be missed because the schedule of assessments per local practice may be less frequent or be influenced by external factors such as scan availability etc. In such cases only a progression event might be recorded. Patients treated in daily practice outside of a clinical trial may have a lower chance to have an objective response recorded to a particular treatment due to an early discontinuation without adequate assessment of tumor progression. In a clinical trial the protocol mandates to continue treatment until progression is recorded with an adequate tumor assessment. To mitigate this bias, a 6-months follow up rule will be applied for certain analyses.

A minimum of 6 months' follow-up time was met if: 1) a patient responded (CR or PR) or progressed or died within six months from index date (from study day 1 to 183), OR 2) a responding patient (CR or PR as best response during analysis window) had a baseline tumour assessment and at least one post-baseline response assessment available at six months or later (on or after study Day 184) OR 3) any patient who had at least one disease response assessment with SD, "indeterminate", "not evaluable" or "other" within six months from index date (from study Day 1 to 183) with at least one assessment or death at six months or later (or on after study Day 184). Patients did not fulfill the minimum of six months' follow-up time if they were non-responding (SD or PD as best response) with a first tumor response assessment beyond six months. Notice for observational cohorts the 6-months follow-up rule will be applied per therapy line.

†Of note: the eligibility/non-eligibility criteria described were also applied to the L-MIND patients prior to their inclusion in the FAS. ‡Matching exercises and comparative analyses were not performed in other pre-specified treatment cohorts due to limited number of patients eligible for matching.

§The nine baseline covariates were: Age (as categorical variable with subgroups <70 vs ≥70 years of age); Ann Arbor Stage I/II vs III/IV; Refractoriness to last therapy line (Yes vs No); Number of prior lines of therapy (1 vs 2/3); History of primary refractoriness (Yes vs No); Prior ASCT (Yes vs No); Elevated LDH (LDH>ULN vs LDH≤ULN); neutropaenia (ANC<1.5x10^9/L vs ANC≥1.5x10^9/L); anaemia (Hb<10 g/dL vs Hb≥10 g/dL).

Source: Source: Incyte, Data on file (RE-MIND2 CSR).[74]

Study endpoints

The RE-MIND2 study included the following endpoints:[74]

- Primary endpoint: OS
- Secondary endpoints:
    - ORR
    - CRR
    - DoR
    - Event-free survival (EFS)
    - PFS
    - TTNT
    - Treatment discontinuation rate due to AEs
    - Duration of treatment exposure

The endpoints OS, ORR, CRR, and PFS were analysed for the pooled, BR, and R-GemOx cohorts for the following subgroups:[74]

- Age <70 vs ≥70
- Ann Arbor disease stage I+II vs III+IV
- Refractoriness to last therapy line (Yes vs No)
- Number of prior lines of therapy (1 vs 2/3)
- History of primary refractoriness (Yes vs No)
- Prior ASCT (Yes vs No)

Statistical analysis of study endpoints

The following efficacy endpoints were assessed:

1) Time to event including OS (primary endpoint), PFS, TTNT, DoR, EFS
- Standard Kaplan–Meier methodology were used.
- Log-rank test and hazard ratio (HR) along with 95% CI and the associated p-values using Cox proportional hazard model were reported.

2) Binary including ORR and CRR
- Fisher's exact tests were performed and p-values were presented.
- Treatment effect in terms of difference in ORR or CRR between the two cohorts was estimated and exact 95% CI was presented.
- Odds ratio (OR) of ORR or CRR and the ratio of the proportions were presented.

Treatment discontinuation rates per cohort due to AEs and duration of exposure to study treatment were analysed via descriptive statistics.

Sensitivity analyses

To improve the cohort balancing of L-MIND vs observational cohorts, sensitivity analyses were completed in which NN matching was performed to achieve an SMD of ≤0.2 for 11 covariates, including:[74]

- Eight of the nine covariates listed in Table 84 that were used for the primary analysis
    - 'History of primary refractoriness (Yes vs No)' was replaced by two covariates:
        - 'History of primary progressive (Yes vs No)': Best response of PD or SD during treatment
        - 'History of early relapse (Yes vs No)': Progression within six months (183 days) after 1L completion
- ECOG (0 to 1 vs ≥2)

The sensitivity analysis set MAS_Pool_11Cov was generated for systemic therapies pooled and MAS_R-GemOx_11Cov was generated for pre-specified treatments. MAS_Pool_11Cov included 1:1 matched patients from the L-MIND cohort and the observational cohort using the 11 baseline covariates for matching.

Additional sensitivity analyses conducted (Incyte, Data on file; RE-MIND2 CSR) [74]:

- Balancing using overlap weights on ePS.
    - Balancing weight approaches used weights based on the ePS to create a sample in which the distribution of measured baseline covariates was independent of treatment assignment and estimated the average treatment effect in this population. The endpoint analyses are then weighted by the selected balancing weight to estimate effects of treatments (i.e., the ePS weights are employed through the relevant SAS procedure with its WEIGHT option). Robust variance estimation is used to account for the weighted nature of the sample.
        - A four-step process will be used with overlap weights in the FAS population:
            - Create two strata under 2nd therapy line and 3rd therapy line
            - Estimate propensity scores (pi) for each patient in each strata
            - Check overlap between cohorts on ePS distributions and logistic model to estimate propensity scores of each strata as mentioned above;
            - Use overlap weights to balance cohorts of each strata: patients in L-MIND trial will be weighted with $1-pi$ while patients in Observational study will be weighted with pi , where pi is the estimated propensity score of a patient being assigned to the L-MIND cohort.

- Evaluate balance for each baseline covariate using measures described previously (standardized difference and ratio of variances).

- A multiple imputation technique for missing data in baseline covariates applied in the FAS prior to cohort balancing. Note that multiple imputation was used to alleviate the potential problems of bias from systematically missing data as a sensitivity analysis only.
- Matched analysis applying an 18-month survival follow-up period. Patients who had less than 18 months follow-up were excluded from the analysis.

[redacted]

[redacted]

[redacted]

Baseline characteristics

Baseline patient characteristics are presented in Table 86.

Table 86. RE-MIND2 study: selected demographic and baseline characteristics for MAS_Pool and MAS_R-GemOx

Demographics/baseline characteristics/statistics	MAS_Pool*		MAS_R-GemOx‡	
	Tafa+LEN (N=76) n (%)	Systemic therapies pooled (N=76) n (%)	Tafa+LEN (N=74) n (%)	R-GemOx (N=74) n (%)
[redacted]				

[redacted]

Table 87. Complete Response Rate – MAS_Pool and MAS_R-GemOx

Category/Statistic	MAS_Pool*		MAS_R-GemOx‡	
	Tafa+LEN (N=76)	Systemic therapies pooled (N=76)	Tafa+LEN (N=74)	R-GemOx (N=74)
[redacted]				

[redacted]

[redacted]

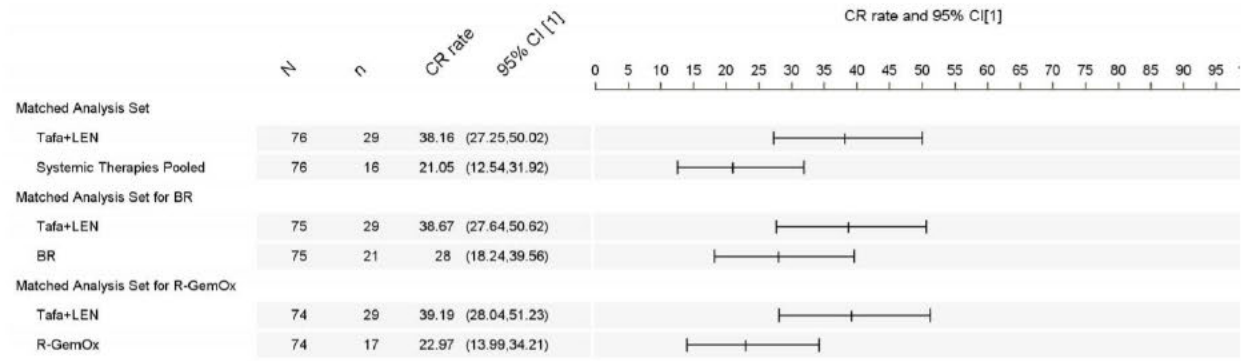


Figure 43. A forest plot of CR for different analysis sets (RE-MIND2)

Abbreviations: BR, bendamustine + rituximab; CR, complete response; CI, confidence interval; LEN, lenalidomide; R-GemOx, rituximab + gemcitabine + oxaliplatin; N, number of patients in each cohort

[1] Chan-Zhang method [76]

The vertical gray line indicates a rate of 0.

Difference in CRR = [(CRR of tafasitamab+lenalidomide cohort) – (CRR of observational cohort)].

Source: Incyte, Data on file (RE-MIND2 CSR).[74]

[redacted]

(a) Subset of L-MIND patients matched with the observational cohort for pooled systemic therapies (**MAS_Pool)**

(b) Subset of L-MIND patients matched with the observational cohort of patients taking R-GemOx (**MAS_R-GemOx)**

Figure 44. Kaplan–Meier plot of duration of response for MAS_Pool, and MAS_R-GemOx (RE-MIND2)

Abbreviations: CI, confidence interval; KM, Kaplan–Meier; LEN, lenalidomide; MAS, matched analysis set; R-GemOx, rituximab+gemcitabine+oxaliplatin; N, number of patients in each cohort; NR, not reached; Tafa, tafasitamab.

Notes: MAS_R-GemOx included 1:1 matched patient from the L-MIND study and R-GemOx as pre-specified treatment. See Table 85 for definitions on MAS_Pool and MAS_R-GemOx.

The median was calculated with Kaplan–Meier method. The 95% CI was calculated by means of Greenwood formula.

Only responders were included in the analysis of DoR.

Source: Incyte, Data on file (RE-MIND2 CSR).[74]

(a) Subset of L-MIND patients matched with the observational cohort for pooled systemic therapies (**MAS_Pool)**

(b) Subset of L-MIND patients matched with the observational cohort of patients taking R-GemOx (**MAS_R-GemOx)**

Figure 45. Kaplan–Meier plot of event-free survival for MAS_Pool, and MAS_R-GemOx (RE-MIND2)

Abbreviations: CR, complete response; CI ,confidence interval; KM, Kaplan–Meier; LEN, lenalidomide; R-GemOx, rituximab+gemcitabine+oxaliplatin; MAS, matched analysis set; N, number of patients in each cohort; Tafa, tafasitamab.

Notes: MAS_Pool included 1:1 matched patients from the L-MIND study and the observational cohort using 9 baseline covariates.

MAS_R-GemOx included 1:1 matched patients from the L-MIND study and MAS_R-GemOx as pre-specified treatment, respectively. See Table 85 for definitions on MAS_Pool and MAS_R-GemOx.

The median was calculated with Kaplan–Meier method. The 95% CI was calculated by means of Greenwood formula.

The hazard ratio was calculated with Cox proportional hazard model.Source: Incyte, Data on file (RE-MIND2 CSR).[74]

[redacted]

(a) Subset of L-MIND patients matched with the observational cohort for pooled systemic therapies (**MAS_Pool**)

(b) Subset of L-MIND patients matched with the observational cohort of patients taking R-GemOx (**MAS_R-GemOx)**

Figure 46. Kaplan–Meier plot of time-to-next treatment for MAS_Pool and MAS_R-GemOx (RE-MIND2)

Abbreviations: CR, complete response; CI ,confidence interval; KM, Kaplan–Meier; LEN, lenalidomide; R-GemOx, rituximab+gemcitabine+oxaliplatin; MAS, matched analysis set; N, number of patients in each cohort; Tafa, tafasitamab.

Notes: MAS_Pool included 1:1 matched patients from the L-MIND study and the observational cohort using 9 baseline covariates.

MAS_R-GemOx included 1:1 matched patients from the L-MIND study and MAS_R-GemOx as pre-specified treatment, respectively. See Table 85 for definitions on MAS_Pool and MAS_R-GemOx.

The median was calculated with Kaplan–Meier method. The 95% CI was calculated by means of Greenwood formula.

The hazard ratio was calculated with Cox proportional hazard model

Source: Incyte, Data on file (RE-MIND2 CSR).[74]

[redacted]

[redacted] and secondary efficacy endpoints: MAS_Pool_11Cov and MAS_R-GemOx_11Cov (RE-MIND2)

Category/Statistic	MAS_Pool_11Cov*		MAS_R-GemOx_11Cov‡	
[redacted]				

Abbreviations: CI, confidence interval; CR, complete response; CRR, complete response rate; HR, hazard ratio; KM, Kaplan–Meier; LEN, lenalidomide; mEFS, median event-free survival; mOS, median overall survival; mPFS, median progression-free survival; mTTNT, median time to next treatment; OR, odds ratio; ORR, objective/overall response rate;

*MAS_Pool_11Cov included 1:1 matched patients from the L-MIND cohort and the observational cohort using the 11 baseline covariates for matching. See Table 85 for definitions on MAS_Pool and MAS_R-GemOx.

‡MAS_R-GemOx_11Cov included 1:1 matched patients from the L-MIND study and R-GemOx as pre-specified treatment using the 11 baseline covariates for matching. See Table 85 for definitions on MAS_Pool and MAS_R-GemOx.

§Brookmeyer and Crowley method.

¶The probability was calculated with Kaplan-Meier method. The CI is calculated by means of Greenwood formula.

#p-value is calculated with Wald test.

**Clopper-Pearson exact method.

††Logistic regression model: Response = Cohort status.

Notes: Analysis window for Tafa + LEN cohort was defined as the interval between index date and data cut-off date (30 November 2019). Analysis window for observational cohorts was defined as the interval between index date for a given line + 44 months (1338 days).

Hazard ratio was estimated using the observational cohort as reference group in Cox Proportional hazard models.

Odds ratio along with their 95% CI was estimated using logistic regression, with observational cohort as the reference group in the model.

No caliper was used for Matched Analysis Set 11 Covariates.

Caliper Width=1.491, Caliper constant=1.05, Seed=2027 was used for Matched Analysis Set 11 Covariates for pre-specified treatments for BR.

Caliper Width=1.0971, Caliper constant=0.69, Seed=2039 was used for Matched Analysis Set 11 Covariates for pre-specified treatments for R-GemOx.

Estimates of HR in PFS are limited and caution should be taken in interpretation due to the unmet assumption of the Cox proportional model. Post-hoc analyses are encouraged to analyze piecewise HR of these endpoints.

[redacted]

[redacted]

[redacted]

Appendix G –Extrapolation

Tafasitamab and Lenalidomide

Following the recommendations by the DMC on survival data extrapolation, six parametric distributions were fitted to extrapolate long-term OS, PFS, and treatment discontinuation data based on the L-MIND study [172]:

- The exponential distribution is a one-parameter function that is considered the simplest parametric model. In the exponential model, the hazard is modelled to be constant over time.
- The Weibull model is a function of two parameters: a shape and a scale. The exponential model is a particular case of the Weibull model where the scale of the parameter is set to be one. As a result, this model is more flexible than the exponential model and can better investigate complex survival patterns.
- The Gompertz distributions are also a function with two parameters: a shape and scale.
- The log-logistic and lognormal distributions share many similarities. They have a hazard function that can be non-monotonic with respect to time. Furthermore, due to their functional forms, the two models typically produce long tails in the survivor function. As a result, the clinical validity of log-logistic and lognormal survival models must be carefully assessed.
- The generalised gamma distribution is a flexible, three-parameter model. The Weibull, exponential, and lognormal distributions are special cases of the generalised gamma distribution. However, the long-term projections may be unduly influenced by the end of the KM curves (which are based on a small number of patients) due to the distribution's flexibility. Therefore, the clinical validity of the projected survival must be assessed, like the lognormal and log-logistic distributions.

The process of selecting a 'best-fitting' distribution involves considerations based on the observed data regarding goodness-of-fit and plausibility of results [172, 173].

In line with guidance from the DMC, the following criteria were considered when selecting the most appropriate parametric fits to the data where incomplete survival data were available [174]:

- Goodness-of-fit statistics: (Akaike Information Criterion [AIC] and Bayesian Information Criterion [BIC])
- Statistically, the best fit to the observed data is the curve with the lowest AIC and BIC
- Visual inspection of the fits in relation to the observed data
- Clinical validity of long-term projections (which was confirmed in discussions with clinical experts)
- Validity of projections in relation to external data (where available)

In addition, the following considerations were also used to determine the best fitting plot:

- Classifications of relative statistical fit compared to the model with the lowest AIC and BIC based on modified Burnham/Anderson and Kass/Raftery rules, similar to those adopted by the ERG in NICE TA612 and NICE TA640 [175-179]:
    - Modified Burnham/Anderson rules for AIC:
        - All models within 4 points of the model with the lowest AIC were classified as 'good' relative statistical fits
        - Models within 4 to 7 points were classified as 'neutral' relative statistical fits
        - Models within 7 to 10 points were considered 'inferior' relative statistical fits
        - Models with a >10-point difference were considered as 'poor' relative statistical fits
    - Modified Kass/Raftery rules for BIC:
        - Models within 10 points of the model with the lowest BIC were considered 'reasonable' relative statistical fits

        - Models with a >10-point difference were classified as 'poor' relative statistical fits
    - Compared to the original studies and the modified version of the rules adopted in NICE TA612 and NICE TA640, slight changes are used for the relative statistical fit classification terminology, as the AIC relative fit groups in Burnham/Anderson are not fully comprehensive (e.g., no term is available for 7- to 10-point differences in AIC) and BIC difference interpretations in Kass/Raftery + Raftery are inverted compared to the AIC classifications in Burnham/Anderson (i.e., in terms of evidence against the distribution rather than evidence for) [177, 179]
- Assessment of the plausibility of the hazard profiles (using smoothed hazard plots)

In cases where complete or close to complete data were available (e.g., time to treatment discontinuation data from RE-MIND2), KM data from the study were applied. In the absence of rules of thumb for corrected AIC (AICC), the modified Burnham/Anderson rules were assumed to be generalisable to AICC.

[redacted]

Figure 47. RE-MIND2 Survival Analysis Steps

Abbreviations: HR = hazard ratio; LEN = lenalidomide; TAFA = tafasitamab

[redacted]

Table 89. Median Treatment Duration for Comparators

Treatment	Median treatment duration (reported in study)	Median treatment duration (model cycles)	Reference
[redacted]			

Abbreviation: R-GemOx = rituximab + gemcitabine and oxaliplatin

Note: Where studies reported the median treatment duration in months, this data was used to calculate the number of cycles.

[redacted]

Figure 48. TTD Curves for the Comparators Using Median Treatment Durations

Abbreviation: TTD= Time to Treatment Discontinuation

[redacted]

Quality assessment and generalizability of estimates

The quality assessments of studies included in the data extraction form were conducted independently by two researchers. Quality assessment of economic evidence was performed using the checklist for assessing economic evaluations outlined in the CRD guidance, which was originally adapted from Drummond et al. 1996 (Table 93) [117, 201].

Table 93. Checklist for quality assessment of economic evaluations

Study design		Data collection		Results analysis and interpretation	
1	Was the research question stated?	8	Was/were the source(s) of effectiveness estimates used stated?	22	Was time horizon of cost and benefits stated?
2	Was the economic importance of the research question stated?	9	Were details of the design and results of the effectiveness study given (if based on a single study)?	23	Was the discount rate stated?
3	Was/were the viewpoint(s) of the analysis clearly stated and justified?	10	Were details of the methods of synthesis or meta-analysis of estimates given (if based on an overview of several effectiveness studies)?	24	Was the choice of rate justified?
4	Was a rationale reported for the choice of the alternative programmes or interventions compared?	11	Were the primary outcome measure(s) for the economic evaluation clearly stated?	25	Was an explanation given if cost or benefits were not discounted?
5	Were the alternatives being compared clearly described?	12	Were the methods used to value health states and other benefits stated?	26	Were the details of statistical test(s) and confidence intervals given for stochastic data?
6	Was the form of economic evaluation stated?	13	Were the details of the patients from whom valuations were obtained given?	27	Was the approach to sensitivity analysis described?
7	Was the choice of form of economic evaluation justified in relation to the questions addressed?	14	Were productivity changes (if included) reported separately?	28	Was the choice of variables for sensitivity analysis justified?
		15	Was the relevance of productivity changes to the study question discussed?	29	Were the ranges over which the parameters were varied stated?
		16	Were quantities of resources reported separately from their unit cost?	30	Were relevant alternatives compared? (ie, were appropriate comparisons made when conducting the incremental analysis?)
		17	Were the methods for the estimation of quantities and unit costs described?	31	Was an incremental analysis reported?
		18	Were currency and price data recorded?	32	Were major outcomes presented in a disaggregated as well as aggregated form?
		19	Were details of price adjustments for inflation or currency conversion given?	33	Was the answer to the study question given?
		20	Were details of any model used given?	34	Did conclusions follow from the data reported?
		21	Was there a justification for the choice of model used and the key parameters on which it was based?	35	Were conclusions accompanied by the appropriate caveats?

Study design	Data collection	Results analysis and interpretation	
		36	Were generalisability issues addressed?

[redacted]

Figure 51. Quality of evidence for economic studies

[redacted]

Table 94. Quality of evidence assessment of Lin et al. 2019

Study questions	Answer
[redacted]	

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[redacted]

Unpublished data

N/A

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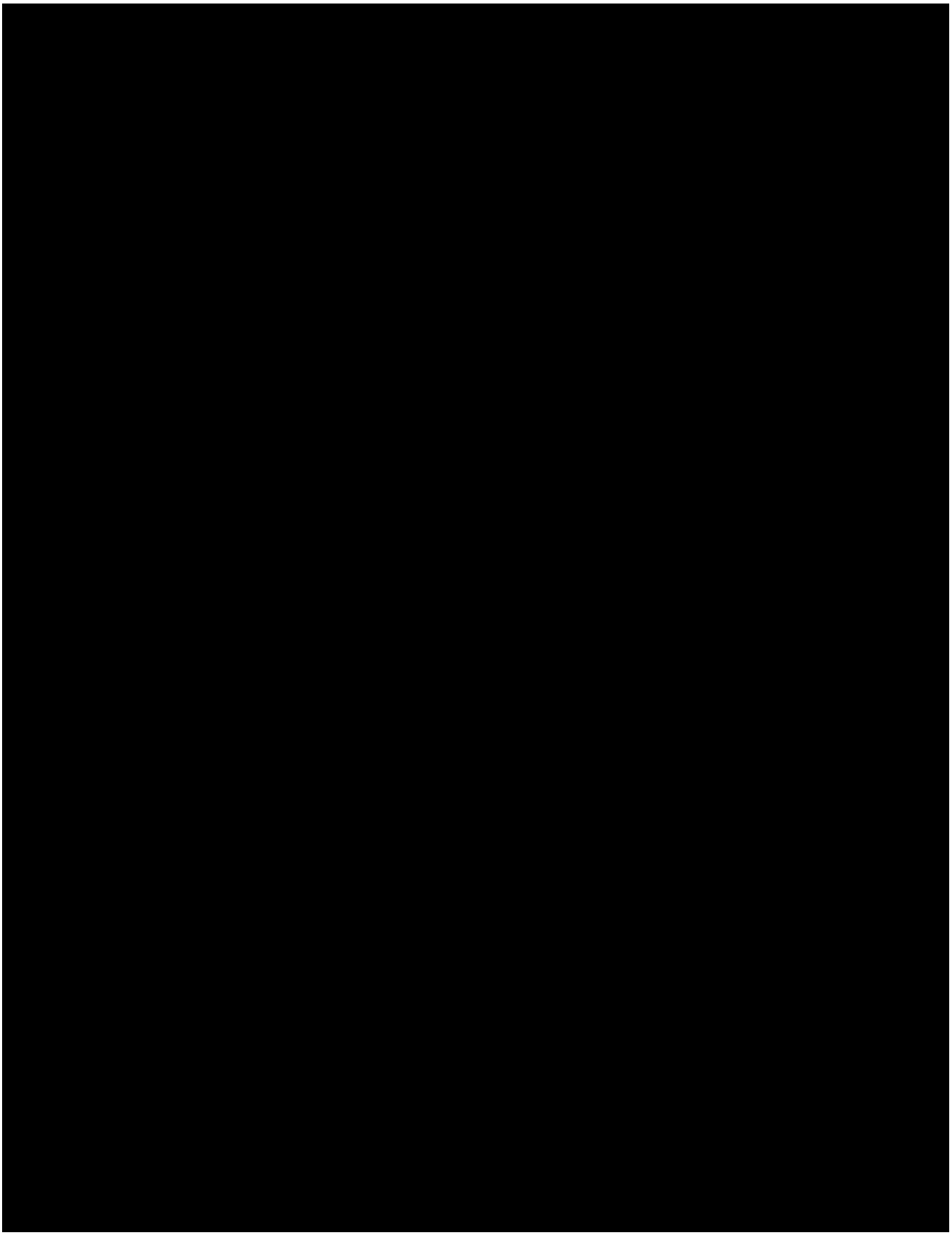
Appendix I – Probabilistic sensitivity analyses (PSA) inputs



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