Medicinrådet

Bilag til Medicinrådets anbefaling vedrørende amivantamab til behandling af EGFR exon 20ins-positiv ikke-småcellet lungekræft

Vers. 1.0

Bilagsoversigt

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

Janssen-Cilag A/S

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20. marts 2023

Til Medicinrådet

Janssen-Cilags tilbagemelding på Medicinrådets anbefaling vedr. amivantamab til behandling af EGFR exon 20ins-positiv ikke-småcellet lungekræft

Janssen-Cilag bemærker at Medicinrådets sekretariat i deres vurdering anerkender en QALY-gevinst ved brug af Rybrevant frem for nuværende standardbehandling (docetaxel og permetrexed) i Danmark.

Derudover bemærker vi at fagudvalget vurderer at Rybrevant er bedre end en bred gruppe af komparatorer (physician's choice) der inkluderer potente behandlinger som immunterapi og tyrosin kinase inhibitorer (TKI)

Valg af komparator
Janssen-Cilag mener dog, at processen vedr. valg af komparator har været kritisabel. Vi har været meget bevidste om, at standardbehandlingen for patientgruppen ikke er velbeskrevet, og derfor har vi forsøgt at få fagudvalget til at mødes med os til et indledende dialogmøde. Det blev afvist, og Medicinrådets sekretariat sendte i stedet for følgende feedback fra fagudvalget:

"Vi har været i dialog med fagudvalget omkring fordelinger af behandlinger i komparatorarmen på baggrund af dansk klinisk praksis. Og her er meldingen, at patienter bliver behandlet iht. alm. retningslinjer for behandling af NSCLC. Rækkefølgen og hvilke præparater patienterne får er bl.a. afhængig af PD-L1-status, sygdomsudbredning og almen tilstand. Nogle gange bliver der forsøgt med osimertinib som 2. linje men det kan også være yderligere kemoterapi eller immunterapi."

På den baggrund valgte vi at basere vores base case på en antagelse om at den relevante komparator var en blanding af tilgængelige behandlinger (physician's choice), men Medicinrådets sekretariat og fagudvalget har i processen ændret komparator til permetrexed/docetaxel. Janssen-Cilag er af den opfattelse at et dialogmøde med fagudvalget kunne have afklaret den relevante komparator tidligt i processen og dermed gjort det muligt for os at udarbejde en mere relevant ansøgning

Janssen-Cilag takker derudover for en god dialog i processen og ser frem til afgørelsen d. 26. april.

Med venlig hilsen
Jeppe S. Christensen
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21.03.2023

DBS/BMC

Forhandlingsnotat

Dato for behandling i Medicinrådet	26.04.2023
Leverandør	Janssen-Cilag
Lægemiddel	Rybrevant (amivantamab)
Ansøgt indikation	Behandling af EGFR exon 20ins-positiv ikke-småcellet lungekræft
Nyt lægemiddel / indikationsudvidelse	Nyt lægemiddel

Prisinformation og aftaleforhold

Amgros har forhandlet følgende pris på Rybrevant (amivantamab):

Tabel 1: Forhandlingsresultat

Lægemiddel	Styrke	Pakningsstørrelse	AIP (DKK)	Forhandlet SAIP (DKK)	Rabatprocent ift. AIP
Rybrevant	350 mg	1 stk.	9.798,48	[redacted]	[redacted]

Amgros har indgået en aftale med leverandøren som gælder fra 03.04.2023 og 4 år frem. Leverandøren har mulighed for at sætte prisen ned i hele aftaleperioden. Prisen er ikke betinget af Medicinrådets anbefaling.

[redacted]

Tabel 2: Forhandlingsresultat - betinget af en anbefaling

Lægemiddel	Styrke	Pakningsstørrelse	AIP (DKK)	Forhandlet SAIP (DKK) Pr.3.4.23	Ekstra Forhandlet SAIP (DKK)	Rabatprocent ift. AIP
Rybrevant	350 mg	1 stk.	9.798,48	[redacted]	[redacted]	[redacted]

Prisen er betinget af Medicinrådets anbefaling.

Informationer fra forhandlingen

[redacted].

Konkurrencesituationen

Der er i dag ingen andre behandlinger til denne patientpopulation.

[redacted]

Tabel 3: Sammenligning af lægemiddeludgifter

Lægemiddel	Styrke	Dosering	Pris pr. pakning (SAIP, DKK)	Antal pakninger pr. år	Lægemiddeludgift Betinget pris ved anbefaling pr. år (SAIP, DKK)
Rybrevant	350 mg	1050	[redacted]	84	[redacted]
Rybrevant	350mg	1400	[redacted]	112	[redacted]

Status fra andre lande

Land	Status	Kommentar	Link
Norge	Under evaluering	[redacted]	
England	Ikke anbefalet		1 Recommendations| Amivantamab for treating EGFR exon 20 insertion mutation-positive advanced non-small-cell lung cancer after platinum-based chemotherapy | Guidance | NICE

Konklusion

Amgros vurderer, at leverandøren på nuværende tidspunkt **ikke** kan give en bedre pris.

[redacted]

Application for the assessment of Rybrevant® (amivantamab) for the treatment of adult patients with locally advanced or metastatic NSCLC with EGFR Exon 20ins whose disease has progressed on or after platinum-based chemotherapy

Reimbursement dossier, version 2.0

This document has been adapted by Quantify Research, based on Janssen Global Value Dossier version 1 for Rybrevant® (amivantamab), originally produced July 14, 2021, by Janssen. The information has both been condensed and complemented with new information to match a Danish setting.

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1. Basic information

Contact information	
Name	*Jeppe Sadjadieh Christensen*
Title	*Country HEMAR manager*
Responsibility	*Market Access/negotiation*
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Overview of the pharmaceutical	
Proprietary name	Rybrevant®
Generic name	Amivantamab
Marketing authorization holder in Denmark	Janssen-Cilag A/S
ATC code	L01FX18
Pharmacotherapeutic group	Antineoplastic
Active substance(s)	Amivantamab
Pharmaceutical form(s)	Concentrate for solution for infusion
Mechanism of action	Amivantamab exerts anti-tumour activity through three mechanisms of action inhibiting key tumour growth and survival regulatory pathways. One arm of this bispecific antibody binds to the extracellular domain of the epidermal growth factor receptor (EGFR) and the other binds to the extracellular domain of the tyrosine-protein kinase mesenchymal epithelial transition (MET) receptor. This blocks the binding of both epidermal growth factor (EGF) and hepatocyte growth factor (HGF) to their receptors. Amivantamab therefore inhibits ligand-induced receptor activation of EGFR and MET and their downstream signalling through proteins such as extracellular signal-regulated kinase (ERK) and Akt, which are components of key pro-growth and pro-survival regulatory pathways [1]. Amivantamab also induces the degradation of EGF and MET receptors, broadening its impact to include ligand-independent receptor-driven disease. Finally, due to reduced fucosylation, amivantamab has enhanced capacity to engage immune effector cells to eliminate antigen-expressing tumour cells through antibody-dependent cellular cytotoxicity. It is thought that the EGFR and MET pathways compensate for each other in situations where one pathway is inhibited, leading to the so called 'kinase switch' drug resistance. Thus, simultaneous inhibition of both EGFR and MET may improve overall treatment efficacy by limiting the compensatory pathway activation [1]. Amivantamab monotherapy has demonstrated clinical activity against emergence of EGFR (e.g., C797S) and MET (e.g., amplification) tyrosine kinase inhibitor (TKI) resistance mutations post-third generation TKI. This unique mechanism of action of amivantamab also provides opportunity to improve clinical outcomes through combination with EGFR TKIs, which target intracellular domains (e.g., lazertinib) [1].
Dosage regimen	Amivantamab is administered intravenously once weekly for 4 weeks, then every 2 weeks thereafter until disease progression or unacceptable toxicity. The dosing of amivantamab monotherapy is weight-based: • 1,050 mg for patients with body weight <80 kg • 1,400 mg for patients with body weight ≥80 kg

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Overview of the pharmaceutical	
Therapeutic indication relevant for assessment (as defined by the European Medicines Agency, EMA)	Amivantamab has received a conditional marketing authorisation from the European Medicines Agency (EMA), for the treatment of adult patients with advanced non-small cell lung cancer (NSCLC) with activating epidermal growth factor receptor (EGFR) Exon 20 insertion (Exon 20ins) mutations, after failure of platinum-based therapy [2].
Other approved therapeutic indications	No
Will dispensing be restricted to hospitals?	Yes
Combination therapy and/or co-medication	N/A
Packaging – types, sizes/number of units, and concentrations	Single vial pack, 350 mg/7 mL (50 mg/mL)
Orphan drug designation	No

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2. Abbreviations

Abbreviation	Definition
1L	First line
2L	Second line
AE	Adverse event
AIC	Akaike information criteria
ATE	Average treatment effect
ATO	Average Treatment Effect for the Overlap Population
ATT	Average Treatment effect on the Treated
AUC	Area under the curve
BIC	Bayesian information criteria
BICR	Blinded independent central review
BMI	Body mass index
BSA	Body surface area
BSC	Best supportive care
CBR	Clinical benefit rate
CEM	Cost effectiveness model
CRISP	Clinical Research platform Into molecular testing, treatment and outcome registry of non-small cell lung carcinoma Patients
CT	Computed tomography
ctDNA	Circulating tumour DNA
DCR	Disease control rate
DKK	Danish krone
DLT	Dose limiting toxicity
DMC	Danish medicines council
DOR	Duration of response
DRG	Diagnosis-related group
DSA	Deterministic sensitivity analysis
ECOG PS	Eastern cooperative oncology group performance status
EGFR	Epidermal growth factor receptor
EGFRm	Epidermal growth factor receptor mutated
EMA	European medicines agency
EMEA	Europe, Middle East and Africa
ESME	Epidemiological Strategy and Medical Economics
ESMO	European Society for Medical Oncology
EU	European union
Exon 20ins	Exon 20 insertion
HR	Hazard ratio
HRQoL	Health related quality of life
HTA	Health technology assessment
ICER	Incremental cost-effectiveness ratio
INV	Investigator-assessed

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IO	Immuno-oncology drug
IPD	Individual patient data
IPW	Inverse probability weighting
IRC	Independent review committee
IRR	Infusion related reaction
ITC	Indirect treatment comparison
IV	Intravenous
K-M	Kaplan-meier
LVEF	Left ventricular ejection fraction
LY	Life years
LYG	Life year gained
MAD	Maximum administered dose
mDOR	Median duration of response
MET	Mesenchymal-epithelial transition
mOS	Median overall survival
mPFS	Median progression free survival
MTD	Maximum tolerated dose
NCCN	National comprehensive cancer network
NGS	Next-generation sequencing
nNGM	National Network Genomic Medicine
NSCLC	Non-small cell lung cancer
ORR	Overall response rate
OS	Overall survival
PD-1	Programmed cell death protein 1
PD-L1	Programmed death-ligand 1
PF	Progression-free
PFS	Progression free survival
PHE	Public health england
PP	Post-progression
PR	Partial response
PRO	Patient reported outcomes
PSA	Probabilistic sensitivity analysis
QALY	Quality-adjusted life years
RCT	Randomised controlled trials
RECIST	Response Criteria in Solid Tumours Version 1.1
RP2D	Recommended phase II dose
RWD	Real world data
RWE	Real world evidence
SC	Subcutaneous
SLR	Systematic literature review
SmPC	Summary of product characteristics
SoC	Standard of care
TEAE	Treatment emergent adverse event
TKI	Tyrosine kinase inhibitor

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TLR	Targeted literature review
ToT	Time-on-treatment
TPS	Tumour proportion score
TTNT	Time to next treatment
TTNT	Time-to-next treatment
UK	United kingdom
US	United states

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3. Tables and Figures

Tables

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Figures

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4. Summary

Non-small cell lung cancer (NSCLC) is the most common type of lung cancer (85% of all cases) [3, 4], making it one of the leading causes of death worldwide [5]. While epidermal growth factor receptor (EGFR) mutation is the most frequent actionable driver pathway event in NSCLC [6, 7], EGFR Exon 20 insertion (Exon 20ins) mutations are ultra-rare and account for about 1% to 12% of all EGFR-mutated (EGFRm) NSCLC tumours, and only 0.1% to 4% of NSCLC cases overall [8].

The yearly incidence of Exon 20ins in Denmark is estimated in the range of 10-16 patients [9]. According to clinicians, approximately half of these patients are estimated to fail first line (1L) treatment (6-8 patients) and therefore eligible for and expected to be treated with amivantamab [10]. Patients with EGFR Exon 20ins have a poorer prognosis than patients with common EGFR mutations in the real world setting, with a 75% of increased risk of death and a 93% increased risk of disease progression or death [11]. Currently, amivantamab is the only targeted therapy approved for EGFR Exon 20ins-positive NSCLC in the EU [2].

Rybrevant® (amivantamab) has received a conditional marketing authorisation from EMA in December 2021, for the treatment of adult patients with advanced NSCLC with activating EGFR Exon 20ins mutations, after failure of platinum-based therapy [2]. It is a first-in-class EGFR mesenchymal-epithelial transition (EGFR-MET) bispecific antibody with an immune cell-directing activity that targets activating and resistant EGFR mutations and MET mutations and amplifications [12]. Amivantamab's efficacy and safety has been investigated in a phase I clinical trial (CHRYSALIS; NCT02609776) [1, 13] in patients with advanced NSCLC. It demonstrated good efficacy in patients who had received prior platinum-based chemotherapy [14] and a favourable safety profile, characterised by low rates of treatment-related discontinuations and mostly low grade toxicities [15, 16].

The population of NSCLC patients with EGFR Exon 20ins is not well recognised and no specific treatment recommendations have been made by European (ESMO) or US (NCCN) clinical guidelines [17, 18]. Similarly, there are no specific treatment recommendations for patients with Exon 20ins in the Danish clinical guidelines, in which only the broader group of EGFR mutations is addressed [19]. Clinical practice (through interviews with clinicians [9]) describes that it is a common understanding that patients with Exon 20ins mutations (unlike other EGFR mutations) do not respond to tyrosine kinase inhibitors (TKIs), the current standard treatment intended for patients with EGFR. For these patients, immunotherapy or immunochemotherapy is offered as a 1L treatment [9] and as there is no clear standard of care for second line (2L).

In lack of specific recommendations for patients with Exon 20ins, clinical practice shows that physicians are left to resort to offer treatments that do not work or have limited effect on these patients, which underlines the urgent unmet need for targeted, more effective, and safe therapies to prolong progression free and overall survival and improve quality of life in these patients. As the benefits of 1L treatments for advanced NSCLC and EGFR Exon 20ins are modest at best, the high unmet medical need is even further pronounced in patients whose disease has progressed during or after the front-line treatment [9]. In a recent published consensus paper from ESMO experts agreed on the importance of considering newly approved and emerging targeted therapies for this specific patient population after failed platinum chemotherapy [43]. According to the same experts, new therapeutic options as amivantamab accentuate the need for adequate testing for EGFR Exon 20ins [43].

Based on the unspecific treatment guidelines and non-mutation specific clinical practice in Denmark, the most relevant comparator is a best supportive care (BSC) mix of all available treatment options, including immunotherapy, non-platinum based chemotherapy and TKIs. Since CHRYSALIS is a single arm trial, indirect treatment comparison with BSC in platinum pre-treated patients with advanced NSCLC and EGFR Exon 20ins was made using real world data (RWD) from US and various European countries. The analysis generated an external control arm based on the real world datasets, and the sources where analysed both separately and as a pooled dataset. In summary, treatment with amivantamab in the CHRYSALIS clinical trial substantially improved clinical outcomes for four key endpoints (ORR, PFS, OS and TTNT) compared with real world therapies, such as BSC mix of treatment classes [10, 20].

To show cost-effectiveness of amivantamab, a health economic model was developed in Microsoft Excel® where amivantamab was compared to BSC (including immunotherapy, non-platinum based chemotherapy and TKI) in the second line, and later line setting, for the target population. The model is using a partitioned survival approach to track a cohort's costs and health outcomes over time from the beginning of current-line treatment until death. The

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model includes a progression-free state, a post-progression state, and death. This model was selected based on it being a widely accepted approach that was used by previous cost effectiveness models (CEMs) in metastatic NSCLC with EGFR. The analysis uses a limited societal perspective in line with DMC guidelines, which includes all relevant costs such as direct health care costs, as well as transportation costs and patient time costs. The time horizon chosen in the base case was 15 years which sufficiently captured the lifetime of the targeted population, given its poor prognosis. Costs and health outcomes where discounted at 3.5 %, in line with the Danish Ministry of Finance's current socio-economic discount rate for this time horizon. The model inputs were based on Danish sources where possible. Efficacy inputs for amivantamab, including OS and PFS were derived from the CHRYSALIS trial. Given that the trial was a single-arm trial, synthetic control methods were used to determine efficacy inputs for the comparator arm, where the pooled EU-US RWD was utilized.

The base case results show that treatment with amivantamab provided a gain of 0.76 life years (LY) and 0.47 quality-adjusted life years (QALY) over the lifetime horizon of 15 years, when compared to BSC (as a mix of available treatment options). Treatment with amivantamab was also associated with higher costs, appr. 600,000 DKK more than BSC which resulted in an incremental cost-effectiveness ratio (ICER) of 1,270,000 DKK. However, the ICER does vary dependent on which specific treatment the patient will receive. The greatest cost-effectiveness ratio is demonstrated when amivantamab is compared to immunotherapy only (with an ICER of appr. 800,000 DKK). The uncertainty of the model results was assessed with deterministic sensitivity analyses (DSA) and a probabilistic sensitivity analysis (PSA) which provided robust results.

In the Excel® model, a budget impact analysis is also presented (and linked to the cost inputs of the CEM in line with DMC guidelines) where costs of introducing amivantamab are shown over a five-year time horizon and compared to a scenario where amivantamab is not introduced. As mentioned above, the number of patients eligible for, and expected to be treated with amivantamab is NSCLC patients with EGFR and Exon 20ins who failed 1L treatment with platinum-based chemotherapy. This corresponds to approx. 6-8 patients in Denmark; therefore, the budget impact analysis is presented based on 8 patients which over the time horizon to a higher extent receive treatment with amivantamab. The results show that the introduction of amivantamab leads to a budget impact of 4.4 million DKK per year (in year 5), and a cumulative budget impact of 18.9 million DKK over a five-year time horizon.

This dossier aims to demonstrate the clinical and health economic evaluation of amivantamab for patients with NSCLC with EGFR and Exon 20ins in 2L, an ultra-rare specific mutation with few patients in Denmark very much in need of more effective and safe therapies to prolong progression free and overall survival and improve quality of life.

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

5.1 The medical condition and patient population

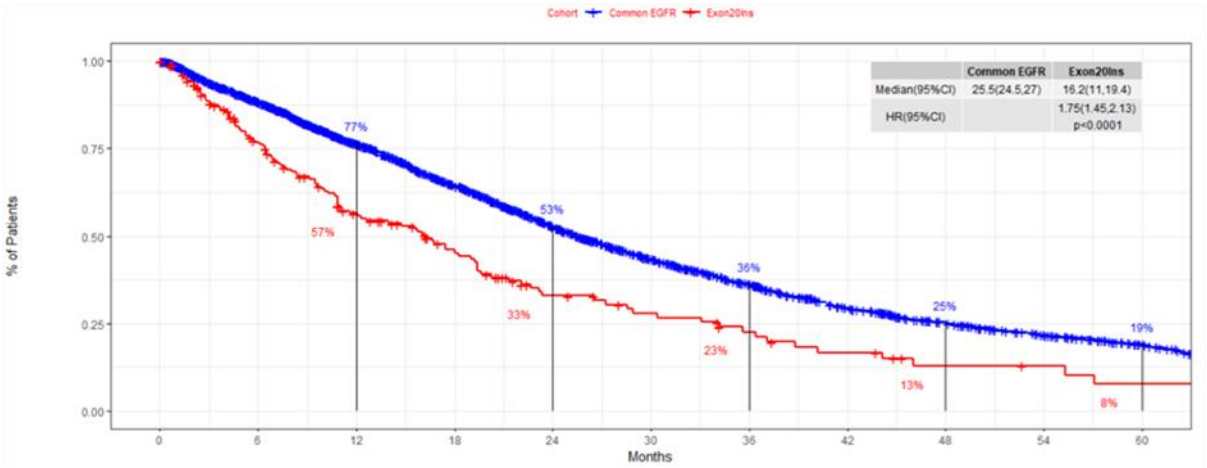
5.1.1 Non-small cell lung cancer (NSCLC) with epidermal growth factor receptor (EGFR) mutation and Exon 20 insertions

Lung cancer is a leading cause of death worldwide [5]. In 2018, 1.8 million died of lung cancer making up 18.4% of all cancer deaths [21]. Non-small cell lung cancer (NSCLC) is the most common type and constitutes 85% of lung cancer cases [3, 4]. Approximately 60% of all NSCLC have metastatic disease at the time of diagnosis [5, 22, 23].

The five-year overall survival rate for NSCLC at all stages is 17% and ranges from 68% for patients with early-stage NSCLC (stage IB), to 15% for patients with stage III NSCLC, and 0% to 10% for patients with metastatic NSCLC (stages IVA to IVB) [22, 24]. Driver mutations are typically somatic mutations that initiate growth in cells driving cell proliferation. Epidermal growth factor receptor (EGFR) mutation is the most common actionable driver pathway event in NSCLC, making up 14% of NSCLC cases in Europe [6, 7]. Mutations in the EGFR gene typically occur in Exons 18 to 21, with a majority of these mutations (90%) comprising Exon 19 deletions and L858R point mutations in Exon 21 [3] which are referred to as classical or sensitising EGFR mutations [4]. The uncommon EGFR mutations, including Exon 20ins mutations, make up the remaining 10% [25, 26]. EGFR Exon 20ins is a heterogenous and rare mutation, which account for about 1% to 12% of all EGFR-mutated (EGFRm) NSCLC tumours and for 0.1% to 4% of NSCLC cases overall [8].

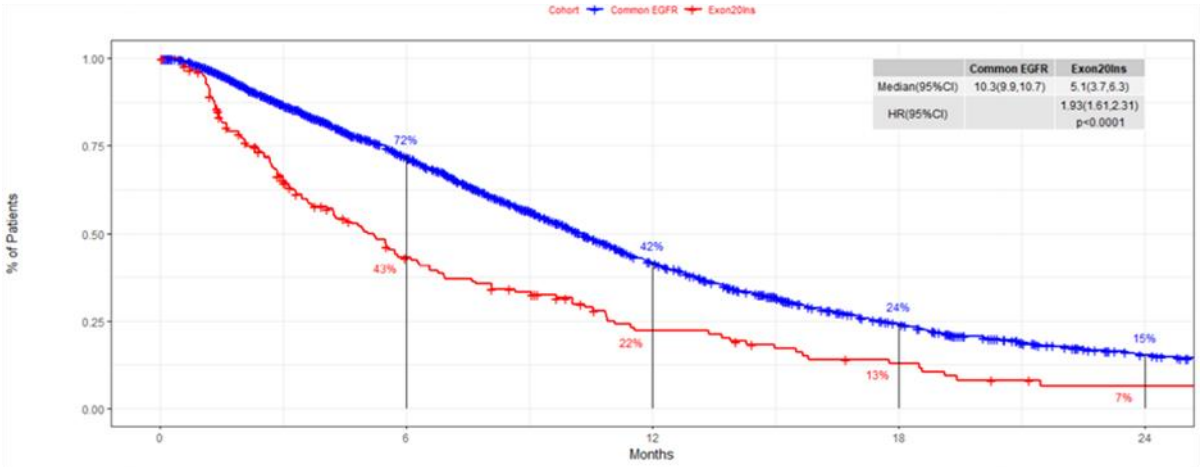
Patients with EGFR Exon 20ins have a poorer prognosis than patients with common EGFR mutations in the real world setting, with a 75% increased risk of death and a 93% increased risk of disease progression or death [11]. Unlike classical EGFR mutation (Exon 19 deletion and Exon 21 L858R), Exon 20ins has been associated with resistance to current treatment standard (TKIs) [4, 25-27], with a ~170% increased risk of disease progression or death [11].

Figure 1. Real world OS data for patients with Exon 20ins (n=181) vs. common EGFR mutations (2,833) [28]



CI = confidence interval; EGFR = epidermal growth factor receptor; Exon 20ins = Exon 20 insertions; HR = hazard ratio; OS = overall survival

Figure 2. Real world PFS data for patients with Exon 20ins (n=181) vs. common EGFR mutations (n=2,833) [29]



CI = confidence interval; EGFR = epidermal growth factor receptor; Exon 20ins = Exon 20 insertions; HR = hazard ratio; PFS = progression free survival

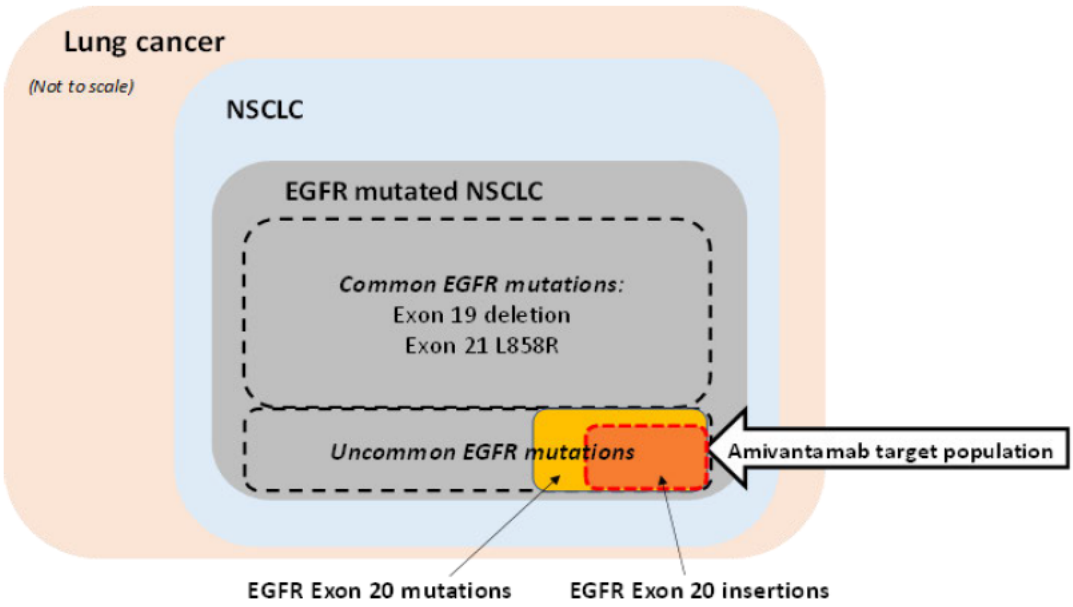
5.1.2 Patient population

The patient population of relevance to this assessment is patients with metastatic or surgically unresectable NSCLC, whose disease has progressed on or after platinum-based double chemotherapy and whose tumours are characterized by EGFR Exon 20ins.

According to the Danish Lung Cancer Group [30], 4,820 people were diagnosed with lung cancer in Denmark in 2018. Approximately 81% (3,880) being NSCLC [30]. Data shows that 58% of the NSCLC patients had adenocarcinoma (non-squamous NSCLC), 24% had squamous NSCLC and the rest of the cases were attributed to other types of NSCLC. With an EFGR testing coverage of 85% among adenocarcinoma patients (48% coverage across all lung cancer patients), 180 patients with EFGR mutations were identified in 2018 (approx. 9.3% of the tested adenocarcinoma patients had EFGR mutations) [30].

Janssen's internal estimations through interviews with key opinion leaders from the Nordics, show a yearly incidence of Exon 20ins within the range of 10-16 patients in Denmark (Table 1 and Figure 3) [9]. These patients have no other approved targeted therapies and typically treated with platinum based chemotherapy in 1L in current clinical practice in [9], which is associated with only a modest increase in survival. After treatment failure in the 1L setting, there is no clear standard of care (SoC) for 2L therapy. Based on Danish clinicians' input and estimations from other countries, more than half of these patients will fail 1L treatment and proceed to 2L treatment [10]. These patients, approximately 6-8 in Denmark, will be eligible for and expected to be treated with amivantamab (Figure 3 and Table 3).

Figure 3. Amivantamab target population



EGFR = epidermal growth factor receptor; NSCLC = non-small cell lung cancer

Table 1. Number of patients in Denmark

Number of patients in Denmark	NSCLC	Non-squamous	EGFR tested	EGFRm (all stages)	Exon 20ins
Number of patients in 2018	3,880	2,272	1928	180	18-30

NSCLC = non-small cell lung cancer; EGFRm = epidermal growth factor receptor mutation; Exon 20ins = Exon 20 insertions

Table 2. Incidence and prevalence in the past 5 years

Year	2017	2018	2019	2020	2021
Incidence in Denmark	10-16	10-16	10-16	10-16	10-16
Prevalence in Denmark					
Global prevalence *	Approx. 5-10 % of all EGFR patents				

* For small patient groups, also describe the worldwide prevalence

[redacted]

The clinical characteristics of patients with NSCLC and EGFR Exon 20ins are similar to patients with classical EGFR mutations and are more commonly seen in women, Asian patients and never-smokers compared with EGFR wildtype [4, 26, 31]. EGFR Exon 20ins is more commonly observed [4] in the following comparisons:

- Never-smokers (67% of Exon 20ins vs. 26% of other uncommon EGFR mutation [p<0.01])[32]
- Older patients (p=0.01 vs. Exon 19 deletion/L858R;[27] p=0.04 vs. sensitising EGFR mutations)[33]
- Patients with adenocarcinoma histology (100% adenocarcinoma for Exon 20ins vs. 76% of G719X, 82% of L861Q/P, 89% of L858R and 93% of Exon 19 deletion [p value not reported])[34]

In the clinical study CHRYSALIS, the median age for patients with EGFR Exon 20ins and prior chemotherapy was 62 years [35]. The majority of patients had a baseline body weight of <80 kg (74.1%) [35], and there were more females than males (59.3% vs. 40.7%). Most patients were diagnosed with Stage IV disease (87.7%) and adenocarcinoma

(96%), almost a quarter of patients had a prior history of brain metastases (22.2%), 36% had an ECOG performance status score of 0.

The dosing of amivantamab monotherapy is weight-based:

- 1,050 mg for patients with body weight <80 kg
- 1,400 mg for patients with body weight ≥80 kg

In the CHRYSALIS trial, mean weight was 64.8 kg and 74.1% of patients has a weight of less than 80 kg [36].

5.2 Current treatment options and choice of comparator(s)

5.2.1 Current treatment options in Denmark

The population of patients with NSCLC who have EGFR Exon 20ins is not well recognised and no specific treatment recommendations have been made by European (ESMO) or US (NCCN) clinical guidelines [17, 18]. Currently, no other targeted therapies are approved for EGFR Exon 20ins-positive NSCLC in the EU than amivantamab (granted conditional approval in December 2021). Similarly, there are no specific treatment recommendations for patients with Exon 20ins in the Danish clinical guidelines [19].

The clinical guidelines prepared by the Danish Lung Cancer Group (last updated in 2021) recommend TKIs (osimertinib as a 1L treatment for NSCLC patients with EGFR-activating mutations [19]. As an alternative, erlotinib, gefitinib or afatinib can be considered [19]. Osimertinib is a first line treatment, but for patients who have not received osimertinib previously, it is an obvious second line choice after progression on a first- or second-generation TKI [19]. For 2L options the guidelines recommend second-line treatment with chemotherapy for patients who progress on first-line osimertinib [19]. This is usually platinum containing chemotherapy but there is lack of data on immunotherapy as the studies (KN-024 and KN-189) that led to the approval of the respective pembrolizumab monotherapy or combination therapy with platinum/pemetrexed/pembrolizumab excluded patients with activating EGFR mutations [19]. Additional targeted treatment can be given where there is clinical documentation [19].

The Danish Medicines Council (DMC) have also recommendations (updated in May 2022) for patients with EGFR activating mutations, where osimertinib is recommended as 1L treatment (in approximately 95% of patients). For patients who cannot be treated with osimertinib, DMC recommends the older TKIs; afatinib, gefitinib and erlotinib [37]. In 2L setting, treatment recommendations are based on PD-L1 expressions and tumour proportion score (TPS). These include immunotherapy (TPS > 50%), chemotherapy (TPS < 1%), and combination of immunochemotherapy (TPS > 1 - 50%) [37].

Clinical practice (through interviews with clinicians) describe that it is a common understanding that patients with Exon 20ins mutations do not respond to TKIs. For these patients, chemotherapy is offered [9]. As there are no national treatment recommendations for advanced or metastatic NSCLC patients with Exon 20ins, the treatment of these patients in clinical practice is somewhat unclear and needs to be investigated further. A summary of the treatment algorithm in Denmark is provided in Figure 4.

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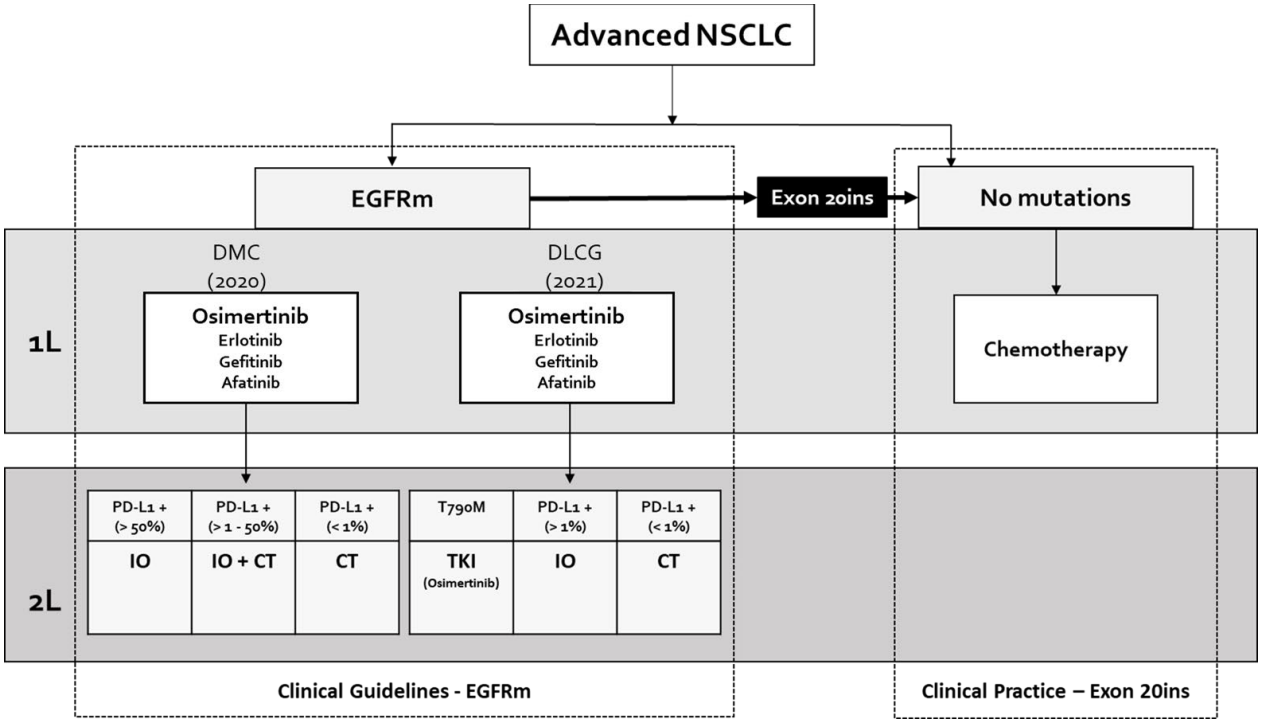
Figure 4. Advanced NSCLC treatment algorithm



CT = Chemotherapy; DLCG = Danish Lung Cancer Group; DMC = Danish Medicines Council; EGFRm = epidermal growth factor receptor mutations; Exon 20ins = Exon 20 insertions; IO = immuno-oncology agent; NSCLC = non-small cell lung cancer; PD-L1 = Programmed death-ligand 1; TKI = tyrosine kinase inhibitor

5.2.2 Unmet need

Patients with EGFR Exon 20ins have a poorer prognosis than patients with common EGFR mutations in the real world setting, with a 75% increased risk of death and 93% increased risk of disease progression or death [11]. Unlike classic EGFR mutation (Exon 19 deletion and Exon 21 L858R), Exon 20ins has been associated with resistance to current treatment standard (TKIs) [4, 25-27], with a ~170% increased risk of disease progression or death [11].

The humanistic burden of NSCLC is substantial [38]. Patients with NSCLC experience reduced health related quality of life (HRQoL) compared with the general population with greater impairments observed in patients receiving later lines of therapy and in patients with late-stage or progressive disease [38]. Preliminary evidence suggests that patients with EGFR Exon 20ins have poor HRQoL due to frequent disease-related symptoms such as fatigue, pain, shortness of breath and cough and negative impacts on daily activities including self-care, social activities, and family life [8, 39]. A patient reported outcomes (PRO) study showed that patients feel sadness, anxiety and fear as a result of their disease as well as reduced ability for physical activities such as walking [40].

Even when considering all currently available treatment options (chemotherapy, TKIs and immuno-oncology drugs (I-Os)), treatment outcomes in this patient population are still poor: in the second- and subsequent-line setting, currently available therapies provide an overall survival (OS) of 8 to 17.1 months and a progression free survival (PFS) of 1.9 to 4.8 months [8]. Outcomes with I-Os appear to be among the lowest in this population [27, 41, 42].

5.2.3 Positioning of Rybrevant® (amivantamab)

Rybrevant® (amivantamab) is intended to be used as monotherapy for the treatment of patients with advanced NSCLC and EGFR Exon 20ins mutations, who have progressed on or after platinum-based doublet chemotherapy. The target population for amivantamab is presented in Figure 3. Amivantamab has received a conditional marketing authorisation from EMA in December 2021, for the treatment of adult patients with advanced NSCLC with activating EGFR Exon 20ins mutations, after failure of platinum-based therapy [2].

Currently, there are no specific recommendations for patients with Exon 20ins and clinical practice shows that physicians are left to resort to offer treatments that do not work or have limited effect on these patients. Therefore, there is a clear lack of effective treatments for patients with advanced NSCLC and EGFR Exon 20ins, and an urgent unmet need for targeted, more effective, and safe therapies to prolong progression free and overall survival and improve quality of life in these patients. This has been highlighted during a recent consensus building process organized by ESMO, where experts agreed on the importance of considering newly approved and emerging targeted therapies for this specific patient population after failed platinum chemotherapy [43]. According to the same experts, new therapeutic options as amivantamab accentuate the need for adequate testing for EGFR Exon 20ins [43].

As the benefits of 1L treatments for advanced NSCLC and EGFR Exon 20ins are modest at best, the high unmet medical need is even further pronounced in patients whose disease has progressed during or after the front-line treatment. As clinical practice shows, clinicians lack effective treatment options and are left to resort to a mix of all available alternatives for the treatment of this specific patient population [9].

Amivantamab provides good efficacy and significantly improved tolerability compared with currently available therapies for this patient population and is now the first approved targeted therapy for patients with metastatic or surgically unresectable NSCLC, whose disease have progressed on or after platinum-based double chemotherapy and whose tumours are characterized by EGFR Exon 20ins mutations [44].

5.2.4 Choice of comparator(s)

As there are no Danish treatment recommendations and a clear lack of treatment options for patients with advanced NSCLC and EGFR Exon 20ins, the treatment of these patients remains somewhat unclear. Although clinical guidelines in Denmark [19], imply that patients with Exon 20ins should be treated first with TKIs as other EGFRm, in clinical practice, as shown earlier these patients are treated as if they have no mutations and offered chemotherapy [9].

In case of treatment failure in the 1L setting, there is no clear SoC for 2L therapy. According to key opinion leaders from the Nordics, a mix of available treatment alternatives will most likely be offered for patients who failed platinum-based therapies [9]. These include IO agents (such as nivolumab and pembrolizumab), immunochemotherapies (such as pembrolizumab + docetaxel/pemetrexed), non-platinum-based chemotherapies (such as docetaxel and pemetrexed) and TKIs (such as osimertinib). Despite the known resistance [42], over 20% of these patients are still treated with TKIs across all lines of therapy [4, 25-27].

Based on clinical practice and the treatment guidelines in Denmark, the most relevant comparators to amivantamab are therefore a best supportive care (BSC) mix of all available treatment options. Since the trial for amivantamab is a single arm trial, comparison must be made indirectly. RWD where therefore collected, not only from the US, but also from European countries such as Germany, France and the UK. This data is applied in the health economic analysis to generate a cost per life year (LY) and per quality adjusted life years (QALY) gained.

5.2.5 Description of the comparator(s)

In a response email from DMC regarding comparator (please see *Appendix K Email from DMC regarding choice of comparator*) DMC states that the main challenge of selecting a relevant comparator is due to lack of specific guidelines. Therefore, post-platinum treated patients with NSCLC and Exon 20ins are offered a variety of available treatments despite known resistance and limited efficacy. As there is no consensus on how these patients should be treated according to the guidelines, nor clinical practice, the most relevant comparator instead of single treatment, is a BSC mix of treatment classes which include immunotherapies, non-platinum chemotherapies and TKIs. Presented below are the product characteristics of the most commonly used treatments per class in the Danish setting, which were also highlighted by the DMC in response to the request for assessment. These include docetaxel (Table 4), pemetrexed (Table 5), pembrolizumab (Table 6) and osimertinib (Table 7).

Table 4. Docetaxel product characteristics

Comparator: Docetaxel	
Generic name, ATC code	Docetaxel, L01CD02
Mechanism of action	Docetaxel is an antineoplastic agent which acts by promoting the assembly of tubulin into stable microtubules and inhibits their disassembly which leads to a marked decrease of free tubulin. The binding of docetaxel to microtubules does

Comparator: Docetaxel	
	not alter the number of protofilaments. Docetaxel has been shown in vitro to disrupt the microtubular network in cells which is essential for vital mitotic and interphase cellular functions [45].
Pharmaceutical form	Concentrate and solvent for solution for infusion [45]
Posology	For treatment after failure of prior platinum-based chemotherapy, the recommended dose is 75 mg/m² as a single agent [45].
Method of administration	• The use of docetaxel should be confined to units specialised in the administration of cytotoxic chemotherapy and it should only be administered under the supervision of a physician qualified in the use of anticancer chemotherapy. Administration should take place in a facility equipped to manage possible complications [45]. • Docetaxel is administered as a 1-hour intraveneous infusion every 3 weeks [45]. • An anti-inflammatory medicine such as dexamethasone should also be given to the patient, starting on the day before the docetaxel infusion. The dose of docetaxel may need to be reduced, or treatment interrupted or discontinued, if the patient develops certain side effects [45].
Should the pharmaceutical be administered with other medicines?	No, docetaxel is indicated as monotherapy for the treatment of patients with locally advanced or metastatic NSCLC after failure of prior chemotherapy [45].
Treatment duration / Criteria for end of treatment	• Docetaxel is administered as a 1-hour intraveneous infusion every 3 weeks [45]. • The dose, duration of treatment and the medicines it is used with depend on the type of cancer being treated and the patient's weight and height [45]. • Patients who experience severe hypersensitivity reactions, such as severe hypotension, bronchospasm or generalised rash/erythema require immediate discontinuation of docetaxel and appropriate therapy. These patients should not be re-challenged with docetaxel [45].
Necessary monitoring, both during administration and during the treatment period:	• Patients should be observed closely for hypersensitivity reactions especially during the first and second infusions. Hypersensitivity reactions may occur within a few minutes following the initiation of the infusion of docetaxel, thus facilities for the treatment of hypotension and bronchospasm should be available [45]. • Patients who have previously experienced a hypersensitivity reaction to paclitaxel may be at risk to develop hypersensitivity reaction to docetaxel, including more severe hypersensitivity reaction. These patients should be closely monitored during initiation of docetaxel therapy [45].
Need for diagnostic or other tests	No

Table 5. Pemetrexed product characteristics

Comparator: Pemetrexed	
Generic name, ATC code	Pemetrexed, L01BA04
Mechanism of action	Pemetrexed is a cytotoxic medicine (a medicine that kills cells that are dividing, such as cancer cells), which belongs to the group 'antimetabolites'. In the body, pemetrexed is converted into an active form that blocks the activity of the enzymes that are involved in producing 'nucleotides' (the building blocks of DNA and RNA, the genetic material of cells). As a result, the active form of pemetrexed slows down the formation of DNA and RNA and prevents the cells from dividing and multiplying. The conversion of pemetrexed into its active form occurs more readily in cancer cells than in normal cells, leading to higher levels of the active form of the medicine and a longer duration of action in cancer cells. This results in the division of cancer cells being reduced, while normal cells are only slightly affected [46].
Pharmaceutical form	Powder for concentrate for solution for infusion [46]

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Comparator: Pemetrexed	
Posology	In patients treated for NSCLC, after prior chemotherapy, the recommended dose of pemetrexed is 500 mg/m² BSA administered as an intravenous infusion over 10 minutes on the first day of each 21-day cycle [46].
Method of administration	• Pemetrexed must only be administered under the supervision of a physician qualified in the use of anti-cancer chemotherapy [46]. • It is administered as an intravenous infusion over 10 minutes on the first day of each 21-day cycle [46]. • To reduce side effects, patients should take a corticosteroid (a type of medicine that reduces inflammation) and folic acid (a type of vitamin), and receive injections of vitamin B12 during treatment with pemetrexed [46].
Should the pharmaceutical be administered with other medicines?	No, it is indicated as monotherapy for the 2L treatment of patients with locally advanced or metastatic NSCLC other than predominantly squamous cell histology [46].
Treatment duration / Criteria for end of treatment	Treatment should be delayed or stopped, or the dose reduced, in patients whose blood counts are abnormal or who have certain other side effects [46].
Necessary monitoring, both during administration and during the treatment period:	• Patients receiving pemetrexed should be monitored before each dose with a complete blood count, including a differential white cell count and platelet count [46]. • Prior to each chemotherapy administration blood chemistry tests should be collected to evaluate renal and hepatic function. Before the start of any cycle of chemotherapy, patients are required to have the following: absolute neutrophil count should be ≥ 1500 cells/mm3 and platelets should be ≥ 100,000 cells/mm3. Creatinine clearance should be ≥ 45 ml/min [46]. • The total bilirubin should be ≤ 1.5 times upper limit of normal. Alkaline phosphatase (AP), aspartate aminotransferase (AST or SGOT) and alanine aminotransferase (ALT or SGPT) should be ≤ 3 times upper limit of normal. Alkaline phosphatase, AST and ALT ≤ 5 times upper limit of normal is acceptable if liver has tumour involvement [46].
Need for diagnostic or other tests	Blood chemistry tests are required to monitor renal and hepatic function pior each administration [46].

Table 6. Pembrolizumab product characteristics

Comparator: Pembrolizumab	
Generic name, ATC code	Pembrolizumab, L01FF02
Mechanism of action	Pembrolizumab, is a monoclonal antibody, a protein that has been designed to recognise and block a receptor ('target') called PD-1. Some cancers can make a protein (PD-L1) that combines with PD-1 to switch off the activity of certain cells of the immune system (the body's natural defenses) preventing them from attacking the cancer. By blocking PD-1, pembrolizumab stops the cancer switching off these immune cells, thereby increasing the immune system's ability to kill the cancer cells. [47]
Pharmaceutical form	Concentrate for solution for infusion [47]
Posology	The recommended dose of pembrolizumab in adults is either 200 mg every 3 weeks or 400 mg every 6 weeks administered as an intravenous infusion over 30 minutes [47].
Method of administration	• Treatment with pembrolizumab must be initiated and supervised by specialist physicians experienced in the treatment of cancer [47]. • Pembrolizumab is for intravenous use. It must be administered by infusion over 30 minutes. Pembrolizumab must not be administered as an intravenous push or bolus injection. When administering pembrolizumab as part of a combination with intravenous chemotherapy, pembrolizumab should be administered first [47].

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Comparator: Pembrolizumab	
Should the pharmaceutical be administered with other medicines?	It can be used on its own or in combination with other cancer medicines for NSCLC [47].
Treatment duration / Criteria for end of treatment	Patients should be treated with pembrolizumab until disease progression or unacceptable toxicity (and up to maximum duration of therapy if specified for an indication). Atypical responses (i.e. an initial transient increase in tumour size or small new lesions within the first few months followed by tumour shrinkage) have been observed. It is recommended to continue treatment for clinically stable patients with initial evidence of disease progression until disease progression is confirmed [47].
Necessary monitoring, both during administration and during the treatment period:	Monitor patients closely for symptoms and signs that may be clinical manifestations of underlying immune-mediated adverse reactions [47].
Need for diagnostic or other tests	If specified in the indication, patient selection for treatment with pembrolizumab based on the tumour expression of PD-L1 should be confirmed by a validated test. When assessing the PD-L1 status of the tumour, it is important that a well-validated and robust methodology is chosen to minimise false negative or false positive determinations. [47].

Table 7. Osimertinib product characteristics

Comparator: Osimertinib	
Generic name, ATC code	Osimertinib, L01XE
Mechanism of action	Osimertinib, is a type of cancer medicine called a tyrosine kinase inhibitor. It blocks the activity of EGFR, which normally controls growth and division of cells. In lung cells, EGFR is often overactive, causing uncontrolled growth of cancer cells. By blocking EGFR, osimertinib helps to reduce the growth and spread of the cancer [48].
Pharmaceutical form	Film-coated tablet [48]
Posology	The recommended dose is 80 mg osimertinib once a day [48].
Method of administration	This medicinal product is for oral use. The tablet should be swallowed whole with water and it should not be crushed, split or chewed [48].
Should the pharmaceutical be administered with other medicines?	No, it is indicated as a monotherapy for the treatment of NSCLC patients [48].
Treatment duration / Criteria for end of treatment	Patients with locally advanced or metastatic lung cancer should receive treatment until disease progression or unacceptable toxicity. Treatment duration for more than 3 years was not studied [48].
Necessary monitoring, both during administration and during the treatment period:	Periodic monitoring with electrocardiograms and electrolytes should be considered in patients with congestive heart failure, electrolyte abnormalities, or those who are taking medicinal products that are known to prolong the QT interval [48]. In patients with cardiac risk factors and those with conditions that can affect Left Ventricular Ejection Fraction (LVEF), cardiac monitoring, including an assessment of LVEF at baseline and during treatment, should be considered. In patients who develop relevant cardiac signs/symptoms during treatment, cardiac monitoring including LVEF assessment should be considered [48]. Elderly patients (>65 years) or patients with low body weight (<50 kg) may be at increased risk of developing adverse events of Grade 3 or higher. Close monitoring is recommended in these patients [48].
Need for diagnostic or other tests	A validated test should be performed using either tumour DNA derived from a tissue sample or circulating tumour DNA (ctDNA) obtained from a plasma sample [48].

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5.3 The intervention

Amivantamab is a first-in-class EGFR-MET bispecific antibody with an immune cell-directing activity that targets activating and resistant EGFR mutations and MET mutations and amplifications[49]. It is efficacious with durable responses in patients with EGFR Exon 20ins, who have progressed on or after platinum-based chemotherapy (overall response rate [ORR] 40%, mPFS >8 months, mOS 22.8 months and mDOR of 11.1 months) [50]. Amivantamab reduced the risk of disease progression or death (mPFS 8 vs. 3 months) and death (mOS 23 vs. 13 months) by 50% vs. BSC (physician's choice of real world therapies) in a synthetic control analysis[51, 52]. It has a safety profile characterised by low rates of treatment-related discontinuations. Mostly by Grade 1 and 2 toxicities as well as manageable infusion related reactions (IRRs) [49, 53]. PRO data from a limited patient sample showed amivantamab had a modest initial improvement in overall NSCLC symptom severity with positive signals demonstrated in terms of cough and chest pain [54]. For the product characteristic, see Table 8.

Table 8. Amivantamab product characteristics

Amivantamab	
Pharmaceutical form	Concentrate for solution for infusion
Posology	Amivantamab is administered intravenously once weekly for 4 weeks, then every 2 weeks thereafter until disease progression or unacceptable toxicity. The dosing of amivantamab monotherapy [49, 50] is weight-based : • 1,050 mg (3 vials) for patients with body weight <80 kg • 1,400 mg (4 vials) for patients with body weight ≥80 kg
Method of administration	Amivantamab should be administered intravenously by a healthcare professional with appropriate medical support to manage IRRs if they occur. According to the FDA label, prior to initial infusion of amivantamab (Week 1, Days 1 and 2), antihistamines, antipyretics and glucocorticoids should be administered to reduce the risk of IRRs. For subsequent doses, antihistamines and antipyretics should be given prior to all infusions [49] . According to the EMA label, additional supportive medications (e.g., additional glucocorticoids, antihistamine, antipyretics and antiemetics) should be administered as clinically indicated [50].
Should the pharmaceutical be administered with other medicines?	Amivantamab is intended to be used as monotherapy for the treatment of adult patients with locally advanced or metastatic NSCLC and EGFR Exon 20ins mutations, whose disease has progressed on or after platinum-based chemotherapy, for whom there are no other recommended therapies [49, 50].
Treatment duration / Criteria for end of treatment	Amivantamab is administered intravenously once weekly for 4 weeks, then every 2 weeks thereafter until disease progression or unacceptable toxicity [49, 50].
Necessary monitoring, both during administration and during the treatment period:	Patients should be monitored for any signs and symptoms of IRRs during administration of infusion [50].
Need for diagnostic or other tests	EGFR Exon 20ins are under-detected with conventional biomarker testing, with PCR-based methods projected to miss 50% or more of these patients, necessitating use of a more comprehensive method (next-generation sequencing [NGS]) to maximise efficient and cost-effective identification of this patient population[51, 52]. NGS can be used to detect all relevant EGFR mutations simultaneously comprehensively, conveniently and efficiently, including Exon 20ins, identifying patients who are most likely to respond to effective targeted treatments [18, 53]. NGS-based platforms have the potential for all Exon 20ins (>70) to be identified (depending on the NGS software design) [52, 54].

6. Literature search and identification of efficacy and safety studies

No systematic literature review (SLR) results are included in this application due to the lack of relevant studies useful for a comparison against CHRYSALIS. A SLR was initially conducted to summarize and analyze existing evidence on patients with EGFR Exon 20ins. No randomized clinical trials (RCT) were found to report information on the patient population, and only 12 single arm trials were identified [55-66]. These trials were all for emerging treatments that are not currently used in Denmark or for TKIs that are only one of the treatment options for patients in Denmark. As mentioned in section 5.2.4 and in line with Nordic clinician opinions, no clear SoC exists for patients with Exon 20ins. This is especially true for those patients who failed platinum-based therapies (2L), where a mix of available treatment alternatives will most likely be offered [9]. Due to the lack of available data, a RWD database study using all types of comparators was preferred as the source for the efficacy for BSC-treated patients. This enabled all comparators to be included from the same source, and the RWD populations could be adjusted to match characteristics of CHRYSALIS thereby reducing bias.

7. Efficacy and safety

7.1 Efficacy and safety of amivantamab compared to best supportive care for adult patients with locally advanced or metastatic NSCLC with EGFR Exon 20ins whose disease has progressed on or after platinum-based chemotherapy

Amivantamab has received a conditional marketing authorization from EMA, for the treatment of adult NSCLC patients with activating EGFR Exon 20ins mutations, after failure of platinum-based therapy [2]. It is the first approved treatment in the EU specifically targeting EGFR Exon 20ins mutations for NSCLC. The conditional marketing authorization is based on results from the Phase 1 CHRYSALIS study evaluating amivantamab as a monotherapy in patients after previous treatment with platinum-based therapy.

Currently, amivantamab is being investigated in a phase I clinical trial (CHRYSALIS; NCT02609776) [1] (initial results published in August 2021 [13]) in patients with advanced NSCLC including:

- Cohort C: Treatment with amivantamab monotherapy in patients with primary EGFR mutation and MET amplification/mutation after progression on any EGFR TKI
- Cohort D: Treatment with amivantamab monotherapy in patients with primary EGFR Exon 20ins mutations not previously treated with a TKI with specific Exon 20 activity, including those who had received platinum-based doublet therapy
- Cohort E: Patients with EGFR Exon 19 deletion or Exon 21 L858R activating mutation and have progressed after 1st or 2nd-line treatment with a 3rd generation TKI, e.g., osimertinib (receiving amivantamab in combination with lazertinib)

The indication for amivantamab is based on post-platinum patients with Exon 20ins (mainly from Cohort D), to be referred to as 'post-platinum' patients hereafter [67].

A confirmatory phase III study (PAPILLON) in newly diagnosed patients with NSCLC and EGFR Exon 20ins started in Q4 2020. In this study efficacy and safety of amivantamab in combination with chemotherapy will be compared with that of chemotherapy alone. See Table 9 for short information.

Table 9. Ongoing studies not included in the assessment

Reference (title, author, journal, year)	Trial name	NCT number	Dates of study (start and expected completion date)	Objectives
A Randomized, Open-label Phase 3 Study of Combination Amivantamab and Carboplatin-Pemetrexed Therapy,	PAPILLON	NCT04538664	• Start: October 13, 2020 • Estimated primary completion date: January 12, 2022	The purpose of this study is to compare the efficacy, as demonstrated by PFS in participants treated with amivantamab in combination with

Reference (title, author, journal, year)	Trial name	NCT number	Dates of study (start and expected completion date)	Objectives
Compared With Carboplatin-Pemetrexed, in Patients With EGFR Exon 20ins Mutated Locally Advanced or Metastatic Non-Small Cell Lung Cancer			• Expected study completion date: November 8, 2024	chemotherapy, versus chemotherapy alone in participants with locally advanced or metastatic NSCLC characterized by EGFR Exon 20ins mutations.

7.1.1 Relevant studies - CHRYSALIS

CHRYSALIS [1] was a first-in-human, open-label, multicentre, 2-part, phase I dose escalation study in adult patients (aged ≥18 years) with advanced NSCLC with the following objectives:

- Determining the recommended phase II dose (RP2D)
- evaluating the safety and tolerability of amivantamab
- assessing the anti-tumour efficacy of amivantamab

A brief overview of the ongoing phase I clinical trial CHRYSALIS is presented below [1]. The study design, study population and patient selection criteria are described in N/A

Appendix B Main characteristics of included *studies*. Baseline characteristics of included patient populations are presented in *Appendix C Baseline characteristics of patients in studies used for the comparative analysis of efficacy and safety*.

Table 10. CHRYSALIS overview

Study	CHRYSALIS (EDI1001) NCT02609776
Sample size (n)	Primary efficacy population (81)
	Expanded efficacy population (114)
	Expanded safety population (129)
Study design	Phase Ib, single-arm, first-in-human, open-label, multicentre, 2-part, dose escalation study
Patient population	Adult patients (aged ≥18 years) with advanced NSCLC
Intervention(s)	Amivantamab (monotherapy) Amivantamab (in combination with lazertinib)
Comparator(s)	N/A
Follow-up period	Primary efficacy population median follow-up (9.7 months)
	Expanded efficacy population median follow-up (5.1 months)
	Expanded safety population (7.9 months)
Is the study used in the health economic model?	N/A
Reasons for use / non-use of the study in model	N/A
Primary endpoints reported* include results	Part 1 primary endpoints: • DLT Results: • Exploring the safety of pre-defined flat doses of amivantamab ranging from 140 mg to 1,400 mg did not identify a DLT • The RP2D of 1,050 mg was established for patients with a body weight of <80 kg and 1,400 mg for those with a body weight ≥80 kg.

Study	CHRYSALIS (EDI1001) NCT02609776
	Part 2 primary endpoints: • ORR • DOR • CBR according to RECIST • AEs defined by the NCICTCAE in patients treated at the RP2D and RP2CD regimens Primary efficacy population results: • ORR of 39.5% (95% CI: 28.8, 51.0) • mDOR 11.14 months • CBR of 74.1% (95% CI: 63.1, 83.2) Expanded efficacy population results: • ORR of 39.5% (95% CI: 30.4, 49.1) • mDOR 10.84 months • CBR of 72.8% (95% CI: 63.7, 80.7)
Other outcomes reported * include results	Secondary endpoints: • PFS, OS, time to treatment failure • Serum pharmacokinetic parameters of amivantamab • Plasma pharmacokinetic parameters of lazertinib Explanatory endpoints: • NSCLC-SAQ • EQ-5D-5L Primary efficacy population results: • mPFS of 8.3 months (95% CI: 6.5, 10.9) • PFS rate at 6 months 63% (95% CI: 51%, 73%) • PFS rate at 12 months 36% (95% CI: 23%, 49%), respectively • mOS of 22.8 months (95% CI: 14.6, not reached) • OS rate at 12 months 75% (95% CI: 62%, 84%) • OS rate at 18 months 63% (95% CI: 46%, 76%) Expanded efficacy population results: • mPFS of 6.9 months • mOS of 22.8 months

AE = adverse event; CBR = clinical benefit rate; DLT = dose limiting toxicity; EGFR = epidermal growth factor receptor; EQ-5D-5L = European Quality of Life 5 Dimension 5 Level Questionnaire; NCICTCAE = National Cancer Institute Common Terminology Criteria for Adverse Events Version 4.03; NSCLC-SAQ = Non-Small Cell Lung Cancer Symptom Assessment Questionnaire; ORR = overall response rate; OS = overall survival; PFS = progression free survival; PRO = patient reported outcome; RECIST = Response Criteria in Solid Tumours Version 1.1; RP2CD = recommended phase II combination dose; RP2D = recommended phase II dose

7.1.2 Efficacy and safety – results from CHRYSALIS

7.1.2.1 Recommended phase II dose and amivantamab exposure

Part 1 of the CHRYSALIS study, exploring the safety of pre-defined flat doses of amivantamab ranging from 140 mg to 1,400 mg did not identify a Dose Limiting Toxicity (DLT). The RP2D of 1,050 mg was established for patients with a body weight of <80 kg and 1,400 mg for those with a body weight ≥80 kg. Body weight was identified as a primary covariate explaining inter-patient pharmacokinetic variability [35].

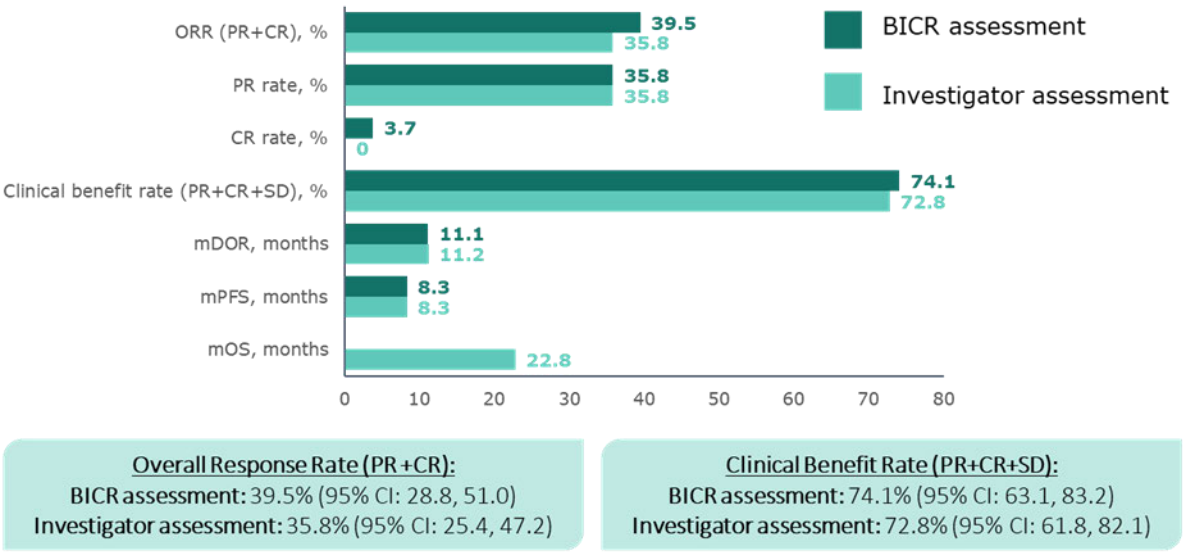
[redacted]

7.1.2.2 Summary of the efficacy evaluation for post-platinum patients

Primary efficacy population results

Amivantamab demonstrated good efficacy with the ORR of 40% (95% CI: 29%, 51%) and mPFS of 8.3 months (95% CI: 6.5, 10.9) in the primary efficacy population (Figure 5) [14].The clinical benefit rate, defined as partial response (PR) or stable disease for at least 12 weeks, was also high at 74% (95% CI: 63%, 83%) (Figure 6) [14]. Most endpoints were assessed in a blinded independent central review (BICR) which is advocated by regulatory authorities as a means of minimising bias.

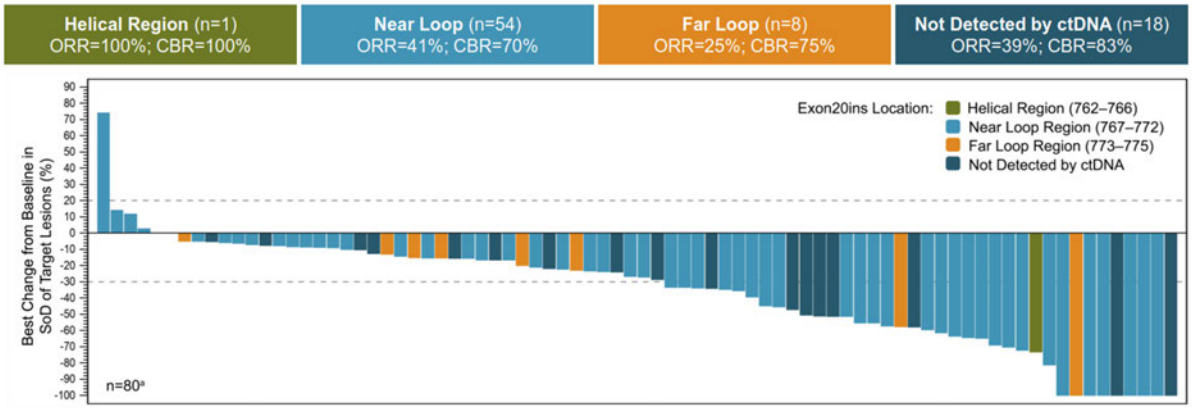
Figure 5. Amivantamab BICR and investigator assessed efficacy in the primary efficacy population (n=81) [68]



BICR = blinded independent central review; CI = confidence interval; CR = complete response; mDOR = median duration of response; mPFS = median progression free survival; ORR = overall response rate; PR = partial response; SD = stable disease

A total of 37 patients in the primary efficacy population (n=81) had a ≥30% tumour reduction based on BICR assessment (Figure 6 and Figure 7). Among patients with stable disease (n=39), the majority experienced a tumour shrinkage of >10% (n=27). The best ORR by insertion region of Exon 20 (detected by ctDNA) is shown in Figure 6. Response rates were consistent across each of the Exon 20ins mutation subtypes identified and anti-tumour activity was observed independent of mutation variation [16, 35, 69, 70].

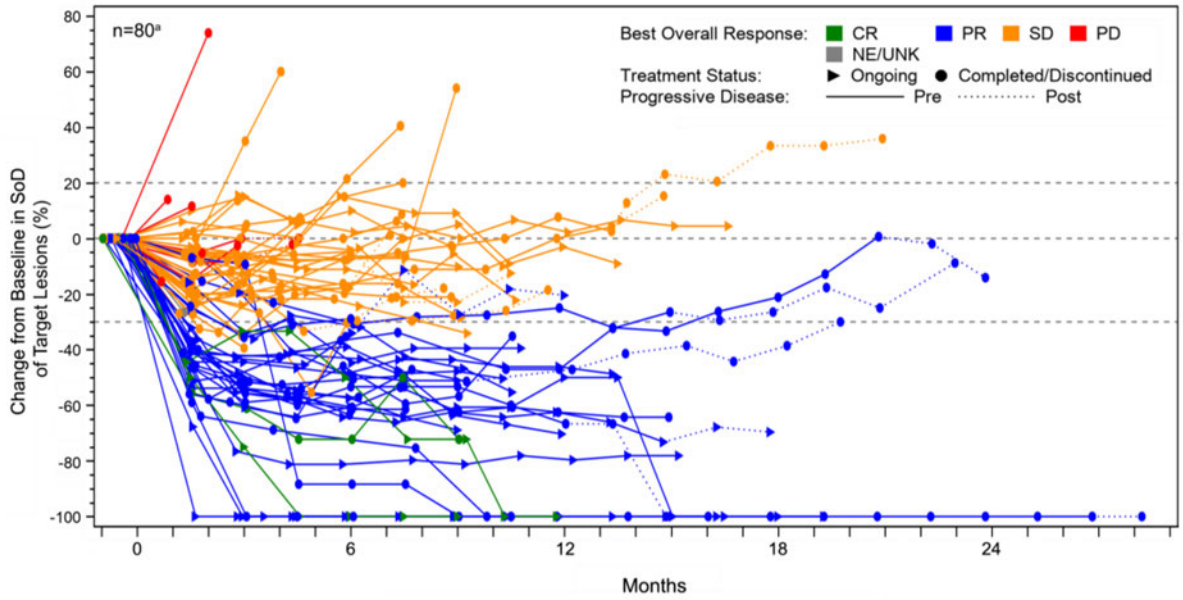
Figure 6. Reduction in target lesions with amivantamab treatment, primary efficacy population (n=80*, BICR assessment) [14]



BICR = blinded independent central review; CBR = clinical benefit rate; ORR = overall response rate; SoD = sum of diameters

*One patient in the primary efficacy population did not have follow-up data

Figure 7. Percentage change from baseline in SoD of tumour target lesions, primary efficacy population (n=80*, BICR assessment) [14]

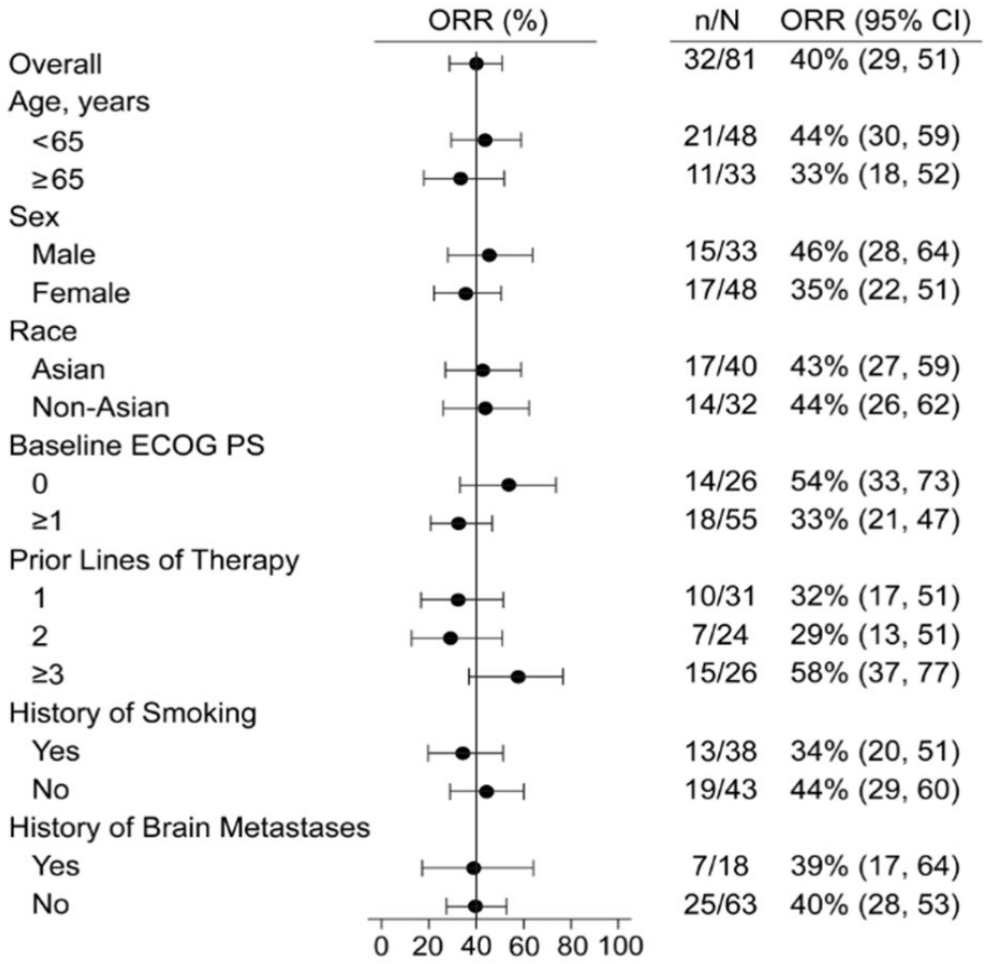


BICR = blinded independent central review; CR = complete response; NE = not evaluable; PD = progressive disease; PR = partial response; SD = stable disease; SoD = sum of diameters; UNK = unknown

*One patient in the primary efficacy population did not have follow-up data

Similarly, the efficacy of amivantamab was consistently observed across all clinically relevant patient subgroups (Figure 8) [14]. The tornado diagram illustrated in Figure 8 shows the ORR for the primary efficacy population in CHRYSALIS. The figure illustrates that there is little to no efficacy variation to be observed between the various subgroups included in the trial. Indicating that regardless of e.g., race, the patient may experience efficacy from the treatment with amivantamab.

Figure 8. Amivantamab efficacy across subgroups, primary efficacy population (n=81, BICR assessment) [14]



BICR = blinded independent central review; CI = confidence interval; ECOG = Eastern Cooperative Oncology Group; ORR = overall response rate; PS = performance status

Note: The race subgroup does not include 9 patients with race not reported and multiple race

Overall, there was an early and sustained treatment response to amivantamab which primarily occurred within two months of treatment [68]. A total of 32 responders in the primary efficacy population were identified through the BICR assessment [14]. The median duration of response (mDOR) for these patients was 11.1 months (95% CI: 6.9, not reached) with the longest response at 21.7 months (Figure 9) [14, 68]. Most responders (63%) had responses lasting ≥6 months [14].

[redacted]

[redacted]

The mPFS of patients in the primary efficacy population, based on the BICR assessment, was 8.3 months (95% CI: 6.5, 10.9) (Figure 10)[14]. [redacted]

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Expanded efficacy population results

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The tornado diagram illustrated in Figure 15 shows the ORR in the expanded efficacy population in CHRYSALIS. As with Figure 8, this figure also illustrates that there is little to no efficacy variation to be observed between the various subgroups included in the trial. Indicating that regardless e.g., race, the patient may experience efficacy from the treatment with amivantamab.

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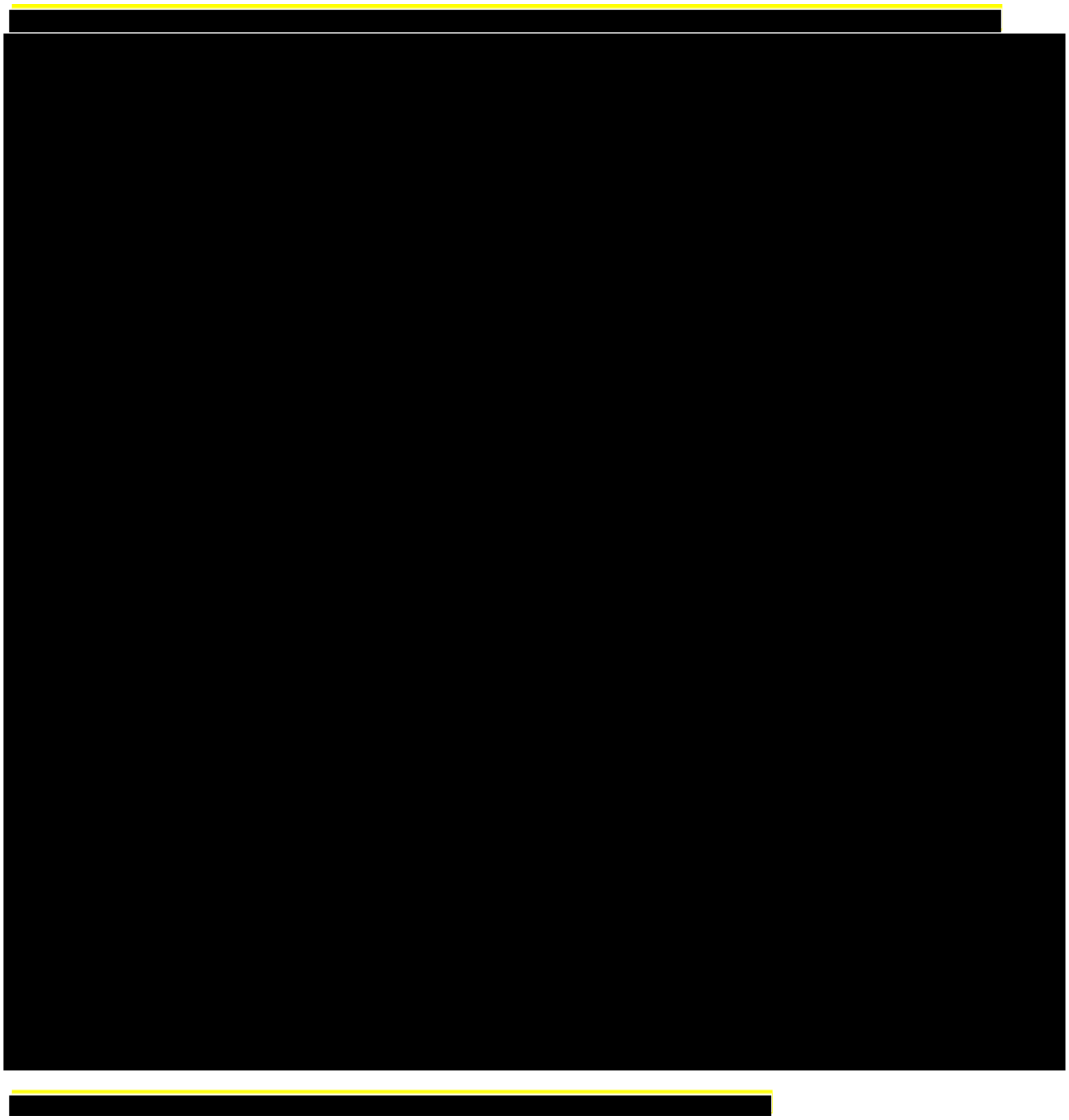

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7.1.2.3 Summary of the safety evaluation for post-platinum patients

Amivantamab demonstrated a manageable safety profile in patients with Exon 20ins disease treated at the RP2D (expanded safety population from the 120-Day Safety Update; n=129 with October 2020 datacut)[15]. [redacted]

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7.1.3 Comparative analyses of efficacy and safety

The efficacy of amivantamab as a treatment for the patient population of relevance to this assessment has been assessed in the phase 1b clinical trial CHRYSALIS. However, as CHRYSALIS is a single-arm trial, there is a need to generate comparative evidence by estimating the relative efficacy of amivantamab vs. the current, SoC treatment options.

The primary objective of the analysis was to compare the efficacy of amivantamab in the CHRYSALIS trial (Cohort D+) to current, standard of care treatment from real world settings in patients with advanced EGFR-mutated NSCLC with Exon 20ins following platinum-based therapy at 2L and subsequent-line (2L+).

After adjustment for key prognostic factors via inverse probability weighting ([IPW] using the Average Treatment effect on the Treated [ATT] approach), amivantamab provided a statistically significant treatment benefit versus BSC (labelled as "physician's choice, PC") in terms of ORR, OS, PFS and time-to-next treatment (TTNT). Results from the pooled EU cohort and the pooled US cohort were consistent, in which amivantamab provided a statistically significant treatment benefit versus BSC across all endpoints (ORR, OS, PFS and TTNT). Therefore, pooling of the EU and US cohorts is justified and provides an analysis based on a larger sample size, leading to a more robust comparison.

7.1.3.1 Method of synthesis

Comparator analysis sets

RWD sources were used to generate an external control arm for Cohort D+ of the CHRYSALIS trial. Patients in the RWD sources were identified by applying inclusion criteria from the CHRYSALIS trial. The adjusted treatment comparisons were conducted to compare amivantamab to BSC and specific treatment classes from these RWD sources. These cohorts were derived from various sources, by identifying patients who fulfilled the inclusion and exclusion criteria from the cohort D+ of the CHRYSALIS trial. Any criteria outlined in Table 13 that could not be applied to patients due to missing data were omitted from the list of inclusion and exclusion criteria applied to that data source (see Table 15 for detailed inclusion and exclusion criteria for the different RWD sources). Merging of data sources is described in *Appendix F Comparative analysis of efficacy and safety Merging of datasets – data pooling.*

Table 13. Inclusion and exclusion criteria applied to CHRYSALIS cohort D+

Inclusion criteria	Exclusion criteria
• **Stage IIIB/C or IV NSCLC** • **EGFR Exon 20ins** • **Age ≥18 years** • **Failure of a platinum-based therapy at any point after initial NSCLC diagnosis** • **Previously received platinum-based therapy after advanced NSCLC diagnosis or in the 12 months before advanced NSCLC diagnosis** • **ECOG PS 0 or 1** • **Haemoglobin ≥10 g/dL, ANC ≥1.5 x10^9/L, platelets ≥75 x10^9/L, AST and ALT ≤3 x ULN, total bilirubin ≤1.5 ULN (subjects with Gilbert's syndrome can enrol if conjugated bilirubin is within normal limits), serum creatinine <1.5 x ULN or calculated/measured creatinine clearance >50 mL/min/1.73m^2** • **No transfusions or use of G-CSF within 7 days prior to testing**	• History of particular cardiovascular comorbidities • Deep vein thrombosis or pulmonary embolism within 4 weeks • Myocardial infarction, angina, stroke, transient ischaemic attack, coronary/peripheral artery bypass graft or any acute coronary syndrome within 6 months • Untreated brain metastases • Other primary cancer diagnoses (with exception of skin cancer other than basal cell or squamous cell skin cancer, or in situ cervical cancer) within 3 years • Leptomeningeal disease • HBV, HCV, other infectious liver disease or HIV • Medical history of ILD, including drug induced ILD or radiation pneumonitis requiring treatment with prolonged steroids or other immune suppressive agents within the last 2 years

ALT: alanine aminotransferase; ANC: absolute neutrophil count; AST: aspartate aminotransferase; EGFR: epidermal growth factor receptor; Exon 20ins: Exon 20 insertion; G-CSF: granulocyte colony stimulating factors; HBV: hepatitis B; HCV: hepatitis C; HIV: human immunodeficiency virus; ILD: interstitial lung disease; NSCLC: non-small cell lung cancer; ULN: upper limit of normal.

The following RWD sources used to provide data for comparators of interest in the analyses were as follows:

- The Clinical Research platform Into molecular testing, treatment and outcome registry of non-small cell lung carcinoma Patients (CRISP)
- The national Network Genomic Medicine (nNGM) (Germany)
- Flatiron Health Spotlight
- ConcertAI
- COTA (the USA)
- The Epidemiological Strategy and Medical Economics (ESME) (France)
- Public Health England (PHE) (England)

The key characteristics of each RW data source are presented in Table 14 and Table 15.

Table 14. Characteristics of the RW data sources included in the analyses – time periods and methodology

Name of data source	Location	Time period of data collection	Methodology
Flatiron, ConcertAI and COTA	US	15 December 2009–16 October 2020	Existing registry
PHE[a]	England	01 Jan 2016 to 31 December 2016 and 01 Jan 2018 to 31 December 2018	Existing registry
NGM	Germany	20 Sep 2013–08 July 2021	Existing registry
CRISP	Germany	27 April 2017–30 June 2021	Existing registry
ESME[b]	France	01 Jan 2015–12 July 2021	Existing registry
CATERPILLAR	Pan-European (France, Germany, Italy, the Netherlands, Portugal, Spain and the UK)	01 January 2011 – 31 May 2021	Chart review; primary data collection using retrospective data

Footnotes: a No ORR/PFS data were available from the PHE cohort; b No ORR data were available for ESME.

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Table 15. Characteristics of the RW data sources included – specific selection criteria

			Specific selection criteria	
Name of data source	**Location**	**Time period of data collection**	**Inclusion criteria**	**Exclusion criteria**
Flatiron	US	December 2009 – October 2020	• Advanced NSCLC and EGFR ex20ins • ≥ 18 years at advanced NSCLC diagnosis • Platinum-based chemotherapy after metastatic diagnosis or in 12 months prior • ≥ 1 LOT after platinum-based chemotherapy • ECOG PS score of 0 or 1 (or missing) at start of qualifying therapy • No record of other malignancy in 3 years before start of qualifying therapy See Minchom et al. for more details [73]	
ConcertAI	US	December 2009 – October 2020	• Advanced NSCLC and EGFR ex20ins • ≥ 18 years at advanced NSCLC diagnosis • Platinum-based chemotherapy after metastatic diagnosis or in 12 months prior • ≥ 1 LOT after platinum-based chemotherapy • ECOG PS score of 0 or 1 (or missing) at start of qualifying therapy • No record of other malignancy in 3 years before start of qualifying therapy See Minchom et al. for more details [73]	

			• Advanced NSCLC and EGFR ex20ins • ≥ 18 years at advanced NSCLC diagnosis • Platinum-based chemotherapy after metastatic diagnosis or in 12 months prior • ≥ 1 LOT after platinum-based chemotherapy • ECOG PS score of 0 or 1 (or missing) at start of qualifying therapy • No record of other malignancy in 3 years before start of qualifying therapy See Minchom et al. for more details [73]	
COTA	US	December 2009 – October 2020		
PHE[a]	England	2016 and 2018[b]	• Age ≥18 years • Stage IIIB/C or IV NSCLC • E20ins diagnosis prior start of line of therapy • Progression on/after prior platinum-based chemotherapy • ECOG<2	• History of particular cardiovascular comorbidities • Deep vein thrombosis or pulmonary embolism within 4 weeks • Myocardial infarction, angina, stroke, transient ischaemic attack, coronary/peripheral artery bypass graft or any acute coronary syndrome within 6 months • Untreated brain metastases • Other primary cancer diagnoses (with exception of skin cancer other than basal cell or squamous cell skin cancer, or in situ cervical cancer) within 3 years • Leptomeningeal disease • HBV, HCV, other infectious liver disease or HIV

				• Medical history of ILD, including drug induced ILD or radiation pneumonitis requiring treatment with prolonged steroids or other immune suppressive agents within the last 2 years
nNGM	Germany	September 2013 – July 2021	See Table 13. Only criteria not applied: no transfusions or use of G-CSF within 7 days prior to testing.	• History of particular cardiovascular comorbidities • Deep vein thrombosis or pulmonary embolism within 4 weeks • Myocardial infarction, angina, stroke, transient ischaemic attack, coronary/peripheral artery bypass graft or any acute coronary syndrome within 6 months • Untreated brain metastases • Other primary cancer diagnoses (with exception of skin cancer other than basal cell or squamous cell skin cancer, or in situ cervical cancer) within 3 years • Leptomeningeal disease • HBV, HCV, other infectious liver disease or HIV • Medical history of ILD, including drug induced ILD or radiation pneumonitis requiring treatment with prolonged steroids or other immune suppressive agents within the last 2 years
CRISP	Germany	December 2015 – June 2021	• Age ≥18 years • Stage IIIB/C or IV NSCLC	N/A

			• E20ins diagnosis prior start of line of therapy • Progression on/after prior platinum-based chemotherapy • ECOG<2 • AST and ALT ≤3 x ULN, total bilirubin ≤1.5 ULN	
ESME[c]	France	January 2015 – April 2021	• Age ≥18 years • Stage IIIB/C or IV NSCLC • E20ins diagnosis prior start of line of therapy • Progression on/after prior platinum-based chemotherapy • ECOG<2	Other primary cancer diagnoses within 3 years before NSCLC diagnosis

Footnotes: a No ORR/PFS data were available from the PHE cohort; b Data was collected from 1st January to 31st December for each year; c No ORR data were available for ESME.

Abbreviations: CRISP: the Clinical Research platform into molecular testing, treatment and outcome registry of non-Small cell lung carcinoma Patients; ESME: Epidemiological Strategy and Medical Economics; nNGM: national Network Genomic Medicine; PHE: Public Health England; US: United States.

The relevant data source was pooled to leverage on the larger sample size. The pooled results provide the most robust and precise evidence for superiority of amivantamab vs BSC and are therefore used in the health economic analysis, thus presented below. Results for the EU cohort and US cohort separately are presented in *Appendix F Comparative analysis of efficacy and safety*.

Analysis methods

Multiple methodological approaches were implemented to adjust for differences in observed baseline characteristics between the CHRYSALIS cohort and the RW data sources which were considered potential confounders.

PS-based IPW and a covariate adjustment approach were used for the comparison of amivantamab versus BSC (labelled "PC"). Where the IPW method is considered the base case, covariate adjustment results are presented to demonstrate consistency in results.

When comparing amivantamab to treatment classes in the pooled EU and pooled US cohorts, the whole RWE population was compared to CHRYSALIS with covariate adjustment adjusting for treatment class and baseline characteristics (as opposed to comparing the populations of each treatment class from RWE separately to CHRYSALIS via IPW methods). This was due to the number of observations available for the individual treatment classes often being low, meaning that IPW was not feasible or stable. However, due to the larger sample size of the EU+US cohort, IPW methods were feasible and so are presented in the report alongside covariate adjustment results. Comparisons versus treatment classes are not presented for individual data sources, as the results were underpowered due to the small sample sizes. Each approach is described in *Appendix F Comparative* analysis of efficacy and safety *Analysis methods*. For completeness, unadjusted (naïve) comparisons are also presented.

Baseline characteristics of the CHRYSALIS cohort were compared to those for the relevant comparators in each RW data source. The characteristics actually adjusted for in each RW data source were based on the confounders identified by the SLR, clinical expert opinion and data availability. The baseline characteristics for CHRYSALIS and the pooled data sources are presented *in Appendix F Comparative analysis of efficacy and safety - Naïve baseline characteristics*, with adjusted baseline characteristics for the pooled data sources are presented in *Adjusted baseline characteristics*. Diagnostic plots demonstrating the distribution of naïve comparison PS scores and ATT PS scores the are presented in *Propensity score weighting results of Appendix F Comparative analysis of efficacy and safety*.

Endpoints of interest

The outcomes analysed for CHRYSALIS versus the RWD sources were ORR, OS, PFS and TTNT. A summary of the endpoints, their definitions and additional information relating to their use in the analyses is provided in *Appendix F Comparative analysis of efficacy and safety - Statistical analysis*. Logistic regression was used for binary outcomes (ORR) and Cox regression for time-to-event outcomes (OS, PFS and TTNT). ORR and PFS in CHRYSALIS were assessed by both, investigator-assessed (INV) and an independent review committee (IRC), but only INV results are available in the RWD sources. Therefore, INV is considered to be the key method of assessment for ORR and PFS in line with the real world database definitions (and thus, clinical practice). No comparison of amivantamab versus treatment classes is presented for CHRYSALIS versus individual data sources due to small sample sizes meaning results were not robust. Additional information on endpoints of interest is presented in *Appendix F Comparative analysis of efficacy and safety - Statistical analysis*.

7.1.3.2 Overall response rate

Results on overall response rate (ORR) for the pooled EU+US cohort are presented below. For ORR results from the separate EU cohort and US cohort, refer to *Appendix F Comparative analysis of efficacy and safety (ORR– EU cohort* and *ORR– US cohort)*.

ORR – EU+US cohort

IPW – ATT approach

[redacted]

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Covariate adjustment based on a multivariable generalized linear regression model

OR and RR estimates for ORR INV, based on a multivariable generalized linear regression model with treatment (amivantamab versus BSC) and baseline characteristics as covariates, are also summarised in

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Unadjusted results

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7.1.3.3 Overall survival

Results on overall survival (OS) for the pooled EU+US cohort are presented below. For OS results from the separate EU cohort and US cohort, refer to *Appendix F Comparative analysis of efficacy and safety* [redacted]

[redacted]

OS – EU+US cohort

IPW – ATT approach

The Kaplan-Meier (KM) plot of OS for amivantamab versus the ATT-weighted BSC (labelled "PC") cohort is presented in Figure 19. [redacted]

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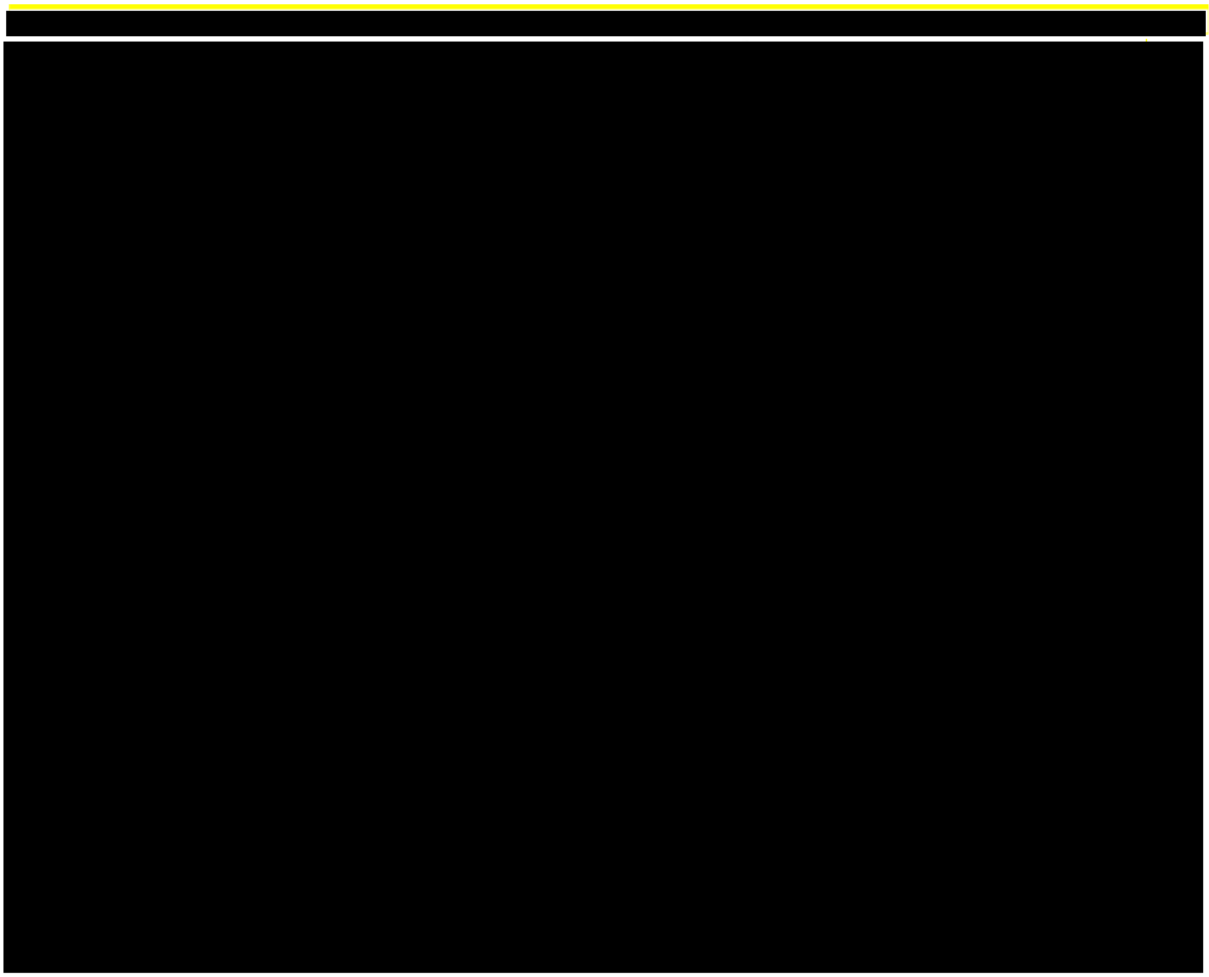

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7.1.3.4 Progression-free survival

Results on progression-free survival (PFS) for the pooled EU+US cohort are presented below. For PFS results from the separate EU cohort and US cohort, refer to *Appendix F Comparative analysis of efficacy and safety*.

PFS – EU+US cohort

IPW – ATT approach

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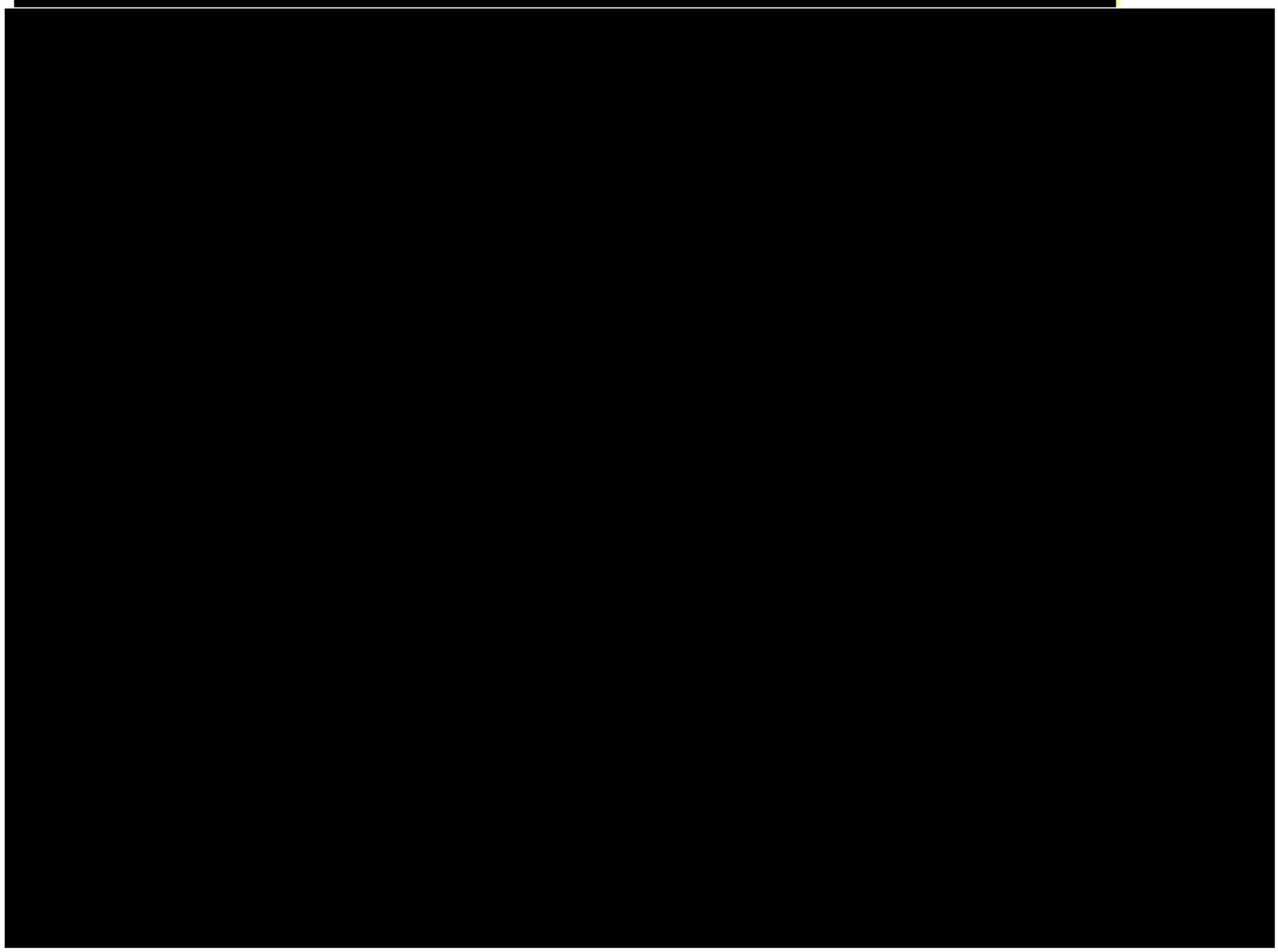

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7.1.3.6 Safety

Due to the lack of safety data availability in the RWD control arm, a review of adverse events is presented in Table 17 for the treatments relevant to this assessment (see section 5.2.5 for more detail on comparators and Table 21 for safety incidence data used in the economic model). The safety data were derived from clinical trials (CHRYSALIS for amivantamab [n=153],[74] AURA3 Trial for TKIs,[75] relevant SmPC for docetaxel) [76, 77] or previous NICE appraisals (TA428 for I-O agents).[78] Where available, data for all grades AEs was presented alongside data for events that were grades 3 to 5.

Table 17. Safety overview for the interventions considered in the assessment.

AE names	Frequency of AEs							
	Amivantamab (from CHRYSALIS safety population n=153, [74])		I-O Agents (from KEYNOTE-010 [78])		EGFR TKIs (from AURA3 Trial[75], AEs reported in at least 10% of patients in any group, rounded as presented in publication, n=279)		Non-platinum-based Chemotherapy (from docetaxel SmPC for 75 mg/m2 single agent[77])†	BSC weighted average based on pooled EU-US RWE weights (Table 18)
	All grades (individual AEs reported in at least 5% of patients)	Grades 3-4	All grades (AEs reported in at least 5% of patients in any group)	Grades 3-5 (AEs reported in at least 0% of patients in any group)	All events	Grades 3-5 (rounded percentages)	Grade 3-4 unless otherwise stated	Severity as reported for each type of treatment (grade 3-5 for I-O agents and EGFR TKIs and grade 3-4 for docetaxel)
Abdominal pain	[redacted]	[redacted]						
Acute kidney injury				1 (0.3%)				0.09%
Acne	[redacted]	[redacted]						
Alanine aminotransferase increased	[redacted]	[redacted]		2 (0.6%)	18 (6%)	3 (1%)		0.45%
Alopecia			3 (0.9%)					
Anemia	[redacted]	[redacted]	10 (2.9%)	3 (0.9%)	21 (8%)	2 (1%)	10.80%	5.21%
Arthralgia	[redacted]		13 (3.8%)					
Arthritis				1 (0.3%)				0.09%

Aspartate aminotransferase increased	[redacted]	[redacted]		2 (0.6%)	14 (5%)	3 (1%)		0.45%
Atrial fibrilation	[redacted]	[redacted]						
Asthenia	[redacted]		20 (5.9%)	1 (0.3%)	20 (7%)	3 (1%)	Severe: 12.40%	5.82%
Autoimmune hepatitis				1 (0.3%)				0.09%
Back pain	[redacted]			1 (0.3%)	29 (10%)	1 (<1%)		0.18%
Blood alkaline phosphatase increased	[redacted]	[redacted]						
Blood creatine phosphokinase increased	[redacted]	[redacted]						
Blood bilirubin increased							<2%	0.88%
Cerebrovascular accident				1 (0.3%)				0.09%
Chronic obstructive pulmonary disease				1 (0.3%)				0.09%
Cellulitis	[redacted]	[redacted]						
Colitis				3 (0.9%)				0.27%
Confusional state				1 (0.3%)				0.09%
Constipation	[redacted]				39 (14%)	0		
Cough	[redacted]				46 (16%)	0		
Decreased appetite	[redacted]	[redacted]	46 (13.6%)	3 (0.9%)	50 (18%)	3 (1%)		0.54%
Dermatitis acneiform	[redacted]	[redacted]						
Diarrhea	[redacted]	[redacted]	24 (7.1%)	2 (0.6%)	113 (41%)	3 (1%)	1.70%	1.20%
Dizziness	[redacted]							
Dry skin	[redacted]				65 (23%)	0		
Dysgeusia			4 (1.2%)					
Dysphagia				1 (0.3%)				0.09%
Dyspnoea	[redacted]	[redacted]		2 (0.6%)	44 (16%)	3 (1%)		0.45%
Epistaxis	[redacted]							
Fatigue	[redacted]	[redacted]	20 (5.9%)	4 (1.2%)				0.36%
Fluid retention							Severe: 0.8%	0.35%

Growth of the eyelashes						
Gingival bleeding						
Gamma-glutamyltransferase increased						
Haemorrhoids						
Headache			28 (10%)	0		
Hypercalcaemia		1 (0.3%)				0.09%
Hypertension						
Hypoalbuminaemia						
Hypokalaemia		1 (0.3%)				0.09%
Hypomagnesiaemia						
Hyponatraemia		1 (0.3%)				0.09%
Hypopituitarism		1 (0.3%)				0.09%
Hypophosphataemia						
Hypoproteinaemia						
Hypothyroidism	25 (7.4%)					
Hypotension						
Hypoxia						
Infection	17 (5%)	3 (0.9%)			5.00%	2.20%
Infected dermal cyst						
Insomnia						
IRR						
International normalised ratio increased						
Leukopenia			22 (8%)	0		
Lymphopenia						
Malaise			11 (4%)	0		
Mental status changes						
Myalgia	9 (2.7%)					
Musculoskeletal pain						
Musculoskeletal chest pain						
Muscular weakness						
Nail disorders					Severe: 0.8%	0.35%

Nasopharyngitis	[redacted]			28 (10%)	0		
Nausea		37 (10.9%)	1 (0.3%)	45 (16%)	2 (1%)	3.3%	1.72%
Neutropenia		1 (0.3%)		22 (8%)	4 (1%)	G4: 54.20%	24.23%
Oedema peripheral		5 (1.5%)					
Pain in extremity							
Paraesthesia		3 (0.9%)					
Paraneoplastic syndrome			1 (0.3%)				0.09%
Paronychia				61 (22%)	0		
Peripheral motor neuropathy						2.5%	1.10%
Pericardial effusion							
Peripheral neuropathy		2 (0.6%)					
Peripheral sensory neuropathy						0.8%	0.35%
Pleural effusion			1 (0.3%)				0.09%
Pneumonia			3 (0.9%)				0.27%
Pneumonitis			6 (1.8%)				0.55%
Pneumonia aspiration							
Pneumonitis chemical			1 (0.3%)				0.09%
Productive cough							
Pruritus		25 (7.4%)		35 (13%)	0		
Psoriasis			1 (0.3%)				0.09%
Pulmonary embolism			1 (0.3%)				0.09%
Pulmonary sepsis							
Pulseless electrical activity							
Pyrexia		10 (2.9%)	1 (0.3%)	18 (6%)	0		0.09%
Rash		29 (8.6%)	1 (0.3%)	94 (34%)	2 (1%)		0.27%
Rash maculo-papular			1 (0.3%)				0.09%
Rash papular							
Respiratory failure							
Respiratory tract infection							

Renal vein thrombosis	[redacted]					
Skin reaction					0.8%	0.35%
Sepsis						
Syncope						
Skin fissure						
Stomatitis		13 (3.8%)	41 (15%)	0	1.7%	0.75%
Sudden death						
Thrombocytopenia			28 (10%)	1 (<1%)	G4: 1.70%	0.84%
Toxic epidermal necrolysis						
Toxic leukoencephalopathy		1 (0.3%)				0.09%
Tubulointerstitial nephritis		1 (0.3%)				0.09%
Type 1 diabetes mellitus		1 (0.3%)				0.09%
Transitional cell carcinoma						
Uveitis						
Visual impairment						
Vomiting		12 (3.5%)	31 (11%)	1 (<1%)	0.8%	0.44%
Weight decreased						

Abbreviations: AE= adverse event, G4 = grade 4, IRR = infusion related reaction

* Not reported as frequency under 5%, † Other mentioned AEs include: Febrile neutropenia, Hypersensitivity (no severe), Anorexia, Arrhythmia (no severe), Hypotension, Constipation, Alopecia, Myalgia, Pain

Regarding serious adverse events, 9.4% of I-O patients reported SAEs [78] and 17.9% of TKI patients [79]. Discontinuation of treatment due to an adverse event was 13.6% for I-O patients [78] and 7% for TKI patients [75]. No further information regarding side effects was available from the docetaxel SmPC.

8. Health economic analysis

8.1 Model

An economic model was developed in Microsoft Excel® to conduct a cost-effectiveness analysis of amivantamab vs. comparators in the 2L and later line setting for the target population. The target population was adult patients with advanced NSCLC with activating EGFR Exon 20ins mutations, after failure of platinum-based therapy. This population is reflective of the main efficacy data sources used in the cost-effectiveness analysis (i.e., CHRYSALIS trial) and the license of amivantamab in Europe.

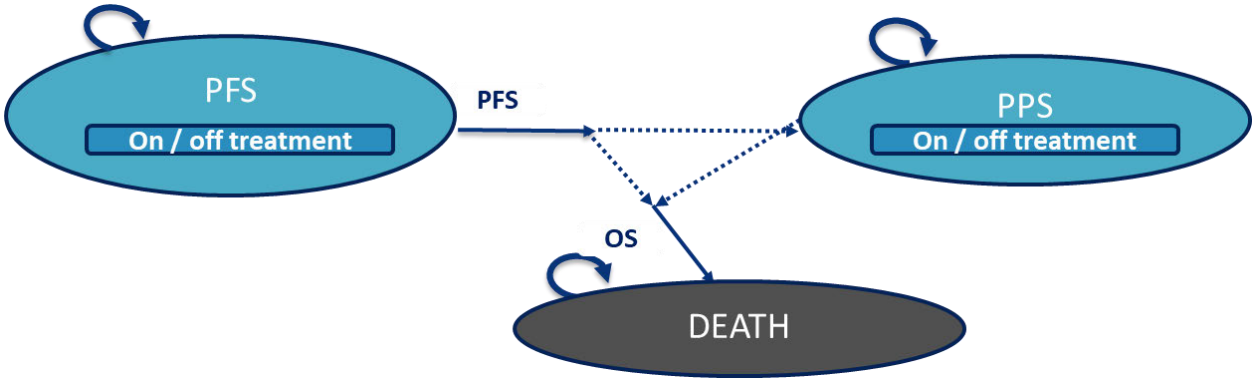
8.1.1 Model structure

The model was developed using a partitioned survival approach to track a cohort's costs and health outcomes over time from the beginning of current-line treatment until death. The model includes a progression-free (PF) state, a post-progression (PP) state, and death. This model was selected based on it being a widely accepted approach that was used by previous CEMs in metastatic NSCLC with EGFR,[80-87] including the model developed for osimertinib in the treatment of patients with NSCLC with EGFR T790 mutation, whose disease has progressed on or after EGFR TKI therapy.[88] Additionally it allows for direct incorporation of OS and PFS statistical data.

All patients started in the PF health state, and in each cycle, the cohort was distributed into three health states (i.e., PF, PP, and death) as shown in Figure 31. The percentage of patients in a state at any given time were estimated using an area under the curve (AUC) approach. That is, the allocation of patients into health states was based directly on comparators' specific PFS and OS functions. OS was capped by the general population mortality, and PFS was capped by OS. Once progressed, patients could not return to the PF state; they continued living with progressed disease or die. The costs and health benefits accrued in each cycle (i.e., four-week cycle) in each health state were used to estimate the expected outcomes and costs for each treatment comparator.

In the PFS state, response rates were not considered due to the data limitation. Given the small sample size in the CHRYSALIS trial, stratification by response will further decrease the patient number and therefore create more uncertainties around the long-term projection. In addition, response-stratified data were not available from real world evidence (RWE) to inform the indirect treatment comparison (ITC).

Figure 31. Model Diagram



Abbreviations: OS = overall survival, PFS = progression-free survival, PPS = post-progression state

The model considered up to two distinct lines of treatment (i.e., current [while in the PF state] and subsequent [while in the PP state]), patients that did not receive active treatment in the subsequent line were assumed to receive BSC.

Time-on-treatment (ToT) was modeled using one of two options to estimate the time patients spend on their initial treatment:

- Extrapolation of time-to-treatment discontinuation (TTD) data from relevant data sources. TTD data were only available for amivantamab. No TTD data were available from the comparator RWE sources; however, the model functionality is included should data become available in the future
- Assuming equal ToT to the time in the PF disease state (i.e., treatment discontinuation occurs when patients progress)

Furthermore, time on treatment can be capped by stopping rules (if specified by the user). For example, the summary of product characteristics (SmPC) for durvalumab specified a maximum of 12 months for treatment duration.[89]

The proportion of patients in the PP health state was estimated by taking the difference of OS and PFS survival functions. In the PP health state, patients receive a basket of subsequent treatments and BSC following the discontinuation of current-line treatment. In the PP state, there is a user defined percentage for patients receiving each type of treatment class, specified separately for the proportion of the cohort who received different types of treatment class in the PF state (for further details, see Subsequent Treatment). Efficacy of subsequent treatments is already implicitly captured in OS extrapolations and, thus, only the impact on the cost of subsequent treatment was considered in the model.

8.1.2 Perspective

The base case analysis used a limited societal perspective in line with DMC guidelines, which includes direct medical costs, transportation costs, and patient time costs.

8.1.3 Time horizon and cycle length

The time horizon for the base case was 15 years (i.e., lifetime) which sufficiently captured the lifetime of the targeted population given its poor prognosis. The model tracked the cohort of patients over time in discrete time-steps called cycles. The cycle length was four weeks per model cycle, to align with the treatment cycle length for amivantamab.

Half-cycle correction is considered for the model's base case allowing for a better approximation of the AUC. It helps avoid over- or underestimating the AUC. The trapezoidal rule is applied to all outputs to make this correction. For each cycle, instead of using the output calculated for a specific cycle, the average of the output at the current and previous cycles is taken:

$$TrapezoidRule_t = \frac{Out_{t-1} + Out_t}{2}$$

Abbreviations: Out = output, t = time point

8.1.4 Discounting

In accordance with the Danish Ministry of Finance's current socio-economic discount rate for this time horizon, an annual discount rate of 3.5% was applied in the model to the costs and health benefits that occurred beyond the first cycle [90]. For each cycle, these outcomes were multiplied by the discount factor calculated using the following formula: $\frac{1}{(1+r)^t}$, where r is the annual discount rate (for health or cost outcomes) and t is the time from time from index (treatment line start date) in years, rounded down. Both the undiscounted and discounted results are presented within the model.

8.1.5 Comparators

As described in section 5.2.4, the most relevant comparator in Denmark is a BSC mix of all available treatment options, but the model has the possibility to also compare amivantamab to the specific treatment classes (IOs, EGFR TKIs, non-platinum-based chemotherapies).

Due to the lack of direct treatment comparators, the list considered in the model was initially informed by the Janssen RWE study of BSC treatment outcomes in the EGFR Exon 20ins population. Three datasets (used to inform comparators and their efficacy) are included in the cost effectiveness model (CEM), derived from US and European datasets (Flatiron, ConcertAI, COTA, PHE, nNGM, CRISP, and ESME. The treatment list modelled was confirmed to be representative of that used across the Europe, Middle East and Africa (EMEA) market based on feedback from Janssen

affiliates in the EMEA region as part of a joint workshop held in May of 2020 and further verified with external advisors during the EMEA model challenge session conducted in March of 2021 [91, 92].

The treatment distributions based on the different databases are presented in Table 18. The pooled EU RWE column shows the treatment distribution when looking at the pooled data from the PHE, nNGM, CRISP and ESME databases. The pooled US RWE columns presents the treatment distribution of the pooled Flatiron, ConcertAI and COTA databases. The pooled EU and US column shows the treatment distribution when the data from all of these databases are pooled together. A hierarchical approach was adopted for treatment class categorization:

1. If a treatment line contains an I-O agent, it is categorized as I-O agents regardless of other therapies in the treatment line; otherwise, check rule 2.
2. If a treatment line contains an EGFR TKI, it is categorized as EGFR TKIs regardless of other therapies in the treatment line; otherwise, check rule 3.
3. If a treatment line contains a platinum-based chemotherapy (monotherapy or combination therapy), it is categorized as platinum-based chemotherapies; otherwise, check rule 4.
4. If a treatment line contains a non-platinum-based chemotherapy (monotherapy or combination therapy), it is categorized as non-platinum-based chemotherapies; otherwise, it is categorized as other therapies

The comparator options available in the model were grouped by treatment class, with an all-encapsulating comparator reflecting all treatment classes (BSC called SoC in the model). For each treatment class, efficacy inputs were derived for, and applied to, the treatment class as a whole, including BSC (more details on the frequency of the treatments used in the RWE study in Appendix M, while a weighted average of individual treatment costs, based on user-modifiable weights (see Table 18, column Pooled EU-US for the weights used in the base case), was used to estimate costs and safety and adverse event estimates.

In line with Danish clinical practice, the comparator treatment classes featured I-O agents, EGFR TKIs, non-platinum-based chemotherapies, and two placeholder treatment classes. Individual treatments were included within each treatment class, as described in Table 19.

Table 18. EU, US and EU-US Pooled RWE Best Supportive Care (SoC in the model) Treatment Basket*

Treatment	Pooled EU and US RWE	Pooled EU RWE	Pooled US RWE
I-O Agents	31%	28%	35%
EGFR TKIs	25%	27%	22%
Non-platinum-based Chemotherapy Regimens	44%	46%	43%

Abbreviations: EGFR = epidermal growth factor receptor, EU = European, I-O = immuno-oncology, RWE = real world evidence, TKI = tyrosine kinase inhibitor, US = United States

Note: *Therapies received in second line plus of therapy.

The distribution of individual treatments within each treatment class was split evenly between the individual treatments based on clinical expert opinion (Table 19) to reflect Danish clinical practice adequately. The treatment class composition of the BSC comparator is outlined in Table 19, and was aligned with the user-selected efficacy source.

Table 19. Treatment Comparators

Class	Treatment	Treatment Share	Source
I-O Agents	Nivolumab	25%	Split evenly between treatments based on clinical expert opinion
	Pembrolizumab	25%	
	Durvalumab	25%	
	Atezolizumab	25%	
	Placeholder	0%	
EGFR TKIs	Osimertinib	25%	Split evenly between treatments based on clinical expert opinion
	Erlotinib	25%	
	Afatinib	25%	
	Gefitinib	25%	

	Placeholder	0%	
Non-platinum-based chemotherapies	Docetaxel	33%	Split evenly between treatments based on clinical expert opinion
	Pemetrexed	33%	
	Docetaxel + ramucirumab	33%	
	Placeholder	0%	
BSC	I-O agents	31%	Pooled EU-US RWE Data
	EGFR TKIs	25%	
	Non-platinum-based chemotherapy regimens	44%	

Abbreviation: BSC = best supportive care, EGFR = epidermal growth factor receptor, EU = European, I-O = immuno-oncology, RWE = real world evidence, TKI = tyrosine kinase inhibitor, US = United States

8.1.6 Model inputs

The model inputs were based on Danish sources where possible. The CHRYSALIS trial was used to derive clinical inputs for amivantamab, as patient-level data were available. Efficacy inputs for amivantamab, including OS, PFS (INV), PFS (IRC) and TTD, for the n=114 population were derived from the CHRYSALIS trial. Given CHRYSALIS was a single-arm trial, synthetic control methods were used to determine efficacy inputs (OS, PFS and TTNT) for the comparator arms. ITCs of CHRYSALIS vs. RWE data were used to inform the relative efficacy inputs of the treatment comparators. Details on the RWE sources, how they were used to inform the relative efficacy of the comparator versus amivantamab, can be found in section 7.1.3 and in Appendix F Comparative analysis of efficacy and safety. Utilities were derived based on a targeted literature review (TLR) of relevant publications. [93, 94]

Three datasets were utilized for comparator efficacy derivation: the pooled EU RWE, pooled US RWE and pooled EU-US RWE. The pooled EU-US RWE combines the data from both EU and US sources and is therefore considered the most robust source to be used in the base case analysis. In order to compare similar patients from CHRYSALIS and the RWE data sources, the same inclusion and exclusion criteria were applied to all RWE data sources in line with the EMEA label for amivantamab, and the CHRYSALIS trial, where possible. Any criteria that could not be applied to patients due to missing data were omitted from the list of inclusion and exclusion criteria applied to that data source [[95]]. Baseline characteristics of the patients from the RWE data sources are presented in Appendix F Comparative analysis of efficacy and safety (section Baseline characteristics). The ITCs used inverse probability of treatment weights (IPTWs) derived from a propensity score model to account for variables, including, but not limited to, age, sex, race, smoking history, Eastern Co-operative Oncology Group Performance Scale (ECOG PS), and time from initial diagnosis to advanced diagnosis. A summary of the variables adjusted for in each RWE data source are presented in Appendix F Comparative analysis of efficacy and safety (see Table 71).

The key efficacy inputs in the model included OS and PFS (INV). The model further included PFS (independent review committee [IRC]) and TTD (for amivantamab), and time-to-next treatment (TTNT) - (for comparators). For each endpoint, the model included the option to use KM data directly, extrapolations based on patient-level data (aligned with recommendations in the NICE Decision Support Unit Report [[96]]) or a combination of the two (i.e. piecewise KM and extrapolations). For the comparators (treatment classes and BSC), there was also the option of applying a constant HR to amivantamab to derive their efficacy, assuming the proportional hazards assumption holds.

Where appropriate, parametric survival analyses were conducted by fitting survival functions to patient-level survival data to make long-term extrapolations for the model. Six parametric distributions were fitted to the patient level data. In the base case, PFS for both amivantamab and the comparators, as well as OS for the comparators, was modeled directly from Kaplan Meier (KM) data. OS for amivantamab was modeled through a Weibull extrapolation due to incomplete follow up for KM data. TTD for both amivantamab and comparators was assumed equal to PFS in absence of TTD data for comparators and clinical expectation.

8.1.7 Model outputs

The model outcomes included life years (LYs), quality-adjusted LYs (QALYs), current- and subsequent-line drug acquisition, administration, disease management and AE management costs and incremental cost-effectiveness ratios

(incremental cost-effectiveness ratio [ICER]; cost per QALY). All outputs are available both discounted and undiscounted.

8.1.8 Model validation

An initial review of the global model was performed by Costello Medical. The review included the administration of two checklists by a health economist. These checklists were as follows:

- Quality control checklist: This involved checking through every cell of the model to ensure that all formulae were correct, that macros had been coded correctly, that everything was referenced correctly, that all input numbers were correct, that there were no spelling or grammar mistakes, and that the formatting was consistent
- Internal validation checklist: This involved setting up different scenarios to check that the model responded in the appropriate manner; for example, when all utility values were set to 1, the life years LYs should have equaled the QALYs. The model was be pushed to the extremes to ensure that it could handle extreme values as would be expected

Alongside adaptation of the EMEA model to suit a Danish limited societal perspective, each adaptation to the model was rigorously quality checked by another health economist who was not involved in the programming of the adaptation. Additional scenario and stress testing has also been performed on the model throughout development to ensure it continued to function correctly and as expected. Moreover, the model structure, projection approaches for clinical endpoints, and key assumptions were validated by external clinical and health economic experts to ensure accuracy and completeness. The modelling approach was developed based on a thorough review of published economic modelling approaches and available health technology assessment (HTA) submission reports in NSCLC.

Due to the lack of data for this small patient population, an external validity assessment to Danish clinical practice could not be performed.

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

Table 20. Input data used in the model

Name of estimates	Results from study or indirect treatment comparison	Input value used in the model	How is the input value obtained/estimated
Efficacy: OS Amivantamab	CHRYSALIS See section 7.1.2 for more details	Weibull extrapolation	Weibull extrapolation (based on CHRYSALIS n=114 population)
Efficacy: OS Standard of Care	Indirect treatment comparison See section 7.1.3.3	KM curve	Direct KM from pooled EU-US data base sATT adjusted to the n=114 CHRYSALIS population
Efficacy: PFS Amivantamab	CHRYSALIS See section 7.1.2 for more details	KM curve	Direct KM data (CHRYSALIS n=114)
Efficacy: PFS Standard of Care	Indirect treatment comparison See section 7.1.3.4	KM curve	Direct KM from pooled EU-US data base sATT adjusted to the n=114 CHRYSALIS population
Efficacy: TTD Amivantamab	See PFS details above	Treat until progression	The base case assumption is that treatment discontinuation for amivantamab is equal to PFS based on feedback received from clinical experts at a Janssen-led

Name of estimates	Results from study or indirect treatment comparison	Input value used in the model	How is the input value obtained/estimated
			advisory board that this reflects expected clinical practice.
Efficacy: TTD Standard of Care	See PFS details above	Treat until progression	In line with clinical feedback, the approach taken for amivantamab and the issues with using TTNT data as a proxy for TTD, the base case for comparator treatments assumes that TTD is equal to PFS.
Utility: Progression-Free Survival	Literature values	0.71 (SE: 0.07)	TA484 Committee Papers[94]
Utility: Post Progression Survival		0.57 (SE: 0.06)	

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Table 21. Adverse event inputs used in the model (more detail in Table 17)

AE	Probability of Experiencing Grade 3/4 Adverse Events (one-off)		Disutility	Disutility Duration (Days)*	Data source (Disutility)	For treatment classes: probability of Experiencing Grade 3/4 Adverse Events (one-off)		
	Amivantamab (from CHRYSALIS safety population n=153[74], rounded)	Standard of Care (weighted average of treatment classes)				I-O Agents (from NICE TA428[78])	EGFR TKIs (from AURA3 Trial[75])	Non-platinum-based Chemotherapy (from Docetaxel SmPC for 75 mg/m2 single agent[77])
Anemia	[redacted]	5.21%	-0.314	14	Lloyd 2008[97]	0.9%	0.7%	10.8%
Asthenia	[redacted]	5.83%	-0.314	14	Assumption*	0.3%	1.1%	12.4%**
Infection	[redacted]	2.48%	-0.195	14	Tolley 2013 (severe infection)[98]	0.9%	0.0%	5.0%
Neutropenia	[redacted]	24.22%	-0.090	14	Nafees 2008	0.0%	1.4%	54.2%

Abbreviation: AE = adverse event

Note: The duration of all AEs was based on assumptions due to lack of data. * Due to the data limitation, the model assumes the duration is the same as the AE with highest utility decrement (anemia), ** assumed to be equal to "severe" asthenia, *** assumed to be equal to "muscular weakness", **** assumed to be equal to "respiratory tract infection", "sepsis", "kidney infection" (equal to 0 so not reported in Table 17), "lymph gland infection" (equal to 0 so not reported), "urinary tract infection" (equal to 0 so not reported) and "bacterial infection" (equal to 0 so not reported) combined

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 CHRYSALIS study consisted of adult patients (aged ≥18 years) with advanced NSCLC. Further details are provided in N/A

Appendix B Main characteristics of included *studies*.

Patient population in the health economic analysis submitted: The patient population considered for the base case analysis reflects that of the CHRYSALIS trial (see Table 22).

The Danish patient population: Limited information about NSCLC EGFR with Exon 20ins patients in Denmark is available but the patient population is assumed to be similar to the study and model populations. Although it is not possible to present information on the Exon 20ins patient population in Denmark, information about the general lung cancer patient population is presented in Table 22 for reference [19]. Please note that age discrepancies could exist due to the aggressive nature of this rare mutation.

Table 22. Patient population

Patient population Important baseline characteristics	Clinical documentation / indirect comparison etc.		Used in the model	Danish clinical practice	Danish lung cancer patients in 2018 (all types included) [19]
	Amivantamab: CHRYSALIS EAS (n=114)	BSC: EU+US cohort[a]			
Mean age, years (SE)	62.0	≤55: 26.3% 55–60: 17.5% ≥ 60: 56.1%	61.8 (0.94)	Danish Exon 20ins patients are assumed to be similar to the study population	Men: 72 Women: 71
Male, %	37%	38.6%	38.6%		48.9%
Patients <80 kg, %	80.7%	NR	80.7		NR

NR = not reported

Footnotes: a Excluding ESME.

8.2.2.2 Intervention

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

Intervention in the clinical documentation submitted: For amivantamab, treatment dosing depends on the patient's baseline body weight: patients with a baseline body weight of <80 kg (80.7% of the patient population based on the CHRYSALIS extended efficacy population, n=114) received a 1,050 mg dose and patients with a baseline body weight of ≥80 kg received a 1,400 mg dose at a regimen of once weekly for cycle 1 and every two weeks for cycle 2 and beyond (28-day cycle). In CHRYSALIS, dosing was split for the first treatment in cycle 1 to better manage the risk of infusion-related reactions in the CHRYSALIS trial; 350 mg was administered on Day 1 and 70 mg (for body weight <80 kg) or 1,050 mg (for body weight ≥80 kg) was administrated on day 2 [99].

Intervention as in the health economic analysis submitted: The model dosing is based on the CHRYSALIS data described above. However, the model applies a single administration cost for this 'first dose' of amivantamab as a simplification.

Table 23. Intervention

Intervention	Clinical documentation	Used in the model	Expected Danish clinical practice (EU SmPC [100])
Posology	Once weekly for cycle 1 (split into 2 doses see description above) and every two weeks for cycle 2 and beyond (28-day cycle): • 1,050 mg (3 vials) for patients with body weight <80 kg • 1,400 mg (4 vials) for patients with body weight ≥80 kg	Once weekly for cycle 1 and every two weeks for cycle 2 and beyond (28-day cycle): • 1,050 mg (3 vials) for patients with body weight <80 kg • 1,400 mg (4 vials) for patients with body weight ≥80 kg	Once weekly for cycle 1 and every two weeks for cycle 2 and beyond (28-day cycle): • 1,050 mg (3 vials) for patients with body weight <80 kg • 1,400 mg (4 vials) for patients with body weight ≥80 kg
Length of treatment (time on treatment)	[redacted]	The model assumes that patients would continue on treatment until disease progression following the drug protocol.	• It is recommended that patients are treated with Rybrevant until disease progression or unacceptable toxicity. • Dosing should be interrupted for Grade 3 or 4 adverse reactions until the adverse reaction resolves to ≤ Grade 1 or baseline.
Criteria for discontinuation	N/A	N/A	
The pharmaceutical's position in Danish clinical practice			Rybrevant as monotherapy is indicated for treatment of adult patients with advanced non-small cell lung cancer (NSCLC) with activating epidermal growth factor receptor (EGFR) Exon 20 insertion mutations, after failure of platinum-based therapy.

8.2.2.3 Comparators

The current Danish clinical practice: As there are no Danish treatment recommendations and a clear lack of treatment options for patients with advanced NSCLC and EGFR Exon 20ins, the treatment of these patients remains somewhat unclear. Based on clinical practice and the treatment guidelines in Denmark, the most relevant comparators to amivantamab are therefore a best supportive care (BSC) mix of all available treatment options.

Comparator(s) in the clinical documentation submitted: As CHRYSALIS was a single arm trial, RWD sources were used to generate an external control arm for Cohort D+ of the CHRYSALIS trial. The standard of care treatments given in each setting (as reflected in the data from each relevant data source) were variable. The following treatment classes were considered: TKI-based regimens, IO-based regimens, non-platinum-based chemotherapy regimens, VEGFi-based regimens and Other. The 'Other' basket included investigational drugs, drugs not considered to be part of the standard of care (e.g. breast cancer drugs) and treatments that included a combination of the other treatment classes. Please see Table 97 for an overview of all included drugs.

Comparator(s) in the health economic analysis submitted: The comparator options available in the model were grouped by treatment class, with an all-encapsulating comparator reflecting all treatment classes (BSC). The classes included separately are I-O agents (Nivolumab, Pembrolizumab, Durvalumab, Atezolizumab), EGFR TKIs (Osimertinib, Erlotinib, Afatinib, Gefitinib), non-platinum-based chemotherapies (Osimertinib, Erlotinib, Afatinib). The all-encapsuling comparator reflects all treatment classes, derived from pooled EU-US RWE (Table 97). Due to patients having been treated with platinum-based chemotherapy prior to enrolment (explaining the low platinum-based chemotherapy patient numbers for analysis) and the indication stating clearly that patients should have progressed on platinum-based chemotherapy, it was not included as a comparator in the model.

Table 24 Comparator

Comparator	Clinical documentation	Used in the model	Expected Danish clinical practice
BSC	Dosing was not captured in the RWD and thus is not reported. See list of drugs included above and distribution between classes in Table 18.	The treatment distribution from the RWD was used. See Table 32 for details on drug dosing for each comparator.	Treatments are expected to be used in line with SmPCs which are the source for the model dosages.

8.2.2.4 Relative efficacy outcomes

The relative efficacy outcomes in the submitted clinical documentation: The clinical documentation from where the relative efficacy outcomes for amivantamab and BSC were obtained are described in the Efficacy and safety section.

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.

The 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 CHRYSALIS study and the RWD indirect comparison study.

Table 25 Summary of text regarding *value*

Clinical efficacy outcome	Clinical documentation		Used in the model (value)
	Amivantamab	BSC	
Overall survival (OS)	CHRYSALIS See section 7.1.2 for more details	Indirect treatment comparison See section 7.1.3.3	See section 8.3.1
Progression-free survival (PFS)	CHRYSALIS See section 7.1.2 for more details	Indirect treatment comparison See section 7.1.3.4	See section 8.3.1.2
Time to treatment discontinuation (TTD)	[redacted]	NR	TTD for both amivantamab and comparators was assumed equal to PFS in absence of TTD data for comparators and clinical expectation.

Abbreviations: NR = not reported

Table 26 Summary of text regarding *relevance*

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

Abbreviations: NR = not reported

8.2.2.5 Adverse reaction outcomes

Adverse reaction outcomes in the clinical documentation submitted: Information on adverse events with amivantamab was obtained from the CHRYSALIS study (section 7.1.2 and Appendix E *Safety data for intervention and comparator(s)*).

Adverse reaction outcomes in the health economic analysis submitted: The model includes Grade 3+ adverse events (AEs) that were reported in more than 5% of patients in key trials. AEs were only considered for current-line

treatments, and AEs associated with subsequent-line treatments were not included. The treatment-related AE data were derived from clinical trials (CHRYSALIS for amivantamab [n=153],[74] AURA3 Trial for TKIs,[75] relevant SmPC for Docetaxel) [76, 77] or previous NICE appraisals (TA428 for I-O agents).[78] See Table 27 for a summary of AEs for both arms and Table 21 for a breakdown of the AEs per treatment class. The consequences of AEs were modeled in terms of the accrual of associated management costs and disutilities. The percentage of patients who experienced AEs was calculated at the start of the model and one-off costs and disutilities were incurred.

Table 27. Incidence of Grade 3+ AEs occurring in ≥5% of patients

AE	Amivantamab	BSC
Anemia	[redacted]	5.21%
Asthenia	[redacted]	5.83%
Infection	[redacted]	2.48%
Neutropenia	[redacted]	24.22%
Source	CHRYSALIS (safety population; n=153)[74]	Weighted average of treatment classes

Abbreviations: AE = adverse event

8.3 Extrapolation of relative efficacy

8.3.1 Overall survival

8.3.1.1 Amivantamab – CHRYSALIS

Kaplan-Meier

The OS KM for amivantamab was generated based on the patient-level data from the CHRYSALIS clinical trial (March 2021 data cut-off) for the extended efficacy population of 114 patients. Six parametric distributions were fitted to the CHRYSALIS trial data. Based on visual inspection, assessment of statistical fits and clinical expectations regarding long-term progression risk for the targeted patients, a Weibull distribution was selected as the base case (lowest Akaike information criteria [AIC]/second-lowest Bayesian information criteria [BIC]). The projected mean life expectancy from the Weibull distribution was 27.7 months and 26.8 months with generalized gamma. More details can be found in Appendix G – *Extrapolation*.

[redacted]

8.3.1.2 Best supportive care, current standard of care treatment options

Kaplan-Meier

The OS KM for BSC was generated based on the patient-level data from the Janssen RWD, adjusted to the n=114 CHRYSALIS data. Data presented here are for the pooled EU-US RWD that are used in the base case. As with amivantamab, six parametric distributions (exponential, Weibull, lognormal, loglogistic, Gompertz and generalized gamma) were fitted to KM curves derived from EU-US pooled RWD (sATT adjusted to the CHRYSALIS n=114 population) and are shown in Figure 33. Based on visual inspection and assessment of statistical fits, the loglogistic distribution was considered the best fit to the KM data (lowest BIC and 2nd lowest AIC), with a mean survival of 20.1 months. Due to data maturity, the KM data were used directly in the model. More details can be found in Appendix G – *Extrapolation*.

8.3.2 Progression-free survival

Based on the data maturity for PFS, the KM data were used directly in the analysis; however, extrapolations are considered in a scenario analysis. More details can be found in Appendix G – *Extrapolation*.

8.3.3 Patient distribution across health states

A tabular presentation of the proportion of patients in each state at relevant time points is presented for both intervention and comparator in Table 28.

Table 28. Proportion of patients by health state (PF, PP, alive and dead)

End of Year	Amivantamab				Standard of Care			
	PF	PP	Alive	Dead	PF	PP	Alive	Dead
0	100%	0%	100%	0%	100%	0%	100%	0%
1	35%	38%	74%	26%	14%	38%	52%	48%
2	18%	29%	47%	53%	4%	17%	21%	79%
3	0%	28%	28%	72%	3%	9%	12%	88%
4	0%	16%	16%	84%	2%	4%	6%	94%

End of Year	Amivantamab				Standard of Care			
	PF	PP	Alive	Dead	PF	PP	Alive	Dead
5	0%	9%	9%	91%	0%	4%	4%	96%
6	0%	5%	5%	95%	0%	4%	4%	96%
7	0%	2%	2%	98%	0%	4%	4%	96%
8	0%	1%	1%	99%	0%	4%	4%	96%
9	0%	1%	1%	99%	0%	0%	0%	100%
10	0%	0%	0%	100%	0%	0%	0%	100%
11	0%	0%	0%	100%	0%	0%	0%	100%
12	0%	0%	0%	100%	0%	0%	0%	100%
13	0%	0%	0%	100%	0%	0%	0%	100%
14	0%	0%	0%	100%	0%	0%	0%	100%
15	0%	0%	0%	100%	0%	0%	0%	100%

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

8.4.1 Overview of health state utility values (HSUV)

The health state utility values used in the model originate from the literature. The utility values for the health states are derived from NICE assessment TA484 (renamed to TA713) [94] and the adverse event disutilities originate from peer reviewed sources. The relevant values and sources are detailed in Table 30. In Appendix H – *Literature search for HRQoL data*, the SLR for economic evidence and HRQoL is described, presenting the databases, search terms, search strategy, data extraction as well as quality assessment. A summary of included studies is also presented.

8.4.2 Health state utility values used in the health economic model

European quality of life five-dimension five level scale (EQ-5D-5L) data were collected in CHRYSALIS at Day 1 of each cycle, at the end of treatment and during post-treatment follow-up. [103] However, patient-reported outcome (PRO) assessments were not introduced until Amendment 7 (August 2019) and as a result, the number of responses to the EQ-5D-5L questionnaire was low at the time of data cut-off (more details can be found in Appendix L *Patient reported outcomes in CHRYSALIS*). As such, the European quality of life five-dimension three level scale (EQ-5D-3L) utility values used in the model were not derived from EQ-5D-5L data from CHRYSALIS.

In absence of sufficient data from CHRYSALIS to generate utilities, a number of options from the literature were investigated. The base case utilities were selected from TA484 (renamed to TA713) which was a technology appraisal accepted by NICE for nivolumab for previously treated non-squamous NSCLC (see Table 30). These values were selected for the base case due to the similarity in population (e.g. similar advanced stage of disease, same median age of population, similar balance of males/females, similar ECOG performance-status scores, 100% of patients had received platinum-based therapy in both studies) and were validated at the NICE advisory board. [92] Moreover, NICE selected some specific utility values to avoid selection bias, which means that a thorough discussion was had about the utilities expected in this group of patients before carefully selecting these values. [92] As the median patient age of patients in CHRYSALIS (62 in expanded efficacy population) is the same as the age in the pivotal trial (CheckMate 057 [104]) for that NICE application, the values were expected to be reasonable and were not adjusted for age. Additionally, patient-level data was not available, and mapping of EQ-5D to Danish utility weights was therefore not possible. Data specific to the progression free and progressed disease health states of second-line (2L) and third line plus (3L+) patients were also obtained from Chouaid 2013,[105] for inclusion as a scenario analysis. This study was also in the similar indication of advanced NSCLC, including patients across 25 hospitals in Europe (including Sweden), Canada, Australia and Turkey. In addition to the literature values reported in Chouaid, a weighted average of the 2L and 3L+ values from Chouaid 2013 was generated, weighted by the distribution of 2L and 3L+ patients in CHRYSALIS. This value was used in a scenario analysis (see section 8.7.3 for results). These various utility data options are presented in Table 29. Looking at these literature values, the NICE values from TA484 used in the base case seem to

be in line with the literature for patients that have already received a line of platinum-based chemotherapy, further contributing to the validity of these utility estimates.

Table 29. Health state utilities

Health State	Utility Value	Standard Error	Source
TA484 (base case)			
PF	0.71	0.07#	TA484 Committee Papers[94]
PP	0.57	0.06#	
2L			
PF	0.74	0.01	Chouaid 2013[105]
PP	0.59	0.02	
3L+			
PF	0.62	0.02	Chouaid 2013[105]
PP	0.46	0.02	
2L and 3L+ Weighted			
PF	0.67	0.02	Weighted average of 2L and 3L+ values above
PP	0.51	0.03	

Abbreviations: 2L = second-line, 3L+ = third-line plus, PF = progression-free, PP = post-progression

Calculated as 10% of the mean value

Regarding AEs, the model applies a one-time disutility for impact of AEs on HRQoL. Disutilities were calculated using the data presented in Table 30 and the assumption that the duration of all AEs was two weeks, in absence of other data.

Table 30. Summary of the HSUV used in the model

	HSUV	Standard Error	Source (literature search, study, ITC, etc.)
Health states			
Progression-Free Survival	0.713	0.07	TA484 Committee Papers[94] NICE committee preferred values (for stability reasons) Early EQ-5D results (i.e. during the first 12 weeks after randomization) of CheckMate 057 for European patients alone
Post Progression Survival	0.569	0.06	TA484 Committee Papers[94] NICE committee preferred values (midway between evidence research group and company)
Adverse reactions			
Anemia	-0.314	Assumed 10% variation for SE at	Lloyd 2008[97] Patient valuation study using TTO (n = 26) for different cancer related anemia ranges TTO values • 7.0–8.0 g/dL: 0.297 (95% CI: 0.127)

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	HSUV	Standard Error	Source (literature search, study, ITC, etc.)
		treatment level	• 12.0+ g/dL: 0. 611 (95% CI: 0.112) Calculated as the difference between a "normal" hemoglobin level (12.0+ g/dL) and that associated with Grade 3+ anemia (7-8g/dL): 0.611 – 0.297 = 0.314
Asthenia	-0.314		Due to the data limitation, the model assumes the same as the AE with highest utility decrement (anemia)
Neutropenia	-0.08973 (SE: 0.01543, p <0.0001)		
Infection	-0.195 (Utility of 0.476 [95% CI: 0.432, 0.519] compared to 0.549 [95% CI: 0.506, 0.592])		Tolley 2013 [98] Utility elicitation study for chronic lymphocytic leukemia using TTO (n = 110) including AE substate of PFS responder with severe infection

Abbreviations: TTO = time trade-off, CI = confidence interval

8.5 Resource use and costs

8.5.1 Drug Acquisition Costs

Drug acquisition costs per four-week model cycles were calculated for each treatment based on the dosing schedule and the Danish list price of each pack or vial. Drug costs per treatment regimen were extracted from the Danish-based online drug cost database, Medicinpriser.dk; where multiple pack sizes were available, the option with the cheapest cost per mg was assumed. The drug costs and dosing requirements are presented in Table 31 and Table 32.

Table 31. Drug Acquisition Costs

Treatment	Administration Route	Strength per Unit	# Units per Pack	Cost of Pack	Source
Amivantamab	IV	350 mg	1	DKK 14,070.65	List price for amivantamab in Denmark
Nivolumab	IV	240 mg	1	DKK 10,439.24	Medicinpriser.dk (Accessed October 2022)[106] except afitinib where price for 2021 re-used due to lack of availability
Pembrolizumab	IV	100 mg	1	DKK 21,453.65	
Durvalumab	IV	500 mg	1	DKK 22,624.49	
Atezolizumab	IV	1200 mg	1	DKK 18,533.15	
Osimertinib	Oral	80 mg	30	DKK 30,363.01	
Erlotinib	Oral	150 mg	30	DKK 40,464.88	
Afatinib	Oral	40 mg	28	DKK 9,390.00	
Gefitinib	Oral	250 mg	30	DKK 20,343.65	
Pemetrexed	IV	500 mg	1	DKK 5,860.00	
Docetaxel	IV	160 mg	1	DKK 552.49	
Ramucirumab	IV	500 mg	1	DKK 309.00	
Carboplatin	IV	150 mg	1	DKK 19,448.71	
Bevacizumab	IV	400 mg	1	DKK 203.00	

Abbreviations: DKK = Danish krone, IV = intravenous

Table 32. Drug Dosing and Cost Calculation

Treatment	Dependency	Dose	# of Administrations per Treatment Cycle	Cost per Treatment Cycle	# of Weeks per Treatment Cycle	Source
Amivantamab						
First Cycle						CHRYSALIS[99]
Amivantamab (<80 kg)	Fixed dose	1050 mg	4	DKK 125,271	4	

Treatment	Dependency	Dose	# of Administrations per Treatment Cycle	Cost per Treatment Cycle	# of Weeks per Treatment Cycle	Source
Amivantamab (≥80 kg)	Fixed dose	1400 mg	4	DKK 167,028	4	
Subsequent Cycles						
Amivantamab (<80 kg)	Fixed dose	1050 mg	2	DKK 62,635	4	
Amivantamab (≥80 kg)	Fixed dose	1400 mg	2	DKK 83,514	4	
I-O agents						
Nivolumab	Fixed dose	240 mg	1	DKK 21,454	2	Nivolumab (SmPC)[76]
Pembrolizumab	Fixed dose	200 mg	1	DKK 45,249	3	Pembrolizumab (SmPC)[107]
Durvalumab**	Weight	10 mg/kg	1	DKK 0	2	Durvalumab (SmPC)[89]
Atezolizumab	Fixed dose	1200 mg	1	DKK 30,363	3	Atezolizumab (SmPC)[108]
EGFR TKIs						
Osimertinib	Fixed dose	80 mg	28	DKK 37,767	4	Osimertinib (SmPC)[76]
Erlotinib	Fixed dose	150 mg	28	DKK 8,764	4	Erlotinib (SmPC)[109]
Afatinib	Fixed dose	40 mg	28	DKK 20,344	4	Afatinib (SmPC)[110]
Gefitinib	Fixed dose	250 mg	28	DKK 5,469	4	Gefitinib (SmPC)[111]
Non-platinum-based chemotherapy regimens						
Docetaxel	BSA	75 mg/m^2	1	DKK 112	3	Docetaxel (SmPC)[77]
Pemetrexed	BSA	500 mg/m^2	1	DKK 1,521	3	Pemetrexed (SmPC)[112]
Docetaxel + Ramucirumab						Ramucirumab (SmPC)[113]
Docetaxel	BSA	75 mg/m^2	1	DKK 309	3	
Ramucirumab	Weight	10 mg/kg	1	DKK 1,105	4	
Platinum-based chemotherapy regimens***						
Carboplatin + Pemetrexed						Hayashi 2017[114]
Carboplatin	Fixed dose	900 mg*	1	DKK 1,218	3	
Pemetrexed	BSA	500 mg/m^2	1	DKK 1,105	3	
Carboplatin + Pemetrexed + Pembrolizumab						Langer 2016[115]
Carboplatin	Fixed dose	750 mg*	1	DKK 1,015	3	
Pemetrexed	BSA	500 mg/m^2	1	DKK 1,105	3	
Pembrolizumab	Fixed dose	200 mg	1	DKK 45,249	3	
Carboplatin + Pemetrexed + Bevacizumab						Takashina 2018[116]
Carboplatin	Fixed dose	750 mg*	1	DKK 1,015	3	
Pemetrexed	BSA	500 mg/m^2	1	DKK 1,105	3	
Bevacizumab	Weight	15 mg/kg	1	DKK 21,982	3	

Abbreviations: BSA = body surface area, DKK = Danish krone, EGFR = epidermal growth factor receptor, I-O = immune-oncology, SmPC = summary of product characteristics, TKI = tyrosine kinase inhibitor, # = number

Note: * Calculated using Calvert formula, assuming Globular Filtration Rate (GFR) of 125 ml/min and an area under the curve (AUC) of 6 mg/ml min in doublet therapy and 5 mg/ml min in triplet therapy, dose = AUC (mg/ml min) x [GFR (ml/min) + 25 (ml/min)]; **Durvalumab has a stopping rule

at 52 weeks, so costs are only applied for the first 13 model cycles. ***Platinum-based chemotherapies are only included for subsequent treatment cost calculations

8.5.1.1 Price of Rybrevant® (amivantamab)

For amivantamab, treatment dosing depends on the patient's baseline body weight: patients with a baseline body weight of <80 kg (80.7% of the patient population based on the CHRYSALIS extended efficacy population, n=114) received a 1,050 mg dose and patients with a baseline body weight of ≥80 kg received a 1,400 mg dose at a regimen of once weekly for cycle 1 and every two weeks for cycle 2 and beyond (28-day cycle). In CHRYSALIS, dosing was split for the first treatment in cycle 1 to better manage the risk of infusion-related reactions in the CHRYSALIS trial; 350 mg was administered on Day 1 and 70 mg (for body weight <80 kg) or 1,050 mg (for body weight ≥80 kg) was administrated on day 2 [99]. However, the model applies a single administration cost for this 'first dose' of amivantamab as a simplification. Body weight and BSA are used for weight and BSA-dependent drug dosing, as described in N/A

Appendix B Main characteristics of included *studies*. Given the small patient numbers expected in this population, it is assumed there is no vial sharing between patients in the base case; however, this is explored in a scenario analysis.

8.5.2 Administration-related Costs

All drugs through subcutaneous (SC) or intravenous (IV) infusion were assumed to have been administered in an outpatient setting based on drug labels, the administration-related costs are summarized in Table 33. Patients who received IV treatment were assumed to incur the same cost of administration regardless of the treatment being infused. Medications that are orally administered were assumed not to incur administration costs; however, in the model, a specific administration cost can be applied for oral medications if appropriate.

Table 33. Drug Administration Costs

Mode of Administration	Unit Cost	Source
IV/SC administration	DKK 3,225.00	DRG Takster 2022, DRG group: 17MA98, MDC17 1-dagsgruppe, pat. mindst 7 år, BWAA62(IV)/ BWAA31(SC) - Medication by intravenous infusion[117]
Oral administration	DKK 0	Assumption

Abbreviations: DRG = diagnosis-related group, DKK = Danish krone, IV = intravenous, SC = subcutaneous

8.5.3 Disease Management Costs

The disease management costs captured outpatient visits, chest radiography, computed tomography (CT) scans, electrocardiograms, and community nurse specialists. The model applied differing resource use frequencies in the PF and progressed-disease health states in the base case. Within both health states, the resource use frequencies may be set to be treatment-specific but in the base case resource use was assumed to be independent of treatment, i.e., all treatments incur the same resource use frequencies. These frequencies are presented in Table 34. The resource use frequencies were sourced from an NHS's National Institute for Health Research report that presents the results of a systematic review that were used in an economic evaluation of multiple locally advanced or metastatic non-small cell lung cancer products.[118] In both PFS and PPS, patients are expected to receive regular consultant-led outpatient consultations, and periodic diagnostic tests. In addition, community-based supportive care is provided by the patient's general practitioner and community nursing staff.[118] Due to lack of other local Danish or international sources and the similarities between the publicly funded healthcare systems in the UK and Denmark, this source was considered relevant to include in the assessment. In the terminal phase, resource use is expected to be more intensive. A one off DRG cost was used to reflect Danish treatment practice (see Table 35).

Table 34. Resource Utilization per Cycle (Four-week)

Resource Use	Resource Frequency of Use per Four-week Cycle		Source
	PF	Progressed	
Outpatient visit	0.74	0.61	Brown 2013[118]
Chest radiography	0.52	0.50	
CT scan (chest)	0.05	0.02	
CT scan (other)	0.03	0.03	
Electrocardiogram	0.08	0.07	

Resource Use	Resource Frequency of Use per Four-week Cycle		Source
	PF	Progressed	
Community nurse visit	0.67	0.67	
Clinical nurse specialist	0.92	0.92	

Abbreviations: CT = computed tomography, PF = progression-free

Unit costs for disease management are presented in Table 35. These unit costs were obtained from the diagnosis-related group (DRG) tariffs published by the Danish health authority, the laboratory medical guidance, and the unit costs published by the Medicinraadet [117, 119, 120]. The disease management costs were calculated according to a micro-costing approach based on the following equation:

$$Disease\ management\ cost = MRU\ frequencies * Disease\ management\ unit\ cost$$

Table 35. Unit Costs for Disease Management

Resource	Unit Cost	Source
Outpatient visit	DKK 2,180.00	DRG-taktser 2022, 04MA98, MDC04 1-dagsgruppe, pat. mindst 7 år[117]
Chest radiography	DKK 3,399.00	DRG-taktser 2022, 30PR17, Røntgenundersøgelse (alm), kompliceret[117]
CT scan (chest)	DKK 1,979.00	DRG takster 2022, 30PR07, CT-scanning, ukompliceret, el. osteodensitometri[117]
CT scan (other)	DKK 1,979.00	DRG takster 2022, 30PR07, CT-scanning, ukompliceret, el. osteodensitometri[117]
Electrocardiogram	DKK 918.32	Intern medicin Takstkort 17A, Ekkokardiografi [121]
Community nurse visit	DKK 590.98	Medicinrådet, Værdisætning af enhedsomkostninger: "Sygeplejersker" 1 h, inflated to 2022 price [119]
Clinical nurse specialist	DKK 2,180.00	DRG-taktser 2022, 04MA98, MDC04 1-dagsgruppe, pat. mindst 7 år[117]
Terminal care	DKK 71,612.00	DRG-taktser 2022, 26MP48, "Specialiseret Palliativ indsats, Øvrig"[117]

Abbreviation: CT = computed tomography, DKK = Danish krone

8.5.4 Adverse Event Management Costs

AE management costs resulting from the first treatment modeled were applied as a one-off cost at model initiation, while AE management costs due to subsequent lines of treatment were not considered. Table 36 presents the unit costs of managing each AEs, which were based on the 2021 Danish health authority's DRG tariff costs [117]. AE costs were calculated based on the equation below. The percentage of patients who experienced an AE in a treatment arm was calculated based on the probability of the event occurring (which was treatment dependent) and the number of patients on each respective treatment. The frequency of AEs is included in Table 21.

$$AE\ costs = \ percent\ of\ patients_{per\ AE} * cost_{per\ AE}$$

$$AE\ costs = cost_{per\ AE} * \sum_{n} probability_{AE}^{treatment\ n} * population\ size^{treatment\ n}$$

Table 36. AE Management Costs

AE	Cost per Event	Source
Anemia	DKK 6,450	Assumption: 2 haematologist visits; DRG-takster 2022, 17MA98, MDC17 1-dagsgruppe, pat. mindst 7 år[117]
Asthenia	DKK 3,618	DRG-taktser 2022 01MA98, MDC01 1-dagsgruppe, pat. mindst 7 år[117]
Infection	DKK 29,940	DRG-taktser 2022, 18MA06, Virussygdomme, pat. mindst 18 år, u. kompl. faktorer[117]
Neutropenia	DKK 25,419	DRG-taktser 2022, 16MA10, Øvrige sygdomme i blod og bloddannende organer[117]

Abbreviations: AE = adverse event, DKK = Danish krone

8.5.5 Subsequent Treatment

In the model, the time spent on a subsequent line of treatment was estimated based on the subsequent treatment and the patients' initial treatment (i.e., prior treatment class). In the base case it was assumed that duration of subsequent treatment was independent of the prior (i.e., initial) treatment class. The duration for each subsequent line of treatment was derived from published mean (Migliorino 2017) or median (Park 2019) treatment durations, summarized in Table 37 [122, 123]. Migliorino et al. conducted an economic analysis of the clinical management of NSCLC patients in Italy where data from the observational and multicenter study LIFE that described the treatment of NSCLC patients progressing after first-line treatment in clinical practice. Data on mean length of third line treatment for these patients (n=66) was reported. Park et al. conducted a retrospective analysis of three RCTs (LUX-Lung 3, 6 and 7) in EGFR positive NSCLC patients. The studies captured the post-progression therapy of patients included in the trials and the study reports the medium length of subsequent treatment (any treatment line, but after one TKI line according to study design) in this population. The average duration of subsequent treatment was used to estimate the one-off subsequent treatment costs (i.e. drug acquisition and administration). The subsequent treatment efficacy was assumed to be captured within the OS in the model.

Table 37. Average Duration of Subsequent Line Treatment

Subsequent Treatment	Duration (months)	Source
I-O agents	4.2	Migliorino 2017 (based on nivolumab)[122]
EGFR TKIs	3.9	Park 2019 [123]
Non-platinum-based chemotherapies	2.3	Park 2019 [123]
Platinum-based chemotherapies	3.5	Park 2019 [123]
No treatment	2.3	Assumed equal to non-Pt-chemotherapies

Abbreviations: BSC = best supportive care, EGFR = epidermal growth factor receptor, I-O = immuno-oncology, Pt = Platinum, TKI = tyrosine kinase inhibitor

8.5.5.1 Subsequent treatment costs

Patients who experience progression were assumed to incur a one-off cost associated with subsequent treatment.

Subsequent treatment selection is categorized by treatment class in the same way as the current-line treatment. In addition to the treatment classes modeled at 1L, 'no treatment' is also included as a subsequent treatment option for patients who are not be expected to receive another active treatment (assumed to incur zero acquisition or administration costs per 4-week cycle), but no patients are assumed to receive this subsequent treatment in the model base case. Based on clinical expert feedback, platinum-based chemotherapies are also included as a subsequent treatment, although they are excluded as a direct comparator due to prior treatment with platinum-based chemotherapy.

As highlighted by the DMC email found in Appendix K Email from DMC regarding choice of comparator, there is currently no standard of care for the treatment of NSCLC in Denmark especially with regards to the order in which patients are treated. This is further confirmed by the fact that the Danish guidelines do not make recommendations beyond the second line of treatment. [19] Therefore the distribution of subsequent treatments for each current line treatment, presented in Table 38, was based on data from the comparator RWE (aligned with the selected efficacy source and BSC treatment distribution, i.e., pooled EU-US RWE). Subsequent treatment class distribution for BSC is based on a weighted average of its constituent treatment classes (as per AEs). A summary of the other key assumptions and considerations follows:

- Due to the data limitation, the model assumes the same composition for current and subsequent lines of treatment class (i.e., treatments within a treatment class)
- The individual treatment shares within a subsequent treatment class were assumed the same as the individual treatment shares within the current-line treatment class.
- Patients who received a treatment within a treatment class in the current line do not receive treatment by the same treatment class in the subsequent line
- Patients do not receive amivantamab in the subsequent line of treatment

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Table 38. Distribution of Subsequent Treatments (Pooled EU-US RWE)

Subsequent Treatment	Prior Line of Treatment Class				
	Amivantamab	I-O Agents	EGFR TKIs	Non-platinum-based Chemotherapy	BSC*
Percentage of patients receiving subsequent treatment	69.9%	69.9%	69.9%	69.9%	69.9%
I-O agents	23.7%	0.0%	30.4%	40.4%	25.4%
EGFR TKIs	22.0%	28.9%	0.0%	48.1%	25.4%
Non-platinum-based chemotherapies	41.2%	54.1%	52.9%	0.0%	30.0%
Platinum-based chemotherapies	13.0%	17.0%	16.7%	22.1%	19.2%
No treatment	0.0%	0.0%	0.0%	0.0%	0.0%
Total:	100%	100%	100%	100%	100%

Abbreviations: BSC = best supportive care, EGFR = epidermal growth factor receptor, I-O = immuno-oncology, RWE = real world evidence, TKI = tyrosine kinase inhibitor

Note: *BSC is calculated as a weighted average of treatment classes.

The total costs of subsequent treatments for each comparator arm were calculated based on the average treatment duration (presented in Table 37), distribution (presented in Table 38), and unit costs of subsequent treatments (presented in Table 39), and are presented in Table 40. Subsequent treatment costs were applied to all patients as a one-off cost as they enter the progressed disease health state.

$$\textit{Subsequent Treatment Cost} = \textit{subsequent treatment unit cost} * \textit{distribution of subsequent treatment} * \textit{subsequent duration} * \textit{percentage of patient received subsequent treatment}$$

Table 39. Drug Acquisition Costs – Subsequent Treatment

Treatment	Drug Cost per Four-week Cycle	Administration Cost per Four-week Cycle	Total Cost per Four-week Cycle
I-O agents	DKK 54,464	DKK 6,450	DKK 60,914
EGFR TKIs	DKK 18,086	DKK 0	DKK 18,086
Non-platinum-based chemotherapies	DKK 13,732	DKK 5,375	DKK 19,107
Platinum-based chemotherapies	DKK 32,797	DKK 11,467	DKK 44,264
No treatment	DKK 0	DKK 0	DKK 0

Abbreviations: DKK = Danish krone, EGFR = epidermal growth factor receptor, I-O = immuno-oncology, TKI = tyrosine kinase inhibitor

Table 40. Total Subsequent Treatments Costs

Subsequent Treatment	Prior Line of Treatment Class				
	Amivantamab	I-O Agents	EGFR TKIs	Non-platinum-based Chemotherapy	BSC
I-O agents	DKK 46,110	DKK 0	DKK 59,141	DKK 78,476	DKK 49,389
EGFR TKIs	DKK 11,805	DKK 15,477	DKK 0	DKK 20,091	DKK 13,628
Non-platinum-based chemotherapy	DKK 13,766	DKK 18,049	DKK 17,657	DKK 0	DKK 10,002
Platinum-based chemotherapy	DKK 15,291	DKK 20,048	DKK 19,612	DKK 26,023	DKK 22,570
No treatment	DKK 0	DKK 0	DKK 0	DKK 0	DKK 0
Total	DKK 86,971	DKK 53,574	DKK 96,410	DKK 124,590	DKK 95,589

Abbreviations: BSC = best supportive care, DKK = Danish krone, EGFR = epidermal growth factor receptor, I-O = immuno-oncology, TKI = tyrosine kinase inhibitor

8.5.6 Travel and patient time costs

The Danish healthcare system is a third-party payer system that considers a limited societal perspective which includes costs that are not direct medical costs or are only indirectly related to treatment. Specifically, this limited societal perspective considers the total travel cost for patients who are visiting hospital for their treatment, and the

equivalent cost of the patients' time that they will spend at their hospital visits. The number of visits expected per model cycle due to either treatment administration or disease management are presented in Table 41, and the unit cost of a patient's time and travel are presented in Table 42.

Table 41. Hospital Visits per Treatment Cycle

Treatment	Number of Hospital Visits per Four-week Cycle				
	Due to Treatment Administration		Due to Disease Management		
	PF	Progressed	PF	Progressed	Source
Amivantamab	2.00	0.00	1.40	1.27	Assumed that all tests and procedures occur during outpatient visits and community nurse visits
I-O Agents	1.17	0.00	1.40	1.27	
EFGR TKIs	28.00	0.00	1.40	1.27	
Non-Pt-based chemotherapy	1.33	0.00	1.40	1.27	
BSC	7.97	0.00	1.40	1.27	

Abbreviations: DKK = Danish krone, EGFR = epidermal growth factor receptor, I-O = immuno-oncology, PF = progression-free, TKI = tyrosine kinase inhibitor

Table 42. Unit Costs for Travel and Patient Time for Each Hospital Visit

Type of Cost	Cost	Source
Total travel cost per visit (Round trip)	DKK 100	Medicinrådet, Patient- og pårørenderelaterede omkostninger[119]
Patient time cost per visit (Assuming 2 hours per visit)	DKK 358	Medicinrådet, average hourly wage of an employee in Denmark after tax[119]

Abbreviations: DKK = Danish krone

8.6 Results

8.6.1 Base case overview

The base case analysis was conducted based on the following settings for amivantamab and BSC, seen in Table 43.

Table 43. Base case overview

Settings	Base Case
Type of model	Partitioned survival analysis
Time horizon	15 years
Discount rate (health and cost outcomes)	3.5%
Main comparator (index drug)	BSC (based on EU-US RWE), comprising of: 31% I-O agents (nivolumab, pembrolizumab, durvalumab, atezolizumab) 25% EGFR TKIs (osimertinib, erlotinib, afatinib, gefitinib) 44% Non-platinum-based chemotherapies (docetaxel, pemetrexed, docetaxel+ramucirumab)
Included cost component	Drug and administration, AE management, subsequent treatment, disease management costs
Efficacy: PFS	Amivantamab: direct KM data (CHRYSALIS n=114) Standard of Care: direct KM from pooled EU-US data base sATT adjusted to the n=114 CHRYSALIS population
Efficacy: OS	Amivantamab: Weibull extrapolation (based on CHRYSALIS n=114 population) BSC: direct KM from pooled EU-US data base, sATT adjusted to the n=114 CHRYSALIS population
Efficacy: TTD	Amivantamab: treat until progression SoC: treat until progression
Utility	PF and PD specific utilities based on TA484

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Settings	Base Case
	Utility for progressed disease state as percentage decrement: exclude AE disutility: include
Vial sharing	Exclude

Abbreviations: AE = adverse event, EGFR = epidermal growth factor receptor, EU = European, I-O = immuno-oncology, KM = Kaplan-Meier, OS = overall survival, PD = progressed disease, PF = progression-free, PFS = progression-free survival, RWE = real world evidence, sATT = scaled average treatment effect on the treated, TKI = tyrosine kinase inhibitor, TTD = time-to-treatment discontinuation, US = United States

8.6.2 Base case results

The base case health outcomes and costs are presented in Table 44 and Table 45, respectively. For the most relevant comparator, BSC (as a mix of treatment options), treatment with amivantamab was predicted to yield a 54% increase in LY and 54% increase in QALYs over a lifetime simulation. This evaluation showed that amivantamab had clinical benefits (i.e., prolonged PFS and OS) at additional costs when compared to both BSC as well as the specific treatment classes, with an ICER range of appr. 1,000,000 – 1,5 million DKK (Table 46). The lowest cost-effectiveness ratio was demonstrated when amivantamab was compared to immunotherapy only. For the comparison to BSC the ICER was 1,489,941 DKK.

Table 44. Discounted Health Benefits

Health Benefits	Amivantamab	BSC	I-O agents	EGFR TKIs	Non pt-chemo
Total LYs	**2.17**	**1.40**	**1.22**	**1.13**	**1.38**
PF LYs	0.82	0.55	0.53	0.45	0.63
PP LYs	1.35	0.86	0.70	0.68	0.74
Total QALYs	**1.35**	**0.88**	**0.77**	**0.71**	**0.87**
PF QALYs	0.59	0.39	0.37	0.32	0.45
PP QALYs	0.77	0.49	0.40	0.39	0.42
Disutilities: AEs	0.0005	0.0023	0.0002	0.0003	0.0049

Abbreviations: AE = adverse event, BSC = best supportive care, EGFR = epidermal growth factor receptor, I-O = immuno-oncology, LY = life year, QALY = quality-adjusted life year, TKI = tyrosine kinase inhibitor

Table 45. Discounted Cost Outcomes

Cost Outcomes	Amivantamab	BSC	I-O agents	EGFR TKIs	Non pt-chemo
Total costs	DKK 1,202,526	DKK 494,942	DKK 589,664	DKK 375,481	DKK 463,601
Drug costs	DKK 789,869	DKK 188,766	DKK 333,026	DKK 108,103	DKK 114,553
Administration costs	DKK 76,422	DKK 30,163	DKK 38,251	DKK 0	DKK 44,840
AE management costs	DKK 1,555	DKK 7,446	DKK 338	DKK 441	DKK 16,419
Disease management costs: PF	DKK 64,260	DKK 42,929	DKK 41,087	DKK 35,489	DKK 49,410
Disease management costs: PP	DKK 97,984	DKK 62,284	DKK 50,917	DKK 49,597	DKK 54,152
Disease management costs: One-off - Progression	DKK 0	DKK 0	DKK 0	DKK 0	DKK 0
Disease management costs: One-off - Death (terminal care)	DKK 66,184	DKK 68,063	DKK 68,505	DKK 68,726	DKK 68,134
Subsequent treatment costs	DKK 65,915	DKK 64,839	DKK 35,149	DKK 76,559	DKK 90,737
Travel costs – PF	DKK 3,647	DKK 6,707	DKK 1,761	DKK 17,395	DKK 2,255

Travel costs – PP	DKK 2,237	DKK 1,422	DKK 1,162	DKK 1,132	DKK 1,236
Patient Time – PF	DKK 13,055	DKK 8,721	DKK 8,347	DKK 7,210	DKK 10,038
Patient Time – PP	DKK 21,399	DKK 13,602	DKK 11,120	DKK 10,831	DKK 11,826

Abbreviations: AE = adverse event, BSC = best supportive care, EGFR = epidermal growth factor receptor, I-O = immuno-oncology, LY = life year, QALY = quality-adjusted life year, PF = progression-free, PP = post-progression, TKI = tyrosine kinase inhibitor

Table 46. Discounted Incremental Results

Outcomes	BSC	I-O agents	EGFR TKIs	Non pt-chemo
Incremental costs	DKK 707,584	DKK 612,863	DKK 827,045	DKK 738,925
Incremental LYs	0.76	0.94	1.03	0.79
Incremental QALYs	0.47	0.58	0.64	0.48
ICER (DKK/LY)	DKK 927,398	DKK 650,147	DKK 801,147	DKK 933,151
ICER (DKK/QALY)	**DKK 1,489,941**	**DKK 1,059,614**	**DKK 1,292,765**	**DKK 1,533,154**

Abbreviations: BSC = best supportive care, EGFR = epidermal growth factor receptor, I-O = immuno-oncology, ICER = incremental cost-effectiveness ratio, INMB = incremental net monetary benefits, TKI = tyrosine kinase inhibitor LY = life year, QALY = quality-adjusted life year

8.7 Sensitivity analyses

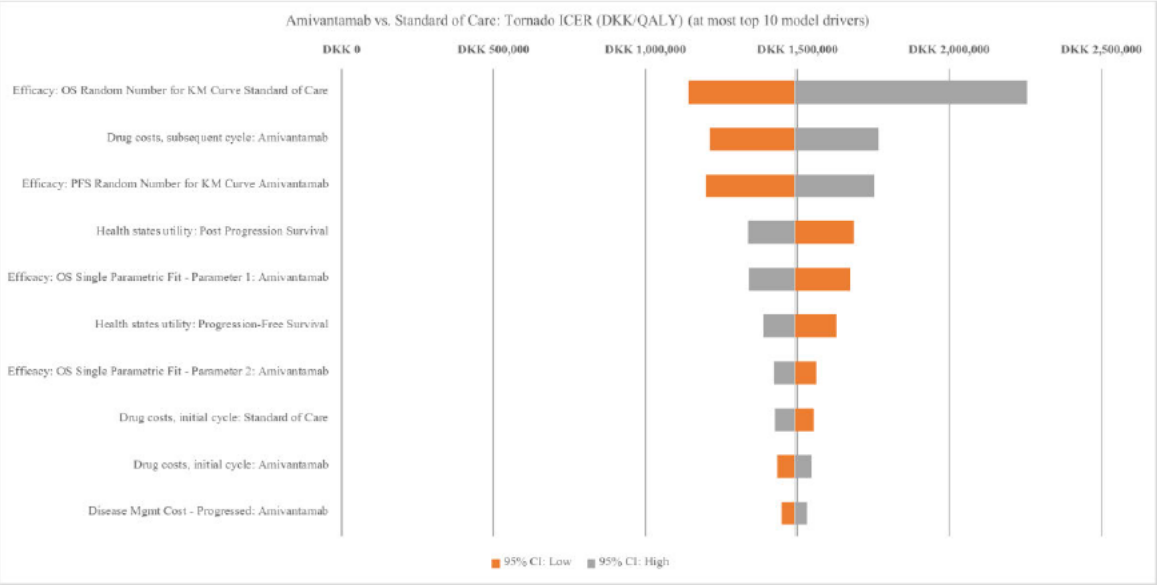
Deterministic sensitivity analyses (DSA) were conducted by systematically varying parameters from the base case one at a time. This allowed for the evaluation of the robustness of key model outcomes to change in a single parameter and helped determine the main drivers of the model's results. The analysis evaluated a lower and upper bound for each model parameter considered. The bounds were derived from descriptive statistics, when available (e.g., 95% CIs).

A probabilistic sensitivity analysis (PSA) was conducted to account for multivariate and stochastic uncertainty in the model. The uncertainty in the individual parameters was characterized using probability distributions and analyzed using Monte Carlo simulation (10,000 replications). In the PSA, the uncertainties around parameters were estimated as shown in Appendix J *Probabilistic sensitivity analyses*. For each PSA iteration, a new set of input parameter values were randomly sampled based on their assigned probability distributions.

8.7.1 Deterministic sensitivity analyses

The key drivers identified for ICERs included the parameters for OS for both amivantamab and BSC. Additionally, varying inputs that affected amivantamab's acquisition cost had significant impacts on the ICERs – the random number for varying amivantamab's PFS KM data and acquisition costs themselves. The tornado plot is presented in Figure 34. The largest single driver of change was the random number for varying the Standard of Care OS KM data..

Figure 34. Tornado Diagram of ICERs: Amivantamab vs. BSC



Abbreviations: BSC = best supportive care, CI = confidence interval, KM = Kaplan-Meier, OS = overall survival, PFS = progression-free survival, QALY = quality-adjusted life year

The impact of changes in price of amivantamab on ICER is presented in Figure 35.

Figure 35. Graphical representation of impact of amivantamab price on the ICER

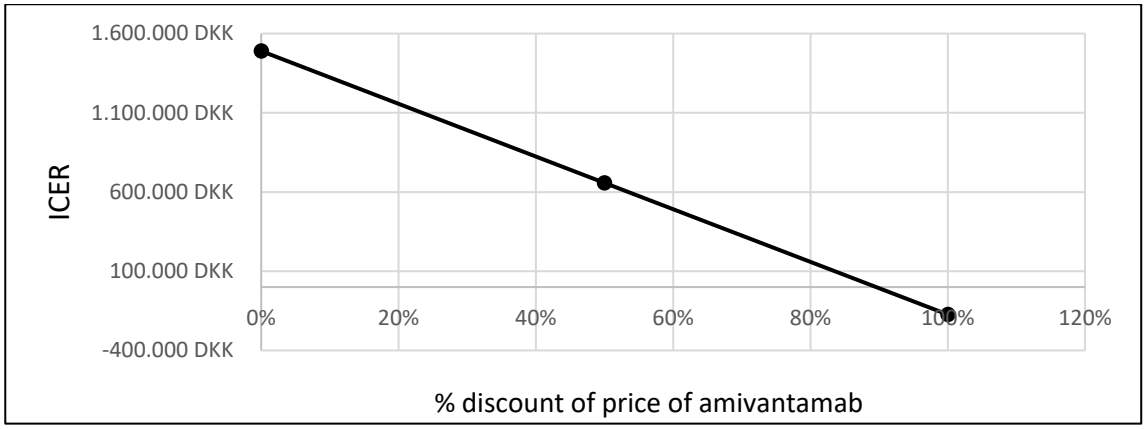


Table 47. One-way sensitivity analyses results for top 10 parameters

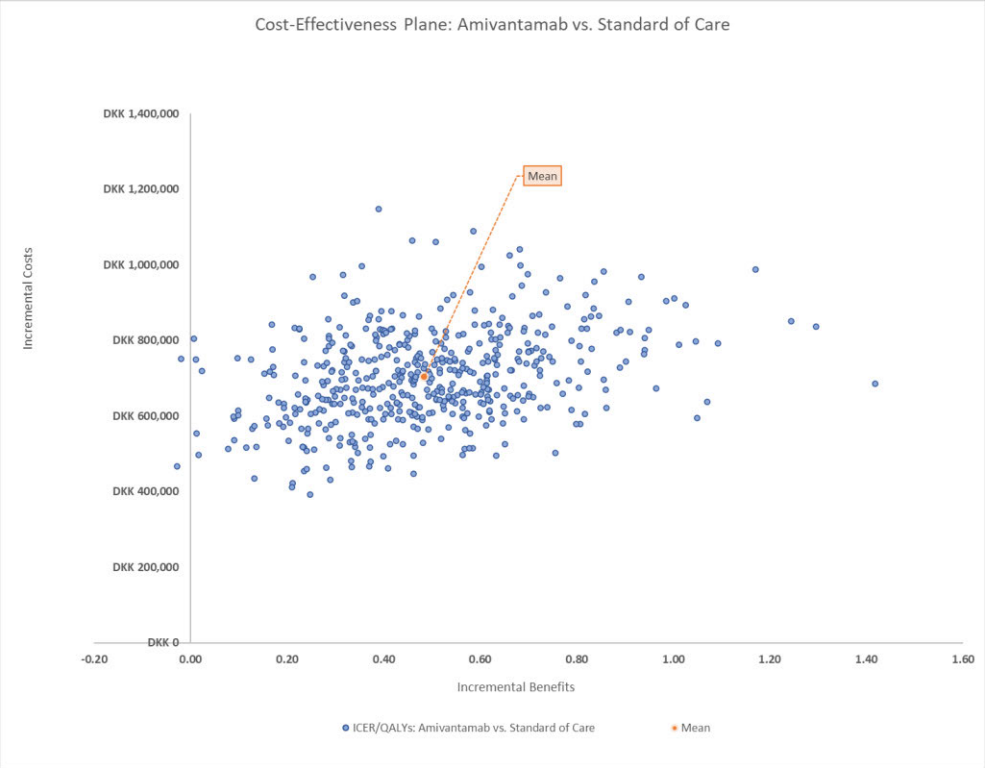
	Lower	Higher
Parameters	**Percentage difference to base case ICER**	**Percentage difference to base case ICER**
Base Case		
Efficacy: OS Random Number for KM Curve Standard of Care	-30%	34%
Drug costs, subsequent cycle: Amivantamab	-23%	16%
Efficacy: PFS Random Number for KM Curve Amivantamab	-24%	15%
Efficacy: OS Single Parametric Fit - Parameter 1: Amivantamab	11%	-11%
Health states utility: Progression-Free Survival	9%	-7%
Efficacy: OS Single Parametric Fit - Parameter 2: Amivantamab	5%	-5%
Drug costs, initial cycle: Standard of Care	4%	-4%
Drug costs, initial cycle: Amivantamab	-4%	4%
Disease Mgmt Cost - Progressed: Amivantamab	-3%	3%

Abbreviations: DKK = Danish krone, KM = Kaplan-Meier, OS = overall survival, PFS = progression-free survival, QALY = quality-adjusted life year

8.7.2 Probabilistic sensitivity analyses

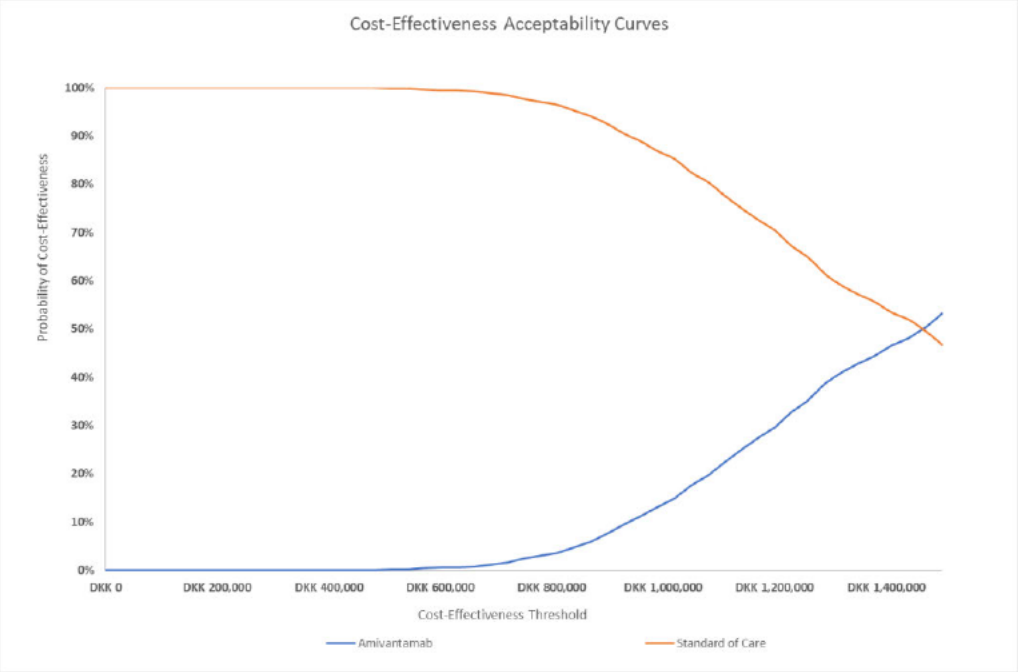
The incremental health outcomes in terms of QALYs gained (discounted, per patient) were plotted against the incremental cost of amivantamab vs. BSC on a cost-effectiveness plane, which is presented in Figure 36. Based on the results of the 10,000 PSA simulations, the mean incremental costs and QALYs were DKK 703,861 and 0.48, respectively, resulting in an average ICER of DKK 1,454,655. More detail about how the uncertainties around parameters were estimated is shown in Appendix J *Probabilistic sensitivity analyses*.

Figure 36. Cost-effectiveness Scatterplot: Amivantamab vs. BSC



Abbreviations: BSC = best supportive care, ICER = incremental cost-effectiveness ratio, QALY = quality-adjusted life year

Figure 37. Cost-effectiveness Acceptability Curves: Amivantamab vs. BSC



8.7.3 Scenario analyses

A number of scenario analyses were explored in which model assumptions or parameters were altered. The results of the scenario analyses carried out are presented in Table 48.

Table 48. Summary of Scenario Analyses (Amivantamab vs. BSC)

#	Description (Scenario Setting)	Incremental Costs	Incremental QALYs	ICER (DKK/QALY)
Base Case		707,584 DKK	0.47	1,489,941 DKK
1	Vial Sharing (Yes)	732,825 DKK	0.47	1,543,091 DKK
2	Reduced time horizon (10 years)	707,268 DKK	0.47	1,493,064 DKK
3	Survival scenario options for amivantamab (OS – generalized gamma)	702,343 DKK	0.44	1,592,747 DKK
4	Survival scenario options for amivantamab (PFS – Weibull)	735,697 DKK	0.48	1,531,740 DKK
5	Amivantamab alternative treatment discontinuation option (TTD KM data)	785,766 DKK	0.47	1,654,567 DKK
6	SoC alternative treatment discontinuation option (TTNT KM data)	653,054 DKK	0.47	1,375,119 DKK
7	Alternative utility values (Chouaid weighted 2L, 3L+)	707,584 DKK	0.43	1,633,138 DKK
8	Alternative data sources for SoC (pooled EU)	706,693 DKK	0.44	1,596,162 DKK
9	Alternative data sources for SoC (pooled US)	722,127 DKK	0.53	1,362,790 DKK
10	Exclusion of AE disutilities	707,584 DKK	0.47	1,495,504 DKK
11	Exclusion of disease management costs	652,431 DKK	0.47	1,373,808 DKK

Abbreviations: 2L = second-line, 3L+ = third-line plus, AE = adverse event, EU = European, ICER = incremental cost-effectiveness ratio, KM = Kaplan-Meier, OS = overall survival, PFS = progression-free survival, QALY = quality-adjusted life year, RWE = real world evidence, SoC = standard of care, TTD = time-to-treatment discontinuation, TTNT = time-to-next treatment, US = United States

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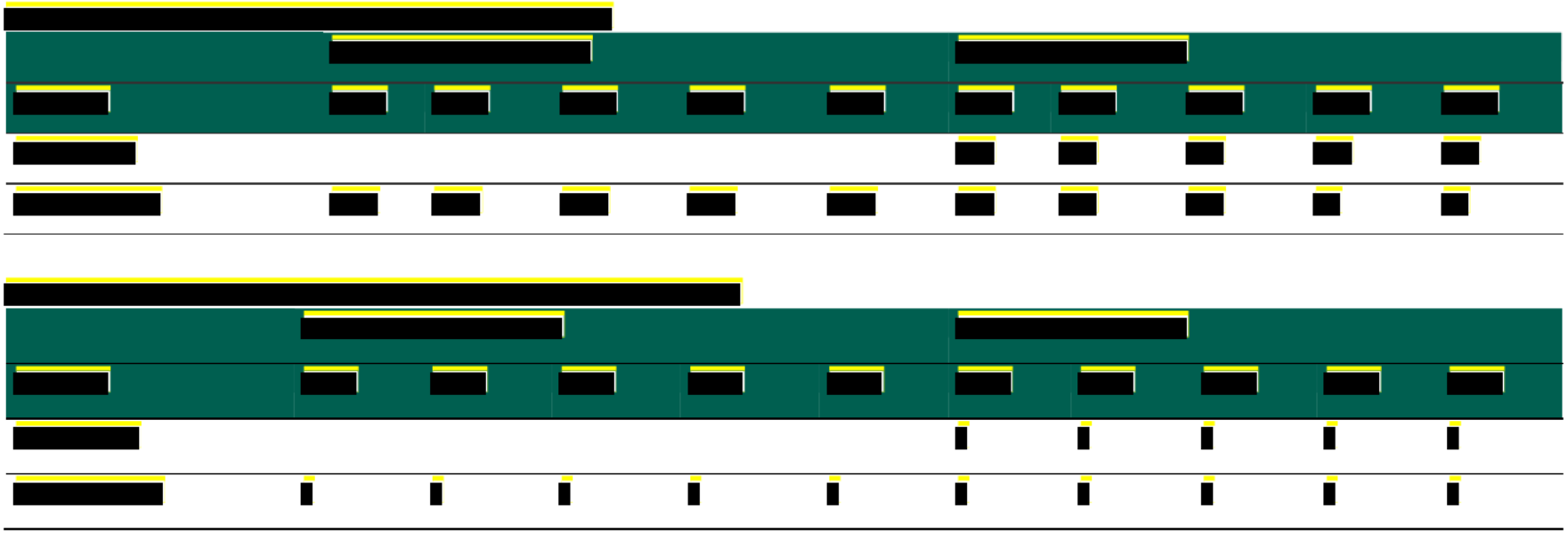
9. Budget impact analysis

The budget impact analysis is embedded within the economic model for amivantamab. Thus, the same resource use and cost inputs described in section 8.5 are used.

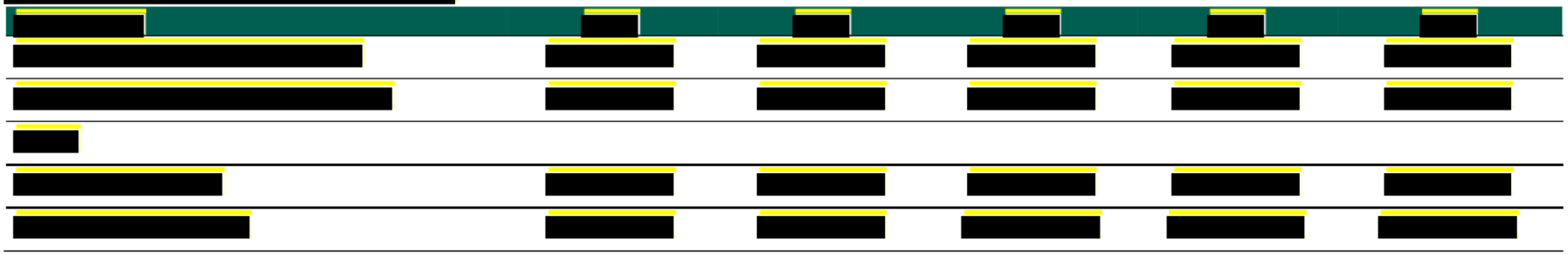
Patient number estimates for Exon 20ins patients identified through EFGR testing were made by Janssen (Table 49). Market shares were also estimated based on Janssen data on file (Table 50). This enables the calculation of a number of patients expected in Denmark on different treatments (Table 51). The budget impact of amivantamab is detailed in Table 52.

Table 49. Number of patients with Exon 20 insertions identified through EFGR testing

Population	Year 1	Year 2	Year 3	Year 4	Year 5
Patients with Exon 20 insertions identified through EFGR testing	8	8	8	8	8



[redacted]



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10. Discussion on the submitted documentation

10.1 Strengths and limitations of the adjusted treatment comparisons

These analyses were conducted to generate comparative evidence for amivantamab, for which the main evidence base is CHRYSALIS, a Phase 1b, single-arm trial, and provide estimates for the comparative efficacy for amivantamab versus BSC (representing the basket of treatments used in real life clinical practice) and versus treatment classes of interest (where feasible). The comparison versus BSC is based on the largest sample size, while the comparison versus treatment classes provides comparative efficacy with greater granularity. From an HTA perspective, the BSC arm represents the most relevant comparator to evaluate the relative efficacy of amivantamab, as this comparator reflects the heterogeneity of the treatment lines and treatments received by this patient population, where no standard of care currently exists. This remains true even for HTA bodies which request comparative analyses versus treatments more representative of the local setting and/or in line with local guidelines, as this is reflective of a control group receiving a broad variety of treatments in clinical practice.

Furthermore, comparative efficacy is presented in terms of multiple relevant efficacy outcomes, including those most relevant to HTA, with ORR, PFS and OS being primary and secondary outcomes in CHRYSALIS. In total, seven data sources across Europe and the US were used to inform the analyses, maximising relevance to markets across these regions; consistency of results across regions also supports their generalisability globally. The prognostic characteristics to be adjusted for were identified through an evidence-based process. Most prognostic variables which were identified as clinically important were available in the external data sources and were therefore adjusted for if the data allowed this.

The adjusted treatment comparisons were conducted using robust statistical methodology. Where feasible, two methods (IPW and covariate adjustment) were employed to adjust comparative analyses between cohorts for differences in prognostic baseline characteristics to avoid confounding, and conclusions were generally aligned across both methods. The prognostic baseline characteristics adjusted for between treatment cohorts were identified by an SLR and subsequently validated by clinical expert feedback with regard to the specific target population of interest. Where IPW was conducted, the ATT was used as the primary analysis. The IPW results can therefore be interpreted as relative treatment effects for amivantamab versus its comparators estimated in the CHRYSALIS patient population, and as such simulates results for a randomized trial in this enrolled population. Alternative IPW approaches were also investigated (ATE and ATO) and were largely consistent with ATT results, supporting the robustness of the results more broadly.

Despite comparative analyses being adjusted for available clinically important prognostic variables, bias due to residual confounding cannot be entirely excluded as with any non-randomised comparison. It was not always feasible across all data sources to adjust for all baseline characteristics identified as relevant prognostic factors. Despite these potential limitations, the comparative results versus all RWD sources were consistent across the external data sources. Larger randomised studies for amivantamab could help to validate the findings of these adjusted treatment comparisons in future.

Small sample sizes represent a further limitation of the analysis and resulted in some comparisons not being feasible. This was particularly so when comparing amivantamab versus treatment classes, where the covariate adjustment method was used to retain an adequate sample size, and for the comparisons versus individual RWD sources. Furthermore, due to the small sample sizes, comparisons versus specific individual treatments were not feasible.

10.2 Strengths and limitations with the health economic evaluation

In the context of model development, the success story of amivantamab in the treatment of advanced NSCLC with EGFR Exon 20ins has resulted in a number of challenges. The model was developed based on the best available evidence and modeling practices. However, due to external constraints (namely the small patient numbers and lack of head-to-head trials), uncertainties exist. Given that amivantamab is currently the only targeted treatment approved, all treatments were prescribed off-label in clinical practice. Since there are no other licensed treatments for this patient population in Europe and there are small patient numbers with heterogeneity on treatments received by

patients as BSC, comparators in the CEM were grouped into treatment classes to maximize patient numbers. In addition, there is no head-to-head clinical study comparing the clinical efficacies of different treatment options in the Exon 20ins indication. As a result, RWE was used to derive the relative efficacy inputs for the comparator arms (as discussed above). Another source of uncertainty is the distribution of patients across comparators in the treatment basket for subsequent lines. Patients may follow very different treatment pathways depending on factors such as response to prior treatments, disease severity, or age. Although it is important to capture the impact of current treatment options on the downstream treatment pathway, such data were not directly available from the CHRYSALIS trial or literature. In the model, the same distribution of treatments (derived from the RWE databases with the assumption that patients do not receive the same treatment class in the subsequent line) is applied regardless of choice of comparator, to minimize the effect of this uncertainty. The user can change the distribution of subsequent treatments, which only affects costs and not efficacy.

The limitations mentioned above can be mitigated by modifying inputs to explore the impact on the model results. Overall, the current model is flexible in terms of the selection of comparators as well as the application of alternative approaches to estimate the PFS, OS, and treatment duration. However, it is important to consider the combinations of these factors for clinical plausibility when deciding on the model settings

This economic evaluation has several strengths. The clinical pathways upon which the model was based reflect the current clinical practice for EGFR Exon 20ins. The model structure, projection approaches for clinical endpoints, and key assumptions were validated by external clinical and health economic experts to ensure accuracy and completeness. The modelling approach was developed based on a thorough review of published economic modelling approaches and available HTA submission reports in NSCLC. The model's approach and programming were well validated. Furthermore, the clinical outcomes of the comparator BSC were informed by an ITC analysis, which was based on individual patient data from seven data sources across Europe and the US. This maximised the relevance of the model results to markets across these regions. From an HTA perspective, the BSC arm may represent the most relevant comparator to evaluate the relative efficacy of amivantamab, as this comparator reflects the heterogeneity of the treatment lines and treatments received by this patient population, where no standard of care currently exists in clinical practice.

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11. List of experts

Double blinding was used when a third party consulted experts to prepare this submission. Physicians were contacted by email and invited to participate in an advisory interview to discuss NSCLC clinical treatment practices in their clinic. Topics include treatment management, diagnosis and testing practices, registries and biobanks, and emerging trends. A 'Discussion Guide' was provided to give a more detailed overview of the topics for discussion. Janssen were not identified to participants, neither at recruitment nor within the interview. Similarly, participants' identity was kept confidential, and their answers anonymized. Therefore, the list of experts consulted cannot be provided.

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

N/A

Appendix B Main characteristics of included studies

No studies identified in the SLR are included in the comparative analyses of amivantamab to BSC, nor part of the health economic analysis. For more information regarding efficacy and safety of amivantamab compared to BSC, please see section 7.1.2. Chrysalis study design, population and selection criteria are presented below. Information about the indirect treatment comparison is also provided.

CHRYSALIS

Description of study design

CHRYSALIS was a first-in-human, open-label, multicentre, 2-part, phase I dose escalation study in adult patients (aged ≥18 years) with advanced NSCLC. The primary study objectives [1] included:

Part 1 (dose escalation phase):

- Determining a recommended phase II monotherapy dose (RP2D) and recommended phase II combination dose (RP2CD) regimen

Part 2 (dose expansion phase):

- Evaluating the safety and tolerability of amivantamab
- Assessing the anti-tumour efficacy of amivantamab as a monotherapy and in combination with lazertinib at RP2(C)D

For both Part 1 and Part 2, the study was divided into three periods: Screening, Treatment and Follow-up [1].

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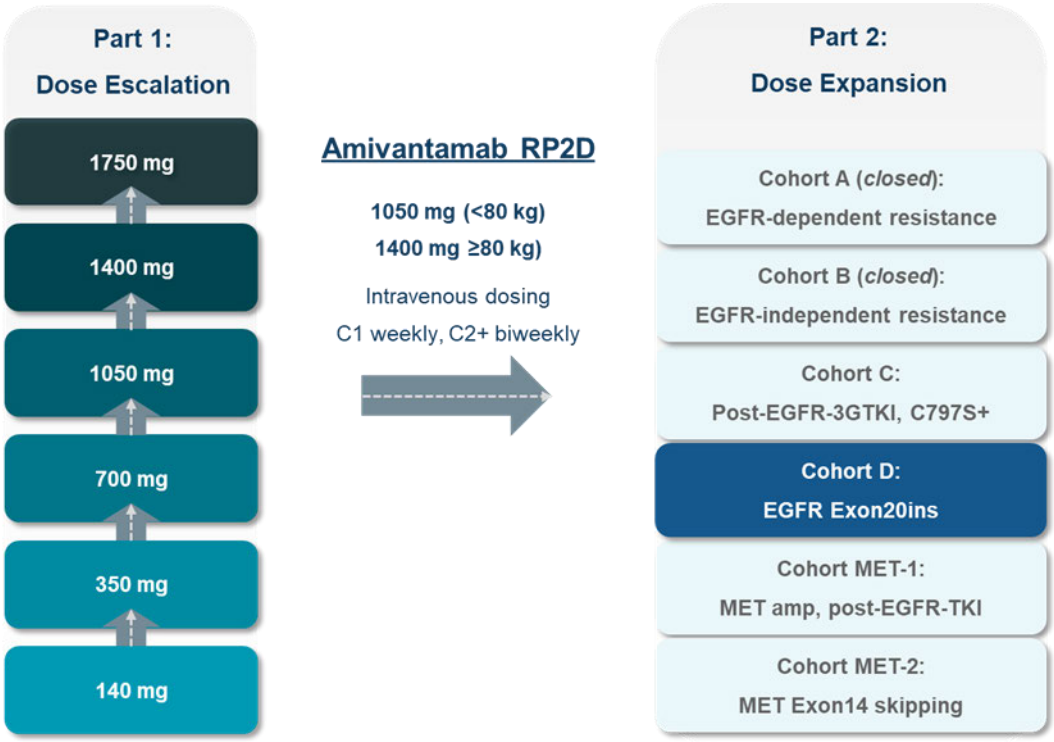
Figure 38. CHRYSALIS study design [70]



EGFR = epidermal growth factor receptor; MET = hepatocyte growth factor; RP2D = recommended phase II dose; TKI = tyrosine kinase inhibitor

During the Screening Period, patient eligibility was determined up to 28 days prior to the first dose of study drug. The Treatment Period began from the first dose of study drug and finished 30 days after the last dose of study drug. Treatment was administered until disease progression, unacceptable toxicity or withdrawal of consent. The follow-up Period began at the end of the Treatment Period and continued until the end of study, death, loss to follow-up or withdrawal of consent, whichever came first. Survival status and subsequent anti-cancer therapy were obtained every 3 months during the follow-up Period. The end of study occurred after all patients completed therapy with study treatment and had at least 6 months of follow-up or discontinued from the study [1].

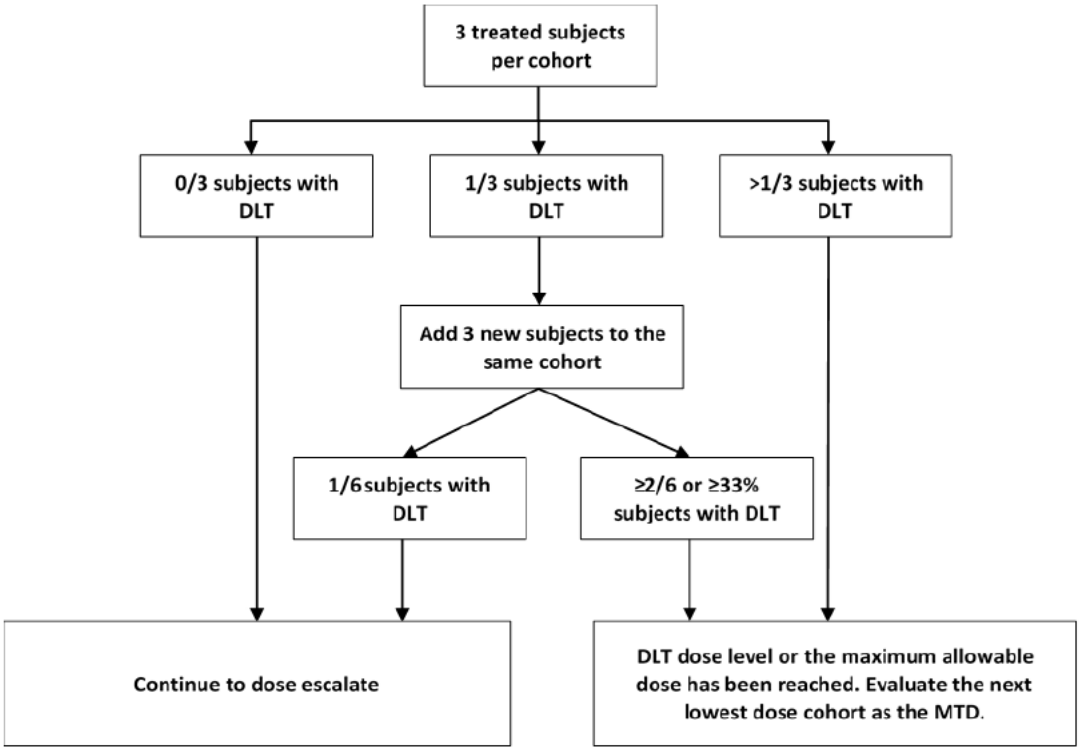
This study was conducted in an outpatient setting. Patients were seen at the study centre on pre-specified days for study drug administration and study evaluations (e.g., AE, monitoring, physical examinations, laboratory assessments and collection of pharmacokinetic samples) [1].

Part 1 (dose escalation)

Part 1, the dose escalation phase, followed a traditional 3+3 design (Figure 39) to determine the maximum tolerated dose (MTD) of amivantamab or the maximum administered dose (MAD) in case of no MTD. The 3+3 study design was based on a commonly used and widely accepted design model for dose escalation in phase I oncology studies and was applied to both the monotherapy amivantamab and combination amivantamab and lazertinib dose escalations [1].

The MTD is defined as the highest dose level at which <33% of patients at a given dose level experience a DLT. The MTD was used to inform the RP2D for amivantamab monotherapy and the RP2CD for amivantamab and lazertinib combination therapy [1].

Figure 39. Dose escalation study design [1]



DLT = dose limiting toxicity; MTD = maximum tolerated dose

For amivantamab monotherapy, the first cohort of three patients received amivantamab at a starting dose of 140 mg, administered as an IV infusion once weekly for four weeks, then every two weeks thereafter. In the absence of a DLT, subsequent cohorts received escalating doses Table 53 [1].

Table 53. Amivantamab dose escalation levels

Dose Level	Amivantamab, mg
1	140
2	350
3	700
4	1,050
5	1,400
6	1,750

Part 2 (dose expansion)

The primary objective of Part 2 was to evaluate the safety, tolerability and anti-tumour activity of amivantamab alone or in combination with lazertinib. In this dose expansion phase, molecularly defined cohorts of patients received RP2D or RP2CD regimens as determined in part 1. Cohorts were designed to characterise the safety and pharmacokinetics of

amivantamab and to explore clinical activity within molecularly defined tumour subgroups. Patients were assigned to the following cohorts [1]:

- Cohort C: Treatment with amivantamab monotherapy in patients with primary EGFR mutations and MET amplification/mutations after progression on any EGFR TKI
- Cohort D: Treatment with amivantamab monotherapy in patients with primary EGFR Exon 20ins mutations not previously treated with a TKI with specific Exon 20 activity, including those who had received platinum-based doublet therapy
- Cohort E: Patients with EGFR Exon 19 deletion or Exon 21 L858R activating mutations and disease progression after 1st or 2nd-line treatment with a 3rd generation TKI, e.g., osimertinib (receiving amivantamab in combination with lazertinib)

Patients in all cohorts were assessed for potential drivers of response or resistance to amivantamab, including but not limited to EGFR and MET pathway alterations [1].

Outcome measures

Table 54 provides a summary of the objectives, primary endpoints and secondary endpoints of the two-part CHRYSALIS study [1].

Table 54. Objectives and outcome measures of the CHRYSALIS study [1]

	Part 1	Part 2
Objectives	• Determine the MTD and the RP2D/RP2CD regimen for patients treated with amivantamab or amivantamab + lazertinib, respectively • Assess the pharmacokinetics and immunogenicity of amivantamab and amivantamab + lazertinib at multiple dose administrations	• Safety, tolerability and anti-tumour activity of the RP2D/RP2CD regimens for patients treated with amivantamab or amivantamab + lazertinib, respectively • Anti-tumour activity of amivantamab at the RP2D, and amivantamab + lazertinib at the RP2CD in cohorts with EGFR or MET mutations who have progressed after treatment with SoC
Primary Endpoint	• DLT	• AEs defined by the NCICTCAE in patients treated at the RP2D and RP2CD regimens • ORR, DOR and CBR according to RECIST
Secondary Endpoints	• PFS, OS, time to treatment failure • Serum pharmacokinetic parameters of amivantamab • Plasma pharmacokinetic parameters of lazertinib	
Exploratory Endpoints*	• NSCLC-SAQ • EQ-5D-5L	

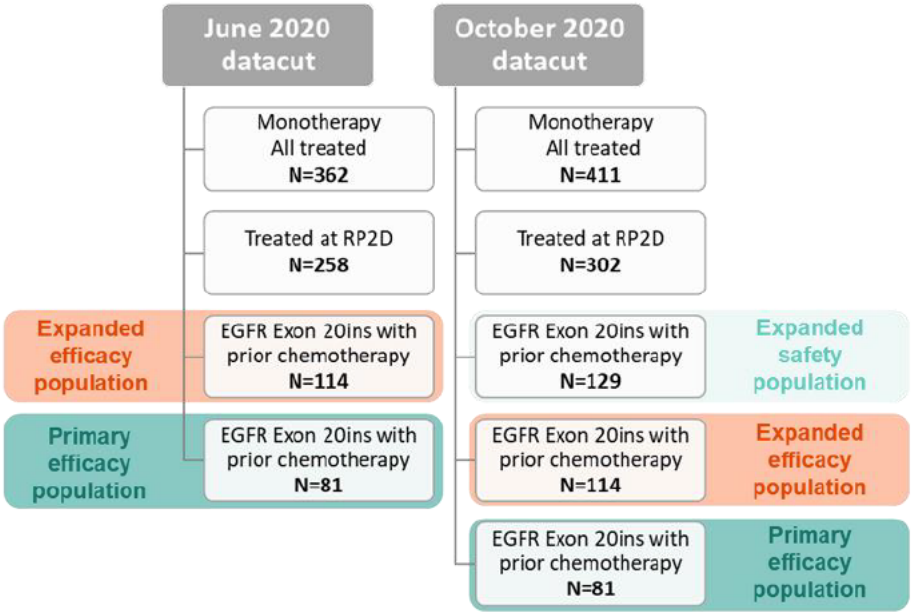
*PROs were not collected from the start of the trial but were added at a later date

AE = adverse event; CBR = clinical benefit rate; DLT = dose limiting toxicity; EGFR = epidermal growth factor receptor; EQ-5D-5L = European Quality of Life 5 Dimension 5 Level Questionnaire; MET = hepatocyte growth factor; MTD = maximum tolerated dose; NCICTCAE = National Cancer Institute Common Terminology Criteria for Adverse Events Version 4.03; NSCLC-SAQ = Non-Small Cell Lung Cancer Symptom Assessment Questionnaire; ORR = overall response rate; OS = overall survival; PFS = progression free survival; PRO = patient reported outcome; RECIST = Response Criteria in Solid Tumours Version 1.1; RP2CD = recommended phase II combination dose; RP2D = recommended phase II dose; SoC = standard of care

Study population

Overall, 362 patients with NSCLC had been treated with varying doses of amivantamab in Parts 1 and 2 of CHRYSALIS as of 8 June, 2020 [67]. Of those, 258 patients had received the current RP2D [67]. With additional follow-up of four months (8 October, 2020 datacut), the total treated population has increased from 362 to 411 patients and the post-platinum safety population with Exon 20ins treated at the RP2D has increased from 114 to 129 patients (Figure 40)[15].

Figure 40. CHRYSALIS post-platinum patient disposition [67]



EGFR = epidermal growth factor receptor; Exon 20ins = Exon 20 insertion; RP2D = recommended phase 2 dose

As of 8 June, 2020, a total of 187 patients with Exon 20ins received ≥1 dose of amivantamab monotherapy in CHRYSALIS [67]. Of those, 114 received amivantamab at the RP2D and 81 were response-evaluable with ≥3 disease assessments as of June 2020; these patients formed the primary efficacy population (with data from October 2020 forming the basis of the proposed US prescribing information) [35, 67]. At the next datacut in October 2020, all 114 patients had ≥3 disease assessments after treatment initiation and were included in the expanded efficacy population. A total of 129 patients with EGFR Exon 20ins were treated with amivantamab by the October 2020 datacut and were included in the expanded safety population (Figure 40) [15].

Table 55. CHRYSALIS patient population definitions

	Primary efficacy population	Expanded efficacy population	Expanded safety population
Number of patients	81	114	129
Definition	Post-platinum EGFR Exon 20ins with ≥3 disease assessments as of 8 June 2020 (enrolled in Cohort D [n=73] or Part 1 [n=4] or Cohort A [n=4] prior to Cohort A closure)	Post-platinum EGFR Exon 20ins with ≥3 disease assessments as of 8 October 2020	Post-platinum EGFR Exon 20ins treated at RP2D
Clinical datacut presented in GVD	8 October 2020	8 October 2020	8 October 2020
Median follow-up	9.7 months	5.1 months	7.9 months
Analyses/ regulatory documents and submissions	Interim CSR (June 2020 datacut) Interim CSR addendum and FDA Biologics License Application (October 2020 datacut)	Interim CSR (safety analysis set; June 2020 datacut) Interim CSR addendum (expanded efficacy population; October 2020 datacut)	FDA 120-Day Safety Update (October 2020 datacut)

Patient selection criteria

Patients enrolled in the study were required to meet all of the inclusion criteria presented in Table 56 to be eligible for participation. Any candidate who met any of the exclusion criteria presented in Table 57 were excluded from participating in the study [1].

Table 56. CHRYSALIS patient inclusion criteria

Inclusion Criteria	
General	Patient must be aged ≥18 and satisfy the legal age of consent in the jurisdiction in which the study is being conducted
	Patient must have histologically or cytologically confirmed NSCLC that is metastatic or unresectable
	Patient must have either progressed after receiving prior therapy for metastatic disease, be ineligible for, or have refused all other currently available therapeutic options. In cases where patients refuse currently available therapeutic options, this must be documented in the study records
	Patient must have ECOG performance status 0 or 1
	Patient must have the following organ and bone marrow function, without history of red blood cell transfusion, platelet transfusion or G-CSF support within 7 days prior to the date of the test: • Haemoglobin ≥10 g/dL • ANC ≥1.5 x 10^9/L • Platelets ≥75 x 10^9/L • AST and ALT ≤3 x upper limit of normal • Total bilirubin ≤1.5 x upper limit of normal • Serum creatine ≤1.5 x upper limit of normal
	Before enrolment, a female patient must be either: • not of childbearing potential (premenarchal, postmenopausal, permanently sterilised or otherwise be incapable of pregnancy), or • of childbearing potential and practicing effective methods of birth control and have a negative serum □-human chorionic gonadotropin at screening, and • agree not to donate eggs for the purposes of assisted reproduction during the study and for 6 months after receiving the last dose of study drug
	A male subject who is sexually active with a woman of childbearing potential must: • agree to use a condom with spermicidal foam/gel/film/cream/suppository • have a partner also practicing a highly effective method of contraception • not donate sperm during the study and for 6 months after receiving the last dose of study drug
	Patients must sign an informed consent form indicating that they understand the purpose of and procedures required for the study and are willing to participate in the study, including the requirement to provide information during the follow-up period
Part 1	Patients must have been diagnosed with EGFR Exon 19 deletion or L858R activating mutation and • have progressed after front-line treatment with first (erlotinib or gefitinib) or second generation (afatinib) TKI, or • have been treated with a third generation TKI (e.g., osimertinib) in either the front-line or second-line setting, and • be ineligible for enrolment in Cohort C
	Patients must have evaluable disease
Part 2	Patients must have disease with a previously diagnosed activating EGFR mutation (includes both inhibitor sensitive primary mutations such as Exon 19 deletion and L858R, as well as marketed TKI-resistant mutations such as Exon 20 insertions or activating MET Exon 14 skipping mutation)

Inclusion Criteria
Documentation of primary activating EGFR or MET mutation eligibility by CLIA-certified laboratory (or equivalent) testing is required
Patients must have measurable disease according to RECIST v1.1
In cohort C, patients with primary EGFR-mutated disease must have a documented EGFR alteration (e.g., C797S) mediating resistance to previous treatment with a third generation EGFR TKI (e.g., osimertinib)
• In patients with primary Exon 20 insertion disease, the documented EGFR alteration may arise following treatment with a TKI with known activity against Exon 20 insertion disease (e.g., poziotinib)
In cohort D, patients must have been previously diagnosed with an EGFR Exon 20 insertion and have not been previously treated with a TKI with known activity against Exon 20 insertion disease (e.g., poziotinib)
In cohort E, patients must have been diagnosed with EGFR Exon 19 deletion or L858R activating mutation, who have progressed after first or second-line treatment with a third generation TKI (e.g., osimertinib)
Patients must agree to the pre-treatment tumour biopsy (or submission of equivalent archival material) and a tumour biopsy at the time of disease progression, as well as corresponding blood samples for ctDNA analysis
• For patients in cohort C equivalent pre-treatment tumour tissue must have been collected after progression on the most recent systemic anti-cancer treatment

ALT = alanine aminotransferase; ANC = absolute neutrophil count; AST = aspartate aminotransferase; CLIA = clinical laboratory improvement amendments; MET = hepatocyte growth factor receptor; ctDNA = circulating tumour DNA; ECOG = Eastern Cooperative Oncology Group; EGFR = epidermal growth factor receptor; G-CSF = granulocyte colony stimulating factor; NSCLC = non-small cell lung cancer; RECIST = Response Criteria in Solid Tumours Version 1.1; TKI = tyrosine kinase inhibitor

Table 57. CHRYSALIS patient exclusion criteria

	Exclusion Criteria
General	Patient has uncontrolled inter-current illness, including but not limited to poorly controlled hypertension or diabetes, ongoing or active infection (i.e., has discontinued all antibiotics for at least one week prior to first dose of amivantamab), or psychiatric illness/social situation that would limit compliance with study requirements
	Patients with medical conditions requiring chronic continuous oxygen therapy
	Patient has had prior chemotherapy, targeted cancer therapy, immunotherapy or treatment with an investigational anti-cancer agent within 2 weeks or 4 half-lives whichever is longer, before the first administration of amivantamab. For agents with long half-lives, the maximum required time since last dose is 4 weeks
	Patients with untreated brain metastases
	Patient has a history of malignancy other than the disease under study within 3 years before screening (exceptions are squamous and basal cell carcinomas of the skin and carcinoma in situ of the cervix, or malignancy with minimal risk of recurrence within a year from screening)
	Patient has a history of clinically significant cardiovascular disease
	Patient has leptomeningeal disease
	Patient has known allergies, hypersensitivity or intolerance to amivantamab or its excipients
	Patient has received an investigational drug (including investigational vaccines, but not including anti-cancer therapy) or used an invasive investigational medical device within 6 weeks before the planned first dose of study drug
	Patient is a woman who is pregnant, or breast-feeding, or planning to become pregnant while enrolled in this study or within 6 months after the last dose of study drug
	Patient is a man who plans to father a child while enrolled in this study or within 6 months after the last dose of study drug
	Patient has, or will have, any of the following:
	• An invasive operative procedure with entry into a body cavity, within 4 weeks or without complete recovery before Cycle 1 Day 1

Exclusion Criteria	
	• Significant traumatic injury within 3 weeks before the start of Cycle 1 Day 1 (all wounds must be fully healed prior to Day 1) • Any medical condition that requires intact wound healing capacity and is expected to endanger subject safety if wound healing capacity would be severely reduced during administration of the investigational agent • Expected major surgery while the investigational agent is being administered or within 6 months after the last dose of study drug Patient has any condition for which, in the opinion of the investigator, participation would not be in the best interest of the subject or that could prevent, limit or confound the protocol-specified assessments Any investigative site personnel directly affiliated with this study
Part 1	For cohort E, any previous treatment with systemic anti-cancer immunotherapy, including but not limited to anti-PD-1, anti-PD-L1 and anti-CTLA-4 agents Patient has positive hepatitis B virus surface antigen, hepatitis C antibody or other clinically active infectious liver disease Patient has a history of HIV antibody positive, or tests positive for HIV at Screening Patient has any serious underlying medical or psychiatric condition (e.g., alcohol or drug abuse), dementia or altered mental status or any issue that would impair the ability of the subject to receive or tolerate the planned treatment at the investigational site, to understand informed consent or that in the opinion of the investigator would contraindicate the subject's participation in the study or confound the results of the study Medical history of interstitial lung disease, including drug-induced or radiation pneumonitis requiring treatment with prolonged steroids or other immune suppressive agents within the last 2 years
Part 2	For cohort C, any prior treatment with >2 lines of cytotoxic chemotherapy for metastatic disease (maintenance therapy is not included) **For cohort D, any previous treatment with an EGFR TKI with activity against EGFR Exon 20 insertions (such as poziotinib)** For cohort E, any previous treatment in the metastatic setting with other than a first, second or third generation EGFR TKI

CTLA-4 = cytotoxic T-lymphocyte antigen 4; EGFR = epidermal growth factor receptor; HIV = human immunodeficiency virus; TKI = tyrosine kinase inhibitor

In addition to meeting the overall study criteria, patients enrolled in Cohort D must have been previously diagnosed with an EGFR Exon 20ins mutation and have not been previously treated with a TKI with known activity against Exon 20ins-positive disease (e.g., poziotinib) (Table 58)[1]. Patients in Cohort D make up the majority of the post-platinum patients supporting the amivantamab indication; the primary efficacy population (N=81) included 73 patients enrolled in Cohort D, as well as 4 patients who enrolled in Part 1 and 4 patients who enrolled in Cohort A prior to Cohort A closure [15].

Table 58. CHRYSALIS Cohort D patient selection criteria [1]

Inclusion Criteria	Exclusion Criteria
Patients must have been previously diagnosed with an EGFR Exon 20ins	Any previous treatment with an EGFR TKI with activity against EGFR Exon 20ins (e.g., poziotinib)

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

CHRYSALIS

For the primary efficacy population (n=81), the median age for patients with EGFR Exon 20ins and prior chemotherapy was 62 years (range 42 to 84 years old, Table 59) [35]. The majority of patients had a baseline body weight of <80 kg (74.1%) and therefore received the 1,050 mg dose of amivantamab [35]. Other efficacy population demographics and baseline disease characteristics of note [35] include:

- There were more females (appr. 60 %) than males (appr. 40%)
- Approximately half of all patients were Asian
- Most patients were diagnosed with stage IV disease and adenocarcinoma
- Approximately a quarter of patients had a prior history of brain metastases
- Median time from initial diagnosis was 17-18 months

The median number of the previous lines of therapies was 2 (range 1 to 7) [35]. Among the response-evaluable patients treated at RP2D, 9 were treatment naïve and 1 received platinum doublet chemotherapy in the adjuvant setting [69]. The remaining 29 patients (74%) had received prior platinum doublet chemotherapy in the metastatic setting [16, 69]. Of those, 17 patients had received ≥1 additional line of therapy (TKI, chemotherapy, immunotherapy) before study entry [69].

Patient demographic and baseline characteristics were similar across the primary efficacy, expanded efficacy and expanded safety populations (Table 59).

Table 59. CHRYSALIS patient demographics and baseline characteristics of patients with EGFR Exon 20ins and prior chemotherapy [14, 15, 70]

Baseline assessment	Primary efficacy population with Exon 20ins (n=81)	Expanded efficacy population with Exon 20ins (n=114)	Expanded safety population with Exon 20ins (n=153)
Median age, years (range)	62.0 (42, 84)	62.0 (36, 84)	61 (35, 84)
Male / Female, n (%)	33 (41)/48 (59)	44 (39)/70 (61)	59 (39)/94 (61)
Race, n (%)			
Asian	40 (49)	59 (52)	95 (62)
Black	2 (3)	3 (3)	3 (2)
White	30 (37)	42 (37)	45 (29)
Not reported	9 (11)	10 (9)	10 (7)
ECOG performance status, n (%)			
0	26 (32)	33 (29)	41 (27)
1	54 (67)	80 (70)	111 (73)
2	1 (1)	1 (1)	1 (1)
Disease characteristics and prior treatments			
Median time from initial diagnosis, months (range)	17 (1, 130)	17 (1, 130)	18 (1, 130)
Adenocarcinoma, n (%)	77 (95)	109 (96)	147 (96)
Median prior lines, n (range)	2 (1, 7)	2 (1, 7)	2 (1, 10)

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Baseline assessment	Primary efficacy population with Exon 20ins (n=81)	Expanded efficacy population with Exon 20ins (n=114)	Expanded safety population with Exon 20ins (n=153)
Prior systemic therapies, n (%)			
Platinum-based chemotherapy[a]	81 (100)	114 (100)	153 (100)
IO[b]	37 (46)	49 (43)	65 (43)
EGFR TKI (3rd generation)	6 (7)	8 (7)	13 (9)
EGFR TKI (2nd generation)	6 (7)	8 (7)	15 (10)
EGFR TKI (1st generation)	7 (9)	7 (6)	10 (7)
Poziotinib	1 (1)	2 (1)	2 (1)
No prior therapy	0	0	-
Brain metastases	18 (22)	29 (25)	36 (24)
History of smoking			
Yes	38 (47)	49 (43)	59 (39)
No	43 (53)	65 (57)	94 (61)

ECOG = Eastern Cooperative Oncology Group; EGFR = epidermal growth factor receptor; Exon 20ins = Exon 20 insertions; IO = immuno-oncology drug; TKI = tyrosine kinase inhibitor

[a] In the metastatic setting

[b] nivolumab, atezolizumab, pembrolizumab, durvalumab

Indirect treatment comparison

The ATT approach consisted of adjusting the RWD source populations to match the characteristics of CHRYSALIS, so only the RWD source populations were adjusted.

Characteristic	CHRYSALIS EAS	BSC (Pooled EU+US cohort)	BSC (Pooled EU cohort)	BSC (Pooled US cohort)
N	114	321	126	179
Prior lines of treatment				
1	48 (42.1%)	145 (45.2%)	69 (54.8%)	68 (38%)
2	34 (29.8%)	97 (30.2%)	35 (27.8%)	58 (32.4%)
3	15 (13.2%)	47 (14.6%)	16 (12.7%)	29 (16.2%)
4+	17 (14.9%)	32 (10%)	6 (4.8%)	24 (13.4%)
Brain metastasis				
No	85 (74.6%)	202 (62.9%)	80 (63.5%)	113 (63.1%)
Yes	29 (25.4%)	119 (37.1%)	46 (36.5%)	66 (36.9%)
Age groups for US				
≤60	48 (42.1%)			65 (36.3%)
60 - 70	38 (33.3%)			57 (31.8%)
>70	28 (24.6%)			57 (31.8%)
Age groups for pooled EU and EU+US				
<55	30 (26.3%)	88 (27.4%)	39 (31%)	
55-<60	20 (17.5%)	51 (15.9%)	15 (11.9%)	
>60	64 (56.1%)	182 (56.7%)	72 (57.1%)	
Gender				

Male	44 (38.6%)	125 (38.9%)	51 (40.5%)	68 (38%)
Female	70 (61.4%)	196 (61.1%)	75 (59.5%)	111 (62%)
ECOG				
0	33 (28.9%)			53 (29.6%)
1	81 (71.1%)			126 (70.4%)
Number of metastatic locations				
1	42 (36.8%)			56 (31.3%)
2	45 (39.5%)			35 (19.6%)
3	18 (15.8%)			38 (21.2%)
4+	9 (7.9%)			36 (20.1%)
Missing	0			14 (7.8%)
Hemoglobin				
Normal/high	62 (54.4%)			89 (49.7%)
Low	52 (45.6%)			90 (50.3%)
Cancer stage at initial diagnosis				
I	8 (7%)			20 (11.2%)
II	6 (5.3%)			10 (5.6%)
IIIA	6 (5.3%)			13 (7.3%)
IIIB/IV	94 (82.5%)			136 (76%)

ECOG PS: Eastern Cooperative Oncology Group performance status; EAS: efficacy analysis set

Note that there are more variables included in the analysis for the pooled US cohort than for the pooled EU and pooled EU+US cohorts. For the databases with direct individual patient data (IPD) access the variables included are prior lines of treatment, brain metastasis, liver metastasis and age. The pooled US cohort also includes: ECOG, number of metastatic locations, hemoglobin and cancer stage at initial diagnosis (presented in the same table above).

Comparability of patients across studies

To account for differences in patient populations between CHRYSALIS and the RWD sources, the ATT approach was implemented. Therefore, RWD source populations were adjusted to match the characteristics of cohort D in CHRYSALIS. After the adjustment, a good balance in patient characteristics between the two populations was achieved allowing for optimal comparability.

Comparability of the study populations with Danish patients eligible for treatment

Limited information about NSCLC EGFR with Exon 20ins patients in Denmark is available but the patient population is assumed to be similar to the study population and therefore transferability of results to Danish clinical practice should not be affected.

Appendix D Efficacy and safety results per study

Definition, validity and clinical relevance of included outcome measures

Standardized clinical outcome measures were used, thus investigation of the validity of outcome measures was not assessed. Clinical relevance of the same, has been well established in existing literature. Definitions of outcome measures are provided below.

Table 60. Outcome measures in CHRYSALIS

Outcome measure	Definition	Validity	Clinical relevance
DLT	The Dose Limiting Toxicity (DLT) is based on drug related adverse events and includes unacceptable hematologic toxicity, non-hematologic toxicity of Grade 3 or higher, or elevations in hepatic enzymes suggestive of drug-induced liver injury.	N/A	N/A
AE	An adverse event (AE) is any untoward medical occurrence in a participant who received study drug without regard to possibility of causal relationship. A serious adverse event (SAE) is an AE resulting in any of the following outcomes or deemed significant for any other reason: death; initial or prolonged inpatient hospitalization; life-threatening experience (immediate risk of dying) ; persistent or significant disability/incapacity; congenital anomaly.	N/A	N/A
ORR	Overall response rate (ORR) is defined as the percentage of participants who achieve either a CR or PR as per Response Evaluation Criteria In Solid Tumors Criteria (RECIST v1.1). CR: disappearance of all target lesions and non-target lesions. All lymph nodes must be non-pathological in size (< 10 mm short axis) and normalisation of tumour marker levels; PR: at least a 30% decrease in the sum of diameters of target lesions, taking as reference the baseline sum diameters and Persistence of one or more non-target lesion(s) and/or maintenance of tumour marker level above the normal limits.	N/A	N/A
DOR	Duration of response (DOR) will be calculated as time from initial response of CR (disappearance of all target lesions and non-target lesions. All lymph nodes must be non-pathological in size ([<] 10 [mm] short axis) and normalisation of tumour marker levels) or PR (at least a 30 [%] decrease in the sum of diameters of target lesions, taking as reference the baseline sum diameters and persistence of one or more non-target lesion(s) and/or maintenance of tumour marker level above the normal limits or durable stable disease (neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for progressive disease (PD), taking as reference the smallest sum diameters while on study and persistence of one or more non-target lesion(s) and/or maintenance of tumour marker level above the normal limits) to progressive disease (PD) or death due to underlying disease, whichever comes first, only for participants who achieve CR or PR.	N/A	N/A

Outcome measure	Definition	Validity	Clinical relevance
CBR	Clinical benefit rate is defined as the percentage of participants achieving complete response (CR): disappearance of all target lesions and non-target lesions. All lymph nodes must be non-pathological in size (less than [<] 10 millimeter [mm] short axis) and normalisation of tumour marker levels or partial response (PR): at least a 30 percent (%) decrease in the sum of diameters of target lesions, taking as reference the baseline sum diameters and persistence of one or more non-target lesion(s) and/or maintenance of tumour marker level above the normal limits or durable stable disease (neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for progressive disease (PD), taking as reference the smallest sum diameters while on study and persistence of one or more non-target lesion(s) and/or maintenance of tumour marker level above the normal limits.	N/A	N/A
PFS	Progression-free survival (PFS) is defined as the time from first infusion of study drug to PD or death due to any cause.	N/A	N/A
OS	Overall survival (OS) is defined as the time from first infusion of study drug to death due to any cause.	N/A	N/A
AE	Adverse events (AEs) as defined by the NCICTCAE	N/A	N/A
TTF	Time to treatment failure (TTF) is defined as the time from the first infusion of the study drug to discontinuation of treatment for any reason, including disease progression, treatment toxicity, death, and will be utilized to capture clinical benefit for patients continuing treatment beyond RECIST v1.1 defined disease progression.	N/A	N/A

AE = adverse event; CBR = clinical benefit rate; DLT = dose limiting toxicity; NCICTCAE = National Cancer Institute Common Terminology Criteria for Adverse Events Version 4.03; ORR = overall response rate; OS = overall survival; PFS = progression free survival; RP2CD = recommended phase II combination dose; RP2D = recommended phase II dos

Results per study

Table 61. Results from CHRYSALIS

CHRYSALIS [NCT02609776]			
Outcome	**Population**	**N**	**Result (CI)**
ORR	Primary efficacy population	81	39.5% (95% CI: 28.8, 51.0)
mDOR	Primary efficacy population	81	11.14 months
CBR	Primary efficacy population	81	74.1% (95% CI: 63.1, 83.2)
PFS at 6 months	Primary efficacy population	81	63% (95% CI: 51%, 73%)
PFS at 12 months	Primary efficacy population	81	36% (95% CI: 23%, 49%)
mPFS	Primary efficacy population	81	8.3 months (95% CI: 6.5, 10.9)
OS at 12 months	Primary efficacy population	81	75% (95% CI: 62%, 84%)
OS at 18 months	Primary efficacy population	81	63% (95% CI: 46%, 76%)
mOS	Primary efficacy population	81	22.8 months (95% CI: 14.6, not reached)
ORR	Expanded efficacy population	114	39.5% (95% CI: 30.4, 49.1)
mDOR	Expanded efficacy population	114	10.84 months
CBR	Expanded efficacy population	114	72.8% (95% CI: 63.7, 80.7)
mPFS	Expanded efficacy population	114	6.9 months

Table 62. Results from the indirect treatment comparison

				Estimated absolute difference in effect			Estimated relative difference in effect			Description of methods used for estimation
Outcome	Study arm	N	Result (CI)	Difference	95% CI	*P* value	Difference	95% CI	*P* value	
Median OS	Amivantamab	114	22.77 [17.48, NE]	10.15	NR	NR	HR: 0.462	0.331 - 0.647	<0.0001	*The median survival is based on the Kaplan–Meier estimator. The HR is based on a multivariate proportional hazards regression model with treatment and baseline characteristics as covariates.*
	BSC, pooled EU+US cohort	367	12.62 [10.61, 14.23] months							
Median PFS	Amivantamab	114	6.93 [5.55, 8.64]	2.95	NR	NR	HR: 0.543	0.425 - 0.694	<0.0001	*The median progression free survival is based on the Kaplan–Meier estimator. The HR is based on a multivariate proportional hazards regression model with treatment and baseline characteristics as covariates.*
	BSC, pooled EU+US cohort	355	3.98 [3.02, 4.60]							
Median TTNT	Amivantamab	114	12.42 [8.34, 18.79]	7.23	NR	NR	HR: 0.440	0.336 – 0.577	<0.0001	*The median time-to-next-treatment is based on the Kaplan–Meier estimator. The HR is based on a multivariate proportional hazards regression model with treatment and baseline characteristics as covariates.*
	BSC, pooled EU+US cohort	367	5.19 [4.60, 6.28]							

Appendix E Safety data for intervention and comparator(s)

N/A, see section **Error! Reference source not found.**.

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Appendix F Comparative analysis of efficacy and safety

Methods

Overview

Adjusted treatment comparisons were conducted to compare outcomes for amivantamab from the CHRYSALIS trial versus cohorts of similar patients treated in a real world setting. The adjusted treatment comparisons were conducted to compare amivantamab to BSC (labelled as "physician's choice", PC) and specific treatment classes (TKI-based regimens, IO-based regimens and non-platinum-based therapy regimens) from real world data sources. These cohorts were derived from a range of real world data sources, by identifying patients who fulfilled the inclusion and exclusion criteria from the CHRYSALIS trial. Available data sources were the pooled data from PHE (England), the nNGM (Germany), CRISP (Germany), ESME (France), and Flatiron Health Spotlight, ConcertAI and COTA (US). Comparative analyses were performed for CHRYSALIS versus the pooled European data sources (PHE, nNGM, CRISP and ESME) (the EU cohort), the pooled US data sources (Flatiron Health Spotlight, ConcertAI and COTA) and versus the pooled European and US data sources combined (EU+US cohort), as well as versus each of the real world data sources separately, where appropriate.

In order to compare patients from the CHRYSALIS trial with similar patients from the external data sources, the same inclusion and exclusion criteria were applied to all RW data sources in line with the EMA label for amivantamab, and the CHRYSALIS trial, where possible. All treatment lines eligible according to the CHRYSALIS inclusion and exclusion criteria were included in the analyses. Correlation of outcomes across treatment lines for the same patient was accounted for statistically.

To account for differences in patient populations between CHRYSALIS and the real world data sources, the treatment comparisons were adjusted for differences in key prognostic variables at baseline, which were identified a priori by a SLR and validated by clinical experts. The following covariates were considered: age, gender, race (Asian), smoking history, cancer stage at initial diagnosis, number of metastatic locations, brain metastasis, liver metastasis, prior lines of treatment, Eastern Cooperative Oncology Group Performance Status (ECOG PS), haemoglobin, and body mass index (BMI). Adjusted comparative analyses were implemented using IPW and covariate adjustment. IPW was considered the primary analysis. Covariate adjustment was considered when IPW did not achieve a good covariate balance, led to extreme weights or when IPW estimates were unstable due to small sample size. IPW is a propensity score-based method used to mimic randomisation by creating a balance between two treatment groups with respect to prognostic baseline covariates. Where IPW was conducted, ATT approach was used as the primary analysis. These results can be interpreted as relative treatment effects for amivantamab versus its comparators for patients estimated within the CHRYSALIS patient population. Average Treatment Effect (ATE) and Average Treatment Effect for the Overlap Population (ATO) approaches were also investigated in data sources where IPD were available. Covariate adjustment involves estimating the unbiased treatment effects using a multivariable model including all relevant prognostic variables as covariates together with the treatment group indicator.

The outcomes analysed for CHRYSALIS versus the real world data sources were ORR, OS, PFS and TTNT. Logistic regression was used for binary outcomes (ORR) and Cox regression for time-to-event outcomes (OS, PFS and TTNT). ORR and PFS in CHRYSALIS were assessed by both INV and an IRC, but only INV results are available in the real world data sources. Therefore, INV is considered to be the key method of assessment for ORR and PFS in line with the real world database definitions (and thus, clinical practice). No comparison of amivantamab versus treatment classes is presented for CHRYSALIS versus individual data sources due to small sample sizes meaning results were not robust.

ECOG PS was not always available as it is not routinely captured in clinical practice. The analyses including treatment lines for which ECOG PS was missing were used as base case when consistency across results including and excluding missing ECOG was observed and when estimated outcomes for treatment lines with missing ECOG were not worse than those with ECOG 1. This was in order to maximise sample size. Across data sources, some covariates were not adjusted for due to either being identified as not prognostic or a high rate of missingness.

Merging of datasets – data pooling

As described above, data from the four European data sources (CRISP, nNGM, ESME and PHE) were pooled to create an EU cohort, and collectively compared against amivantamab, using the same methods (IPW and covariate adjustment) as for the individual data sources analyses.

Direct access to IPD allowed the pooling of data from CRISP, nNGM and PHE; however, this was not possible for ESME data, which were only remotely available on the servers of the data owners. Only aggregated outcomes data were made available by ESME. For the comparison versus BSC, aggregated outcomes data from ESME were used to reconstruct the unadjusted and ATT-weighted IPD outcome data, which were then combined with the unadjusted and ATT-weighted IPD, respectively, from the other data sources. This is only feasible for the comparison versus BSC, and not versus treatment classes, for which in ESME no IPW-based analyses were performed. Furthermore, adjusted comparisons versus treatment classes which required access to pooled IPD with baseline characteristics (i.e., covariate adjustment and pairwise IPW adjustment per treatment class), were not possible when including ESME. Therefore, for the pooled EU and pooled EU+US cohorts, comparisons versus treatment classes always excluded ESME.

Data from the three US data sources (Flatiron, ConcertAI and COTA) were also pooled to create the US cohort, in line with the methodology for the pooled EU cohort (US data sources had available IPD).

Due to the high consistency between the results and a comparable treatment distribution of the EU and US cohorts, data from all available data sources were pooled to create an EU+US cohort. The large sample size of the EU+US cohort enabled ATT weighting adjustment to be applied for comparisons with individual treatment classes, which is consistent with the preferred approach taken for the comparison between amivantamab and BSC.

For both the EU and EU+US cohort, individual data sources were excluded from endpoint comparisons if no data were available. For both cohorts, no ORR data were included from PHE and ESME and no PFS data were included for PHE.

For the US cohort, since multiple RW data sources were used, some patients were captured multiple times due to overlap of the data sources. De-duplication was used in these instances. For the US cohort, patients in Flatiron were removed from ConcertAI and COTA and patients in ConcertAI were removed from COTA.

Analysis methods

Inverse Probability Weighting (IPW)

PS methods are used to mimic the effect of randomisation by creating a balance between two treatment groups in respect to important baseline covariates. The PS for an individual describes the probability of being assigned to a particular treatment, conditional on all relevant pre-treatment covariates, and is estimated using a multiple logistic regression model. These PS scores represent a summary of all characteristics included in the model for each patient.

The IPW approach translates these subject-specific PS into weights, which in turn are used to generate a pseudo-population in which each covariate combination is balanced between treatment groups, allowing for a population-based interpretation of results. This balancing enables comparison to the trial population as if it had undergone a randomised control trial in which, counter to fact, both treatments were applied to each subject. Balance in covariates across both cohorts, before and after IPW adjustment, was assessed by computing the standardised differences for each covariate. These standardised differences, together with the distribution of weights and the distribution of PS scores, informed judgement of the appropriateness of the weighting approach for each data source.

The ATT weighting scheme was selected for the IPW approach. The ATT approach attempts to generate a comparative arm reflecting the population enrolled in CHRYSALIS by reweighting the real-world cohort to match the amivantamab patients of CHRYSALIS. Treatment lines of treated patients receive a weight of 1, whilst control patients are reweighted by PS/(1-PS). ATT based estimates represent the relative treatment effect in the CHRYSALIS population, and for these analyses, a scaled ATT (sATT) approach was taken. In order to maintain the original sample size for the weighted populations and to properly reflect the associated uncertainty, the ATT weights were multiplied by the ratio

of the original sample size versus the sum of the ATT weights making the sum of these recalculated weights equal to the original sample size. This approach is referred to as the ATT approach throughout this document (although some figures may still be labelled as sATT).

Multivariable regression approach with direct adjustment for covariates

Covariate adjustment based on a multivariable regression (Cox regression for time to event endpoints and logistic regression for binary endpoints) was considered as an alternative to PS based adjustment in adjusting for covariate imbalance and potential confounding. This was of particular use when comparing CHRYSALIS versus RW data sources with small sample sizes (BSC or individual treatment classes). The unbiased treatment effects were estimated using a multivariable model which included all relevant prognostic variables as covariates together with the treatment group indicator. The selected set of prognostic variables as covariates were based on the confounders identified by the SLR and validated by clinical expert. An advantage of covariate adjustment over the PS approach described in the previous section is that it provides a predictive model (including treatment) for the risk (hazard) of the outcome, which gives insight as to which covariates have the strongest influence on risk.

Statistical analysis

Overview of endpoints of interest

The endpoints of interest are ORR, PFS, OS and TTNT. A summary of the endpoints, their definitions and additional information relating to their use in the statistical analyses is provided in Table 63.

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Table 63: Summary of endpoints assessed in the comparative analyses

Endpoint	Definition of endpoint	Additional notes	Data sources endpoint is available from	Data sources endpoint missing
ORR	The proportion of all subjects who achieved a best response of partial response or better	• For CHRYSALIS patients, response evaluation was based on RECIST v1.1 criteria, by both INV and IRC assessment ○ To achieve a maximal comparability, INV and IRC-assessed ORR were used for the comparative analyses[a] • For patients in RW data sources, response was defined as clinically relevant response in the opinion of the investigator; it was generally not possible to check whether RECIST v1.1 criteria were applied.	• US cohort • CRISP • NGM	• ESME • PHE
OS	The interval between index date and date of death	• For patients who are alive or for whom vital status is unknown, this interval was censored at the date the subject is last known to be alive	• US cohort • PHE • CRISP • NGM • ESME • CATERPILLAR	
PFS	The interval between the index date and the date of disease progression or death, whichever occurs first	• For CHRYSALIS patients, disease progression was based on RECIST v 1.1 criteria, by both INV and IRC assessment ○ To achieve a maximal comparability, INV and IRC-assessed PFS were used for the comparative analysesa • For patients in RW data sources, progression was defined as clinically relevant progression in the opinion of the investigator; it was generally not possible to check whether RECIST v1.1 criteria were applied • For patients without a record of subsequent anti-cancer therapy, the interval was censored at the date of last contact with the patient	• US cohort • CRISP • NGM • ESME	• PHE
TTNT	The interval between index date and initiation of subsequent systemic anti-cancer therapy or death, whichever comes first	• For patients without a record of subsequent anti-cancer therapy, the interval was censored at the date of last contact with the patient	• US cohort • PHE • CRISP • NGM • ESME	

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Abbreviations: AE: adverse event; CRISP: the Clinical Research platform Into molecular testing, treatment and outcome registry of non-Small cell lung carcinoma Patients; ESME: the Epidemiological Strategy and Medical Economics; nNGM: the national Network Genomic Medicine; ORR: Overall Response Rate; OS: Overall Survival; PFS: Progression-Free Survival; PHE: Public Health England; TTNT: Time to Next Treatment.

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Binary endpoints

For the binary endpoint (ORR) adjusted treatment effects, in terms of odds ratios (OR) and the corresponding 95% CIs, were generated using logistic regression models. For the IPW approach, a weighted logistic regression model including treatment only was used. For covariate adjustment, an unweighted logistic regression model that includes treatments and relevant covariates was utilised. To estimate treatment effects in terms of response rate ratio (RR), the same framework was implemented using a generalised linear model with the appropriate link (instead of logistic regression).

Time to event endpoints

PFS, OS and TTNT were analysed as time to event endpoints. For each endpoint, the following approaches were considered:

- Unadjusted comparison without inclusion of potential confounders was used.
- The IPW approach provided weights for estimating the treatment effect of amivantamab versus comparators in a weighted Cox proportional hazards (PH) model, to estimate the treatment effect in terms of the hazard ratio (HR) with 95% Wald-type CI and corresponding p-values. A robust sandwich variance estimator was also used. Kaplan-Meier (K-M) curves were generated, based on which median survival with 95% CI was reported for each treatment group.
- The covariate adjustment approach used a multivariable Cox PH model, including treatment and prognostic variables as covariates with a robust sandwich variance estimator.

Baseline characteristics

Naïve baseline characteristics

The naive baseline characteristics of treatment lines of patients across the pooled data cohorts are presented in Table 64, Table 65, Table 66 and Table 67**Error! Reference source not found.**. In Table 65, naïve baseline characteristics for the EU+US pooled cohort are presented by treatment class, note that this table include patients with platinum-based chemotherapy (in the treatment classes "VEGFI + chemo" and "Other"), hence the number discrepancy. The naïve baseline characteristics of the individual databases pooled in the EU cohort are also presented in Table 68, Table 69 and Table 70**Error! Reference source not found.**.

EU+US cohort

Table 64. Baseline characteristics of treatment lines for patients in CHRYSALIS and the EU+US cohort

Characteristic	CHRYSALIS EAS	EU+US cohort [a]
N	114	321
Prior lines of treatment		
1	48 (42.1%)	145 (45.2%)
2	34 (29.8%)	97 (30.2%)
3	15 (13.2%)	47 (14.6%)
4+	17 (14.9%)	32 (10%)
Brain metastasis		
No	85 (74.6%)	202 (62.9%)
Yes	29 (25.4%)	119 (37.1%)
Age		

Characteristic	CHRYSALIS EAS	EU+US cohort [a]
≤55	30 (26.3%)	88 (27.4%)
55≤60	20 (17.5%)	51 (15.9%)
>60	64 (56.1%)	182 (56.7%)
Gender		
Male	44 (38.6%)	125 (38.9%)
Female	70 (61.4%)	196 (61.1%)

Footnotes: Excluding ESME.

Table 65. Baseline characteristics of treatment lines of patients from EU+US cohort, by treatment class

Characteristic	CHRYSALIS EAS	TKI	IO	Non-Plat Chemo	VEGFi + Chemo	Other	Total
N	114	60	89	76	58	66	463
Prior lines of treatment							
1	48 (42.1%)	27 (45.0%)	49 (55.1%)	25 (32.9%)	28 (48.3%)	26 (39.4%)	203 (43.8%)
2	34 (29.8%)	20 (33.3%)	23 (25.8%)	23 (30.3%)	22 (37.9%)	20 (30.3%)	142 (30.7%)
3	15 (13.2%)	8 (13.3%)	10 (11.2%)	18 (23.7%)	4 (6.9%)	12 (18.2%)	67 (14.5%)
4+	17 (14.9%)	5 (8.3%)	7 (7.9%)	10 (13.2%)	4 (6.9%)	8 (12.1%)	51 (11.0%)
Brain metastasis							
No	85 (74.6%)	33 (55.0%)	60 (67.4%)	50 (65.8%)	38 (65.5%)	36 (54.5%)	302 (65.2%)
Yes	29 (25.4%)	27 (45.0%)	29 (32.6%)	26 (34.2%)	20 (34.5%)	30 (45.5%)	161 (34.8%)
Age							
≤55	30 (26.3%)	18 (30.0%)	24 (27.0%)	18 (23.7%)	17 (29.3%)	20 (30.3%)	127 (27.4%)
55–60	20 (17.5%)	4 (6.7%)	16 (18.0%)	13 (17.1%)	7 (12.1%)	14 (21.2%)	74 (16.0%)
≥ 60	64 (56.1%)	38 (63.3%)	49 (55.1%)	45 (59.2%)	34 (58.6%)	32 (48.5%)	262 (56.6%)
Gender							
Male	44 (38.6%)	23 (38.3%)	38 (42.7%)	33 (43.4%)	19 (32.8%)	24 (36.4%)	181 (39.1%)
Female	70 (61.4%)	37 (61.7%)	51 (57.3%)	43 (56.6%)	39 (67.2%)	42 (63.6%)	282 (60.9%)

Note: Platinum chemotherapy included in some treatment classes presented in this table (VEGFi + Chemo and Other)

Abbreviations: ECOG PS: eastern cooperative oncology group performance score; EU: European IO: immuno-oncology agent; EAS: efficacy analysis set; TKI: tyrosine kinase inhibitor; VEGFi: vascular endothelial growth factor inhibitor; US: United States.

EU cohort

Table 66. Baseline characteristics of treatment lines for patients in CHRYSALIS and the EU cohort

Characteristic	CHRYSALIS EAS	EU cohort [a]
N	114	126
Prior lines of treatment		
1	48 (42.1%)	69 (54.8%)
2	34 (29.8%)	35 (27.8%)

Characteristic	CHRYSALIS EAS	EU cohort [a]
3	15 (13.2%)	16 (12.7%)
4+	17 (14.9%)	6 (4.8%)
Brain metastasis		
No	85 (74.6%)	80 (63.5%)
Yes	29 (25.4%)	46 (36.5%)
Liver metastasis		
No	101 (88.6%)	99 (78.6%)
Yes	13 (11.4%)	27 (21.4%)
Age		
≤55	30 (26.3%)	39 (31.0%)
55≤60	20 (17.5%)	15 (11.9%)
>60	64 (56.1%)	72 (57.1%)
Gender		
Male	44 (38.6%)	51 (40.5%)
Female	70 (61.4%)	75 (59.5%)

Footnotes: Excluding ESME.

Abbreviations: ECOG PS: Eastern Cooperative Oncology Group performance score; EAS: efficacy analysis set.

US cohort

Table 67. Baseline characteristics of treatment lines for patients in CHRYSALIS and the US cohort

Characteristic	CHRYSALIS EAS	US cohort
N	**114**	**195**
Prior lines of treatment		
1	48 (42.1%)	76 (39%)
2	34 (29.8%)	62 (31.8%)
3	15 (13.2%)	31 (15.9%)
4+	17 (14.9%)	26 (13.3%)
Brain metastasis		
No	85 (74.6%)	122 (62.6%)
Yes	29 (25.4%)	73 (37.4%)
Age		
<60	48 (42.1%)	72 (36.9%)
60–70	38 (33.3%)	60 (30.8%)
≥70	28 (24.6%)	63 (32.3%)
ECOG PS		
0	33 (28.9%)	55 (28.2%)

Characteristic	CHRYSALIS EAS	US cohort
1	81 (71.1%)	140 (71.8%)
Number of metastatic locations		
1	42 (36.8%)	58 (29.7%)
2	45 (39.5%)	39 (20%)
3	18 (15.8%)	40 (20.5%)
4	9 (7.9%)	44 (22.6%)
Missing	0	14 (7.2%)
Haemoglobin		
Normal/high	62 (54.4%)	92 (47.2%)
Low	52 (45.6%)	103 (52.8%)
Gender		
Male	44 (38.6%)	74 (37.9%)
Female	70 (61.4%)	121 (62.1%)
Cancer stage at initial diagnosis		
I	8 (7%)	22 (11.3%)
II	6 (5.3%)	10 (5.1%)
IIIA	6 (5.3%)	13 (6.7%)
IIIB/IV	94 (82.5%)	150 (76.9%)

Abbreviations: ECOG PS: Eastern Cooperative Oncology Group performance score; EAS: efficacy analysis set

EU data sources

Table 68. Baseline characteristics of treatment lines for patients in CHRYSALIS and ESME

Characteristics	CHRYSALIS EAS	ESME
N	**n=114**	**n=46**
Prior lines of treatment		
1	48 (42.1)	34 (73.9)
2	34 (29.8)	9 (19.6)
3+	32 (28.1)	3 (6.5)
Brain metastasis		
No	85 (74.6)	28 (60.9)
Yes	29 (25.4)	18 (39.1)
Liver metastasis		
No	101 (88.6)	32 (69.6)

Characteristics	CHRYSALIS EAS	ESME
Yes	13 (11.4)	14 (30.4)
Age at index		
<60	48 (42.1)	22 (47.8)
60 - <70	38 (33.3)	16 (34.8)
>=70	28 (24.6)	8 (17.4)
Number of metastatic locations		
0 or 1	42 (36.8)	15 (32.6)
2	45 (39.5)	5 (10.9)
3	18 (15.8)	14 (30.4)
4+	9 (7.9)	12 (26.1)

Abbreviations: EAS: efficacy analysis set.

Table 69. Baseline characteristics of treatment lines for patients in CHRYSALIS and NGM

Characteristics	CHRYSALIS EAS	NGM
N	**114**	**96**
Prior lines of treatment		
1	48 (42.1%)	50 (52.1%)
2	34 (29.8%)	25 (26%)
3	15 (13.2%)	16 (16.7%)
4+	17 (14.9%)	5 (5.2%)
Brain metastasis		
No	85 (74.6%)	61 (63.5%)
Yes	29 (25.4%)	35 (36.5%)
Liver metastasis		
No	101 (88.6%)	77 (80.2%)
Yes	13 (11.4%)	19 (19.8%)
Age		
<=55	30 (26.3%)	28 (29.2%)

Characteristics	CHRYSALIS EAS	NGM
55- <=60	20 (17.5%)	3 (3.1%)
>60	64 (56.1%)	65 (67.7%)
Gender		
Male	44 (38.6%)	43 (44.8%)
Female	70 (61.4%)	53 (55.2%)

Abbreviations: EAS: efficacy analysis set.

Table 70. Baseline characteristics of treatment lines for patients in CHRYSALIS and PHE

Characteristics	CHRYSALIS EAS	PHE
N	**114**	**10**
Prior lines of treatment		
1	48 (42.1%)	6 (60%)
2	34 (29.8%)	3 (30%)
3	15 (13.2%)	0
4+	17 (14.9%)	1 (10%)
Brain metastasis		
No	85 (74.6%)	9 (90%)
Yes	29 (25.4%)	1 (10%
Liver metastasis		
No	101 (88.6%)	7 (70%)
Yes	13 (11.4%)	3 (30%)
Age		
<=55	30 (26.3%)	3 (30%)
55- <=60	20 (17.5%)	3 (30%)
>60	64 (56.1%)	4 (40%)
Gender		

Male	44 (38.6%)	2 (20%)
Female	70 (61.4%)	40 (40%)

Abbreviations: EAS: efficacy analysis set.

Adjusted baseline characteristics

The baseline characteristics for the CHRYSALIS EAS and the RW data source populations, adjusted using the IPW method (ATT approach), for amivantamab versus BSC are presented in this section. The ATT approach consisted of adjusting the RW data source populations to match the characteristics of CHRYSALIS, so only the RW data source populations were adjusted.

The baseline characteristics adjusted for in each RWE data source analysis are presented in Table 71. Variables for the analyses were selected based on an evidence-informed process considering the strength of the prognostic factor, degree of imbalance between studies, clinical expert opinion and data availability.

Table 71. Baseline Characteristics Adjusted for in Comparative Analyses

Baseline characteristics	EU+US cohort	US cohort	EU cohort	PHE	nNGM	CRISP	ESME
Age	✓	✓	✓	✓	✓	✓	✓
Gender	✓	✓	✓	✓	✓	✓	✓
Race (Asian)							
Smoking history							✓
Cancer stage at initial diagnosis		✓			✓		
Number of metastatic locations		✓			✓	✓	✓
Brain metastasis	✓	✓	✓	✓	✓	✓	✓
Prior lines of treatment	✓	✓	✓	✓	✓	✓	✓
ECOG		✓		✓			
Haemoglobin		✓					
Liver metastasis			✓	✓	✓	✓	✓
BMI				✓		✓	

Abbreviations: BMI = body mass index, CRISP = the Clinical Research platform Into molecular testing, treatment and outcome registry of non-Small cell lung carcinoma Patients, ECOG = Eastern Cooperative Oncology Group, ESME = the Epidemiological Strategy and Medical Economics, nNGM = the national Network Genomic Medicine, NSCLC = non-small cell lung cancer, PHE = Public Health England

After adjustment, a good balance was achieved and the corresponding diagnostic plots demonstrating this are presented in *Propensity score weighting results*.

For the pooled EU+US cohort and the pooled EU cohort, the external cohort was first balanced versus CHRYSALIS by pooling all data sources where direct access to IPD was available (i.e., excluding ESME). All common variables across these data sources were included in the adjustment (Table 72 and Table 74**Error! Reference source not found.**). The ESME cohort was balanced using the variables included in the ESME base case, presented in Table 76. In Table 73**Error! Reference source not found.**, adjusted baseline characteristics for the EU+US pooled cohort are presented by treatment class, note that this table include patients with platinum-based chemotherapy (in the treatment classes "VEGFI + chemo" and "Other"), hence the number discrepancy.

EU+US cohort

Table 72. Baseline characteristics for CHRYSALIS EAS (n=114) versus the IPW ATT weighted EU+US cohort (BSC, labelled PC)

Characteristic	CHRYSALIS EAS	EU+US cohort[a]	Total[b]
N	114	321	435
Prior lines of treatment			
1	48 (42.1%)	135 (42.2%)	183 (42.2%)
2	34 (29.8%)	96 (30%)	130 (30%)
3	15 (13.2%)	41 (12.9%)	56 (12.9%)
4+	17 (14.9%)	48 (14.9%)	65 (14.9%)
Brain metastasis			
No	85 (74.6%)	239 (74.5%)	324 (74.5%)
Yes	29 (25.4%)	82 (25.5%)	111 (25.5%)
Age			
≤55	30 (26.3%)	81 (25.3%)	111 (25.5%)
55≤60	20 (17.5%)	58 (18%)	78 (17.9%)
>60	64 (56.1%)	182 (56.7%)	246 (56.5%)
Gender			
Male	44 (38.6%)	124 (38.6%)	168 (38.6%)
Female	70 (61.4%)	197 (61.4%)	267 (61.4%)

Footnotes: a Excluding ESME; b sum of ATT weights.

Abbreviations: ATT: average treatment effect among the treated; EAS: efficacy analysis set; IPW: inverse probability weighting; PC: physician's choice.

Table 73: Baseline characteristics of treatment lines of patients from EU+US cohort, by treatment class

Characteristic	CHRYSALIS EAS	TKI	IO	Non-Plat Chemo	VEGFi + Chemo	Other	Total[a]
N	114	60	89	76	58	66	463
Prior lines of treatment							
1	48 (42.1%)	29 (47.6%)	37 (41.9%)	32 (42.3%)	24 (42.1%)	28 (41.8%)	198 (42.8%)
2	34 (29.8%)	20 (32.5%)	27 (30.6%)	23 (30%)	19 (32.7%)	21 (31.2%)	144 (31.1%)

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Characteristic	CHRYSALIS EAS	TKI	IO	Non-Plat Chemo	VEGFi + Chemo	Other	Total[a]
3	15 (13.2%)	6 (10.2%)	12 (13.4%)	10 (12.7%)	7 (12%)	8 (12%)	58 (12.5%)
4+	17 (14.9%)	6 (9.7%)	13 (14.1%)	11 (15%)	8 (13.1%)	10 (15%)	65 (14.0%)
Brain metastasis							
No	85 (74.6%)	45 (75.5%)	66 (74.2%)	57 (75.4%)	43 (74.7%)	49 (75%)	345 (74.5%)
Yes	29 (25.4%)	15 (24.5%)	23 (25.8%)	19 (24.6%)	15 (25.3%)	17 (25%)	118 (25.5%)
Age							
≤55	30 (26.3%)	13 (21.8%)	22 (25%)	19 (24.7%)	15 (25.4%)	17 (26.1%)	116 (25.1%)
55–60	20 (17.5%)	13 (21.3%)	16 (18.4%)	13 (17.6%)	9 (15.1%)	12 (18.6%)	83 (17.9%)
≥ 60	64 (56.1%)	34 (57%)	50 (56.6%)	44 (57.7%)	35 (59.5%)	37 (55.3%)	294 (63.5%)
Gender							
Male	44 (38.6%)	23 (38.4%)	33 (37.5%)	31 (40.5%)	22 (37.5%)	24 (37.1%)	177 (38.2%)
Female	70 (61.4%)	37 (61.6%)	56 (62.5%)	45 (59.5%)	36 (62.5%)	42 (62.9%)	286 (61.8%)

Note: Platinum chemotherapy included in some treatment classes presented in this table (VEGFi + Chemo and Other)

Footnotes: a Sum of ATT weights.

Abbreviations: ECOG PS: eastern cooperative oncology group performance score; EU: European IO: immuno-oncology agent; EAS: efficacy analysis set; TKI: tyrosine kinase inhibitor; VEGFi: vascular endothelial growth factor inhibitor; US: United States.

EU cohort

Table 74. Baseline characteristics for CHRYSALIS EAS (n=114) versus the IPW ATT weighted EU cohort (BSC, labelled PC)

Characteristic	CHRYSALIS EAS	EU cohort[a]	Total[b]
N	**114**	**126**	**240**
Prior lines of treatment			
1	48 (42.1%)	53 (42.4%)	101 (42.2%)
2	34 (29.8%)	39 (30.8%)	73 (30.3%)
3	15 (13.2%)	16 (12.9%)	31 (13%)
4+	17 (14.9%)	18 (14%)	35 (14.5%)
Brain metastasis			
No	85 (74.6%)	94 (74.3%)	179 (74.4%)
Yes	29 (25.4%)	32 (25.7%)	61 (25.6%)
Liver metastasis			
No	101 (88.6%)	110 (87.7%)	211 (88.1%)
Yes	13 (11.4%)	16 (12.3%)	29 (11.9%)
Age			
≤55	30 (26.3%)	30 (23.9%)	60 (25.1%)
55≤60	20 (17.5%)	22 (17.1%)	42 (17.3%)
>60	64 (56.1%)	74 (59%)	138 (57.6%)

Characteristic	CHRYSALIS EAS	EU cohort [a]	Total[b]
Gender			
Male	44 (38.6%)	49 (39.2%)	93 (38.9%)
Female	70 (61.4%)	77 (60.8%)	147 (61.1%)

Footnotes: a Excluding ESME; b sum of ATT weights

Abbreviations: ATT: average treatment effect among the treated; efficacy analysis set; PC: physician's choice.

US cohort

Table 75. Baseline characteristics for CHRYSALIS EAS (n=114) versus the IPW ATT weighted US cohort (BSC, labelled PC)

Characteristic	CHRYSALIS EAS	US cohort	Total[a]
N	**114**	**206**	**320**
Prior lines of treatment			
1	48 (42.1%)	87 (44.4%)	135 (43.6%)
2	34 (29.8%)	58 (30%)	92 (29.9%)
3	15 (13.2%)	25 (12.7%)	40 (12.8%)
4+	17 (14.9%)	25 (12.9%)	42 (13.7%)
Brain metastasis			
No	85 (74.6%)	147 (75.1%)	232 (74.9%)
Yes	29 (25.4%)	48 (24.9%)	77 (25.1%)
Age			
<60	48 (42.1%)	80 (41.3%)	128 (41.6%)
60–70	38 (33.3%)	65 (33.1%)	103 (33.2%)
≥70	28 (24.6%)	50 (25.6%)	78 (25.2%)
ECOG PS			
0	33 (28.9%)	54 (27.7%)	87 (28.1%)
1	81 (71.1%)	141 (72.3%)	222 (71.9%)
Number of metastatic locations			
1	42 (36.8%)	72 (37%)	114 (36.9%)
2	45 (39.5%)	76 (39.2%)	121 (39.3%)
3	18 (15.8%)	31 (15.9%)	49 (15.9%)
4	9 (7.9%)	15 (7.9%)	24 (7.9%)
Missing	0 (0%)	0 (0%)	0 (0%)
Haemoglobin			

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Characteristic	CHRYSALIS EAS	US cohort	Total[a]
Normal/high	62 (54.4%)	107 (54.9%)	175 169 (54.7%)
Low	52 (45.6%)	88 (45.1%)	140 (45.3%)
Gender			
Male	44 (38.6%)	77 (39.3%)	121 (39.1%)
Female	70 (61.4%)	118 (60.7%)	188 (60.9%)
Cancer stage at initial diagnosis			
I	8 (7%)	15 (7.7%)	23 (7.5%)
II	6 (5.3%)	10 (5.3%)	16 (5.3%)
IIIA	6 (5.3%)	11 (5.5%)	17 (5.4%)
IIIB/IV	94 (82.5%)	159 (81.4%)	253 (81.8%)

Footnotes: a Sum of ATT weights.

Abbreviations: ATT: average treatment effect among the treated; ECOG PS: Eastern Cooperative Oncology Group performance status; EAS: efficacy analysis set; PC: physician's choice.

EU data sources

Table 76: Baseline characteristics for CHRYSALIS EAS (n=114) versus the IPW ATT weighted ESME cohort (BSC, labelled PC)

Characteristic	CHRYSALIS EAS	ESME	Total[a]
N	**114**	**46**	**160**
Prior lines of treatment			
1	48 (42.1)	23 (50.9)	71.4 (44.6)
2	34 (29.8)	14 (30.3)	48.0 (30.0)
3+	32 (28.1)	9 (18.8)	40.6 (25.4)
Brain metastasis			
No	85 (74.6%)	30 (65.7)	115.2 (72.0)
Yes	29 (25.4%)	16 (34.3)	44.8 (28.0)
Liver metastasis			
No	101 (88.6%)	33 (72.4)	134.3 (83.9)
Yes	13 (11.4%)	13 (27.6)	25.7 (16.1)
Age			
<60	48.0 (42.1)	16 (34.2)	63.7 (39.8)
60 - <70	38.0 (33.3)	19 (41.8)	57.2 (35.8)
⩾70	28.0 (24.6)	11 (24.0)	39.0 (24.4)
Number of metastatic locations			
0 or 1	42 (36.8%)	15 (32.9)	57.1 (35.7)

2	45 (39.5%)	17 (37.5)	62.3 (38.9)
3	18 (15.8%)	10 (21.2)	27.8 (17.4)
4+	9 (7.9%)	4 (8.3)	12.8 (8.0)

Footnotes: a Sum of ATT weights.

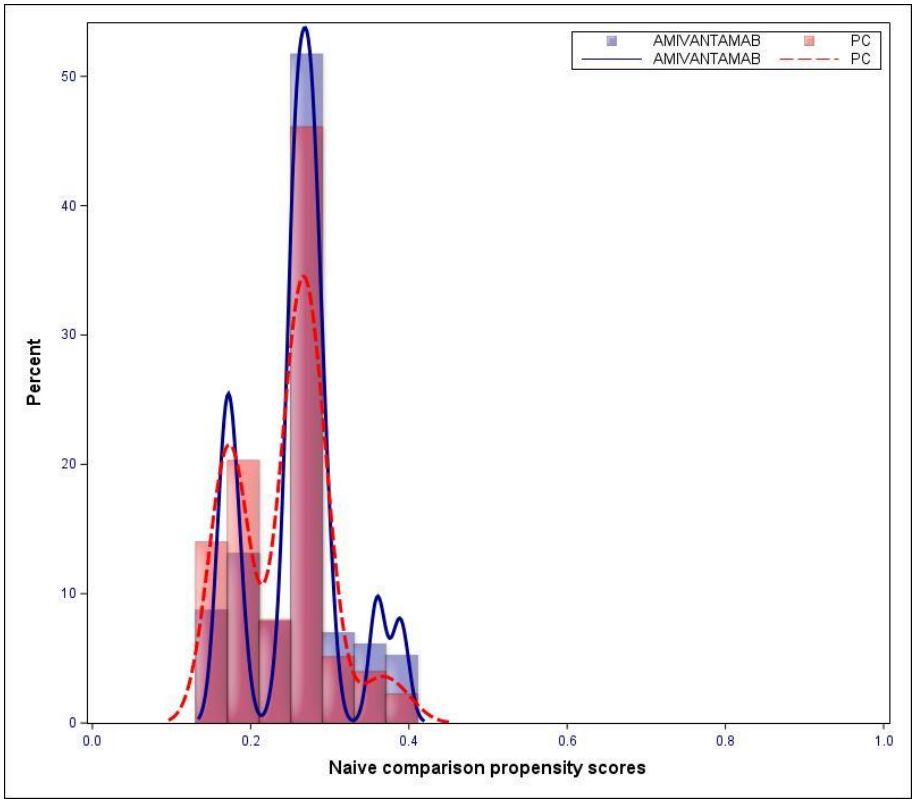
Abbreviations: ATT: average treatment effect among the treated; ECOG PS: Eastern Cooperative Oncology Group performance status; EAS: efficacy analysis set; ESME: The Epidemiological Strategy and Medical Economics; PC: physician's choice.

Propensity score weighting results

EU+US cohort

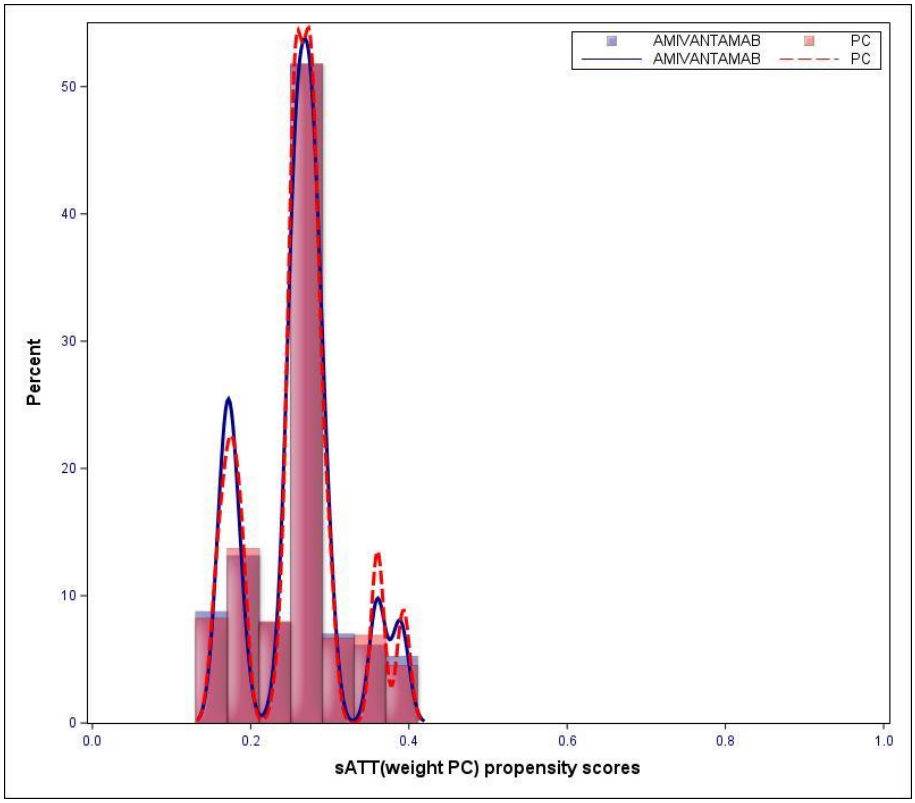
The distribution of naïve comparison PS scores and ATT PS scores by treatment in the EU+US cohort are presented in Figure 41 and Figure 42, **Error! Reference source not found.**respectively. The standardised mean differences after adjusting using the ATT approach for the EU+US cohort are presented in Figure 43**Error! Reference source not found.**.

Figure 41. Distribution of propensity scores for the unweighted population for EU+US cohort



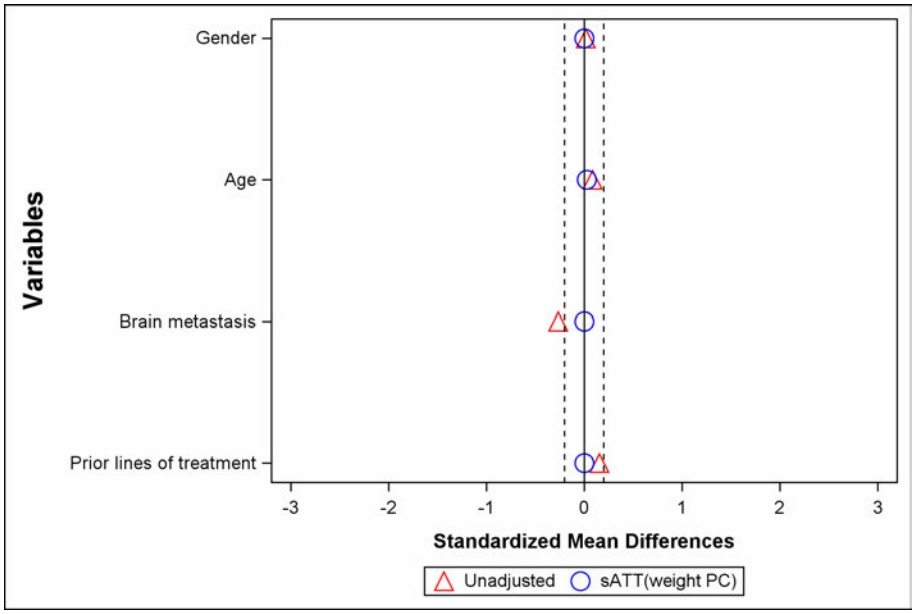
Abbreviations: PC: physician's choice; RW: real world.

Figure 42. Distribution of propensity scores for the ATT weighted population for EU+US cohort



Abbreviations: ATT: average treatment effect among the treated; PC: physician's choice; RW: real world.

Figure 43. Standardised mean difference: ATT(weight PC) for EU+US cohort



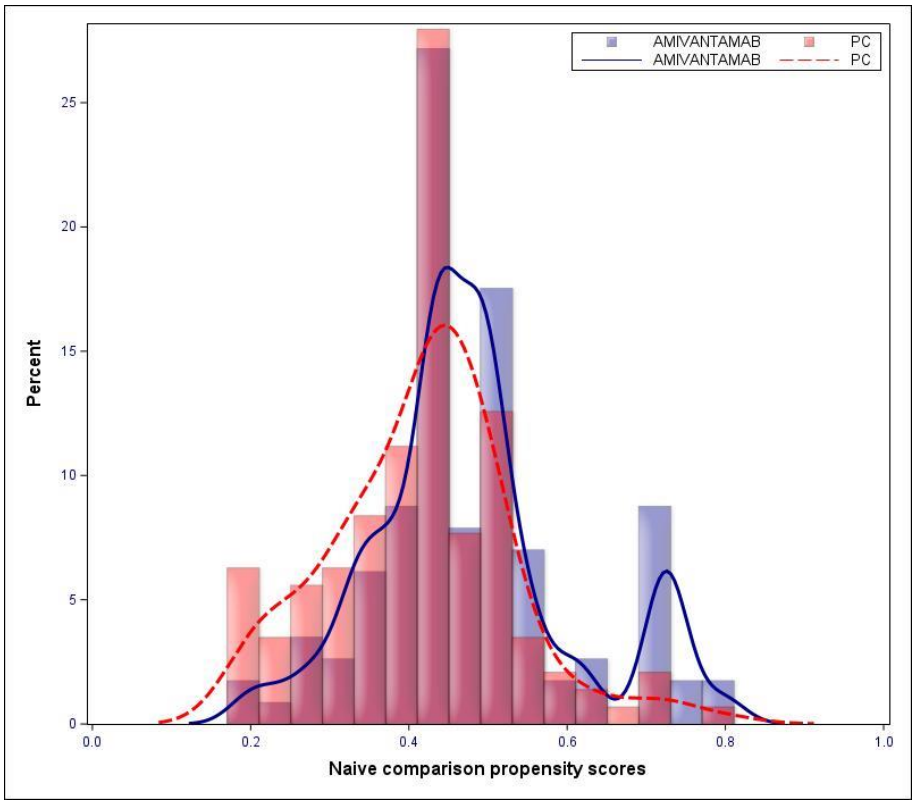
Abbreviations: ATT: average treatment effect among the treated; ECOG: eastern cooperative oncology group; PC: physician's choice.

EU cohort

The distribution of naïve comparison PS scores and ATT PS scores by treatment in the EU cohort are presented in Figure 44 and Figure 45, respectively. The standardised mean differences after adjusting using the ATT approach for the EU cohort are presented in

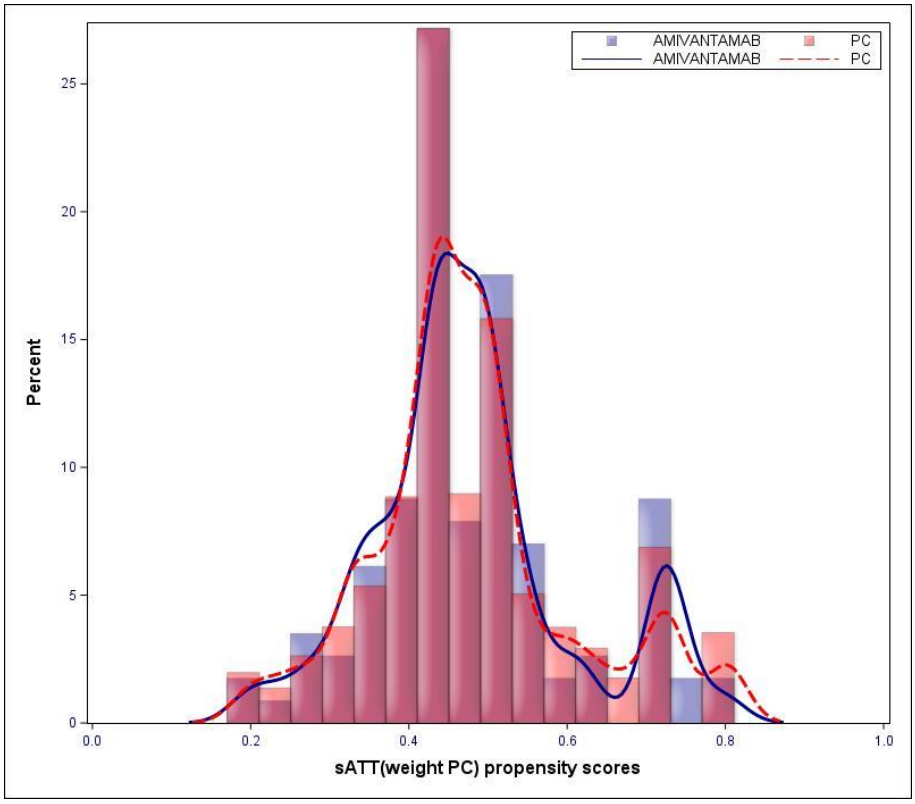
Figure 46, which shows that the standardised mean differences are typically reduced after weighting and there is a good balance of baseline characteristics between the treatment arms.

Figure 44. Distribution of propensity scores for the unweighted population for EU cohort



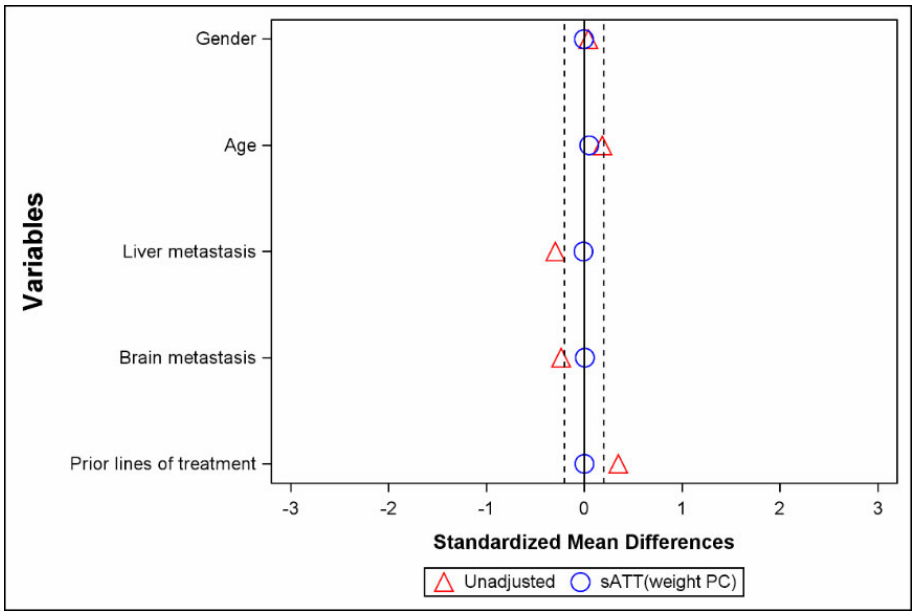
Abbreviations: PC: physician's choice; RW: real world.

Figure 45. Distribution of propensity scores for the ATT weighted population by treatment for EU cohort



Abbreviations: ATT: average treatment effect among the treated; PC: physician's choice; RW: real world.

Figure 46. Standardised mean difference: ATT (weight PC) for EU cohort



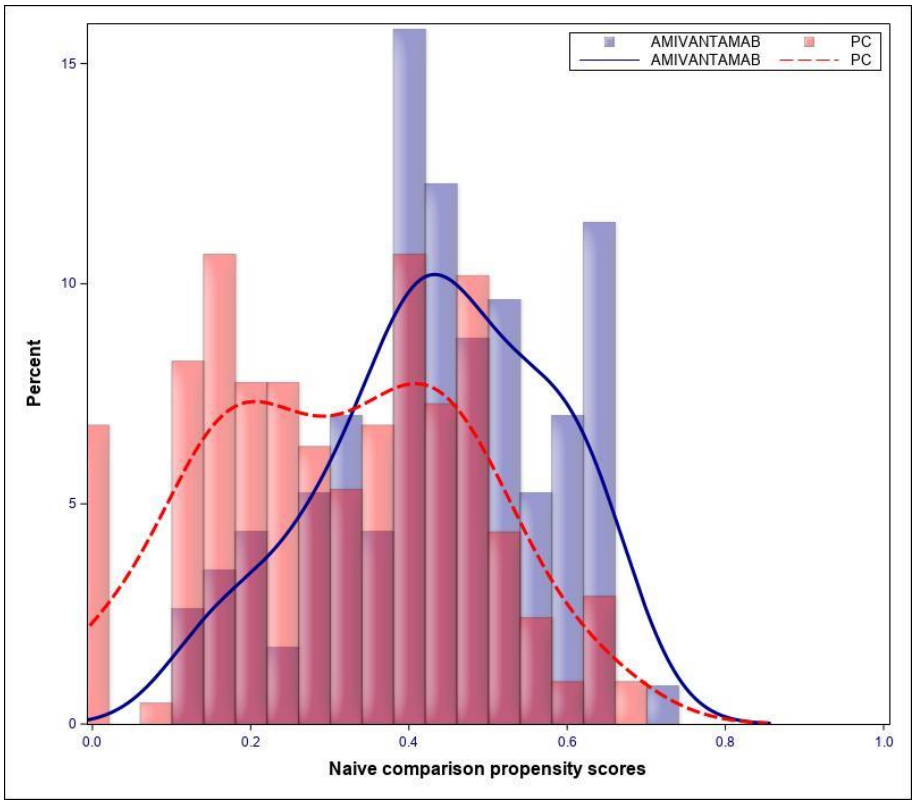
Abbreviations: ATT: average treatment effect among the treated; ECOG: eastern cooperative oncology group; PC: physician's choice

US cohort

The distribution of naïve comparison PS scores and ATT PS scores by treatment in the US cohort are presented in Figure 47 and Figure 48 respectively. The standardised mean differences after adjusting using the ATT approach for the US cohort are presented in

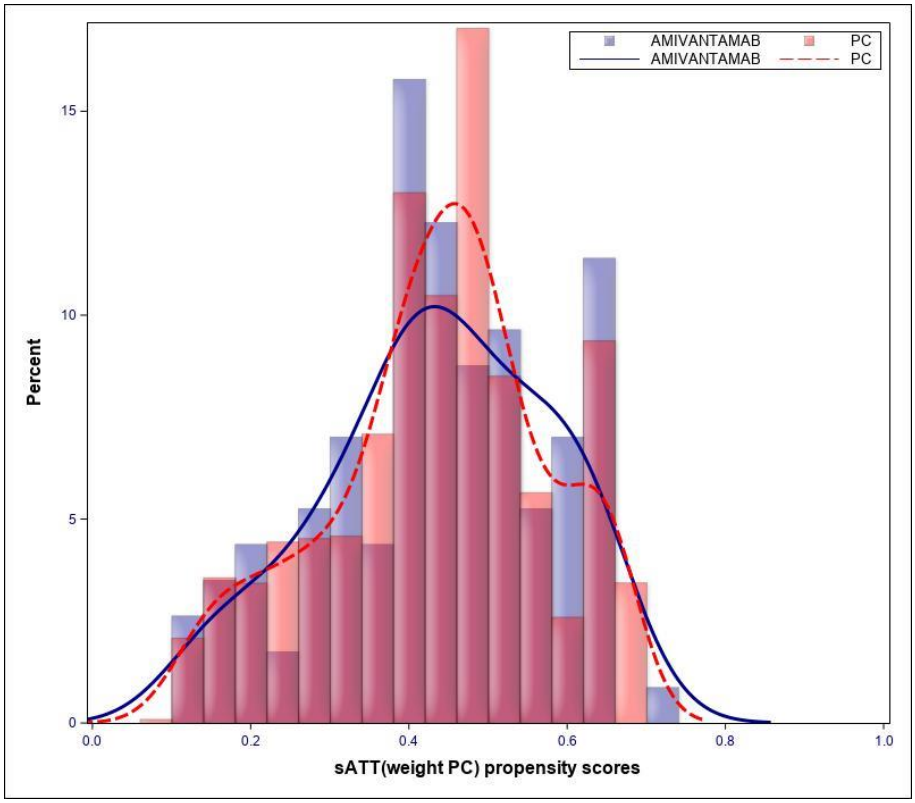
Figure 49, which shows that the standardised mean differences are typically reduced after weighting and there is a good balance of baseline characteristics between the treatment arms.

Figure 47. Distribution of propensity scores for the unweighted population by treatment for US cohort



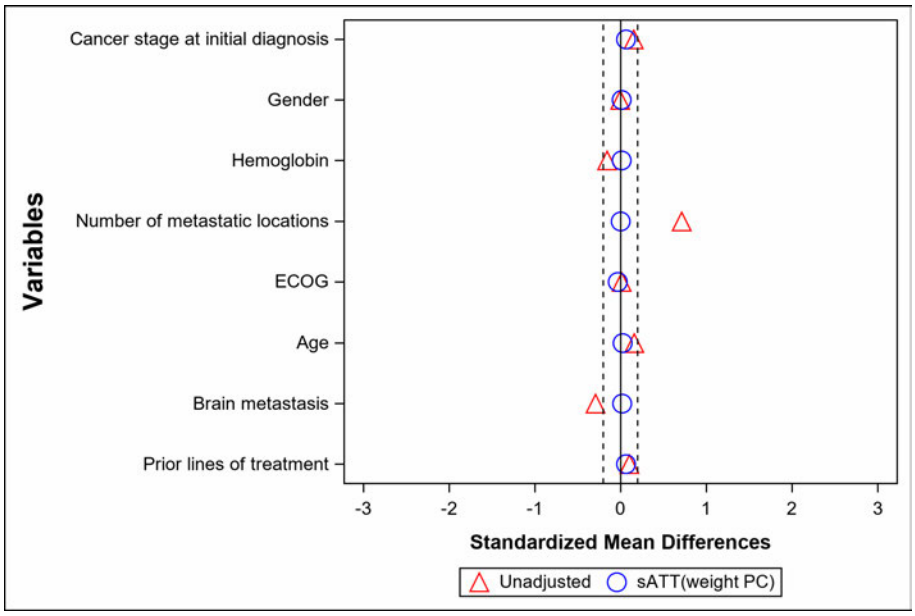
Abbreviations: PC: physician's choice; RW: real world.

Figure 48. Distribution of propensity scores for the ATT weighted population by treatment for US cohort



Abbreviations: ATT: average treatment effect among the treated; PC: physician's choice; RW: real world

Figure 49. Standardised mean difference: ATT (weight PC) for US cohort



Abbreviations: ATT: average treatment effect among the treated; ECOG: eastern cooperative oncology group; PC: physician's choice

Overall response rate

[redacted]

[redacted]

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ORR– US cohort

IPW – ATT approach

[redacted]

Covariate adjustment based on multivariable generalized linear regression model

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

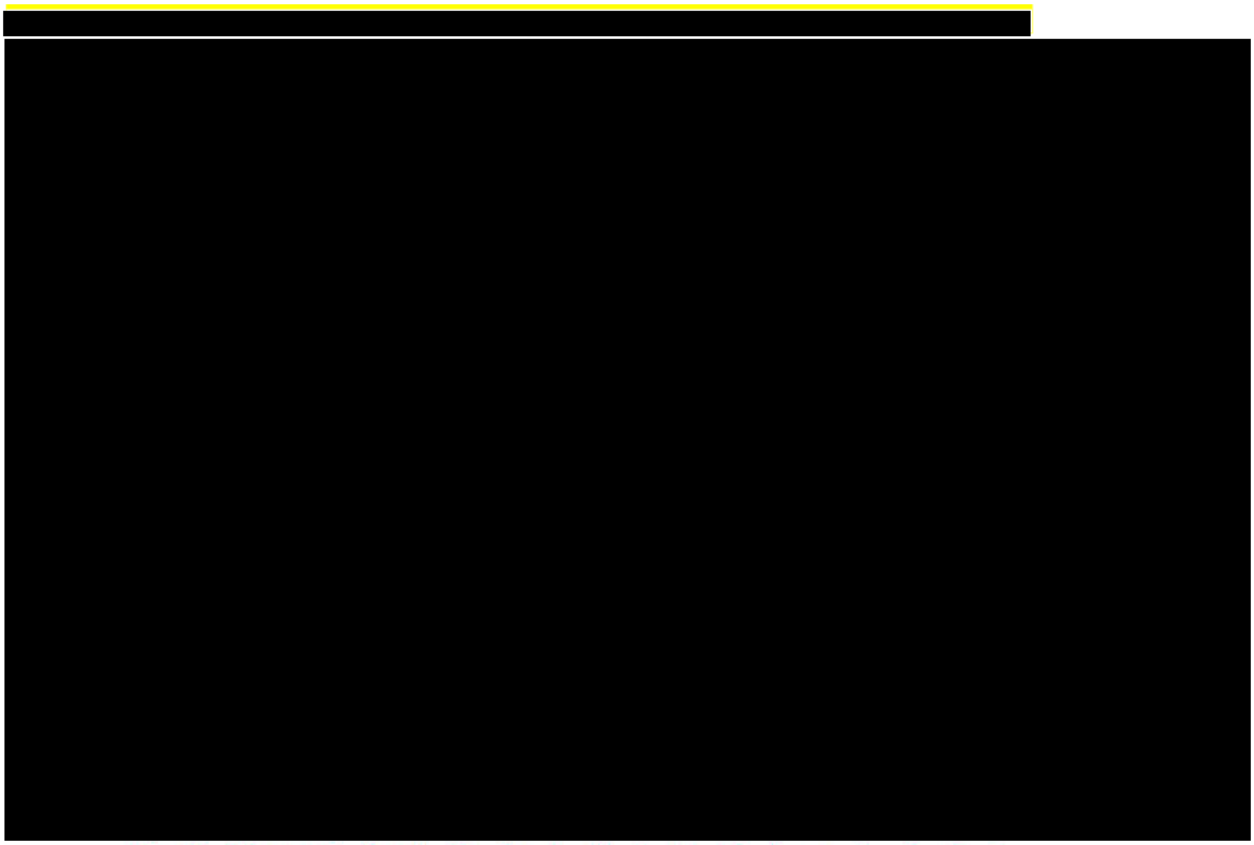
[redacted]

OS – EU cohort

IPW – ATT approach

[redacted]

[redacted]



[redacted]

Covariate adjustment based on multivariate proportional hazard regression

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[redacted]

Unadjusted results

[redacted]

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[redacted]

OS – US cohort

IPW – ATT approach

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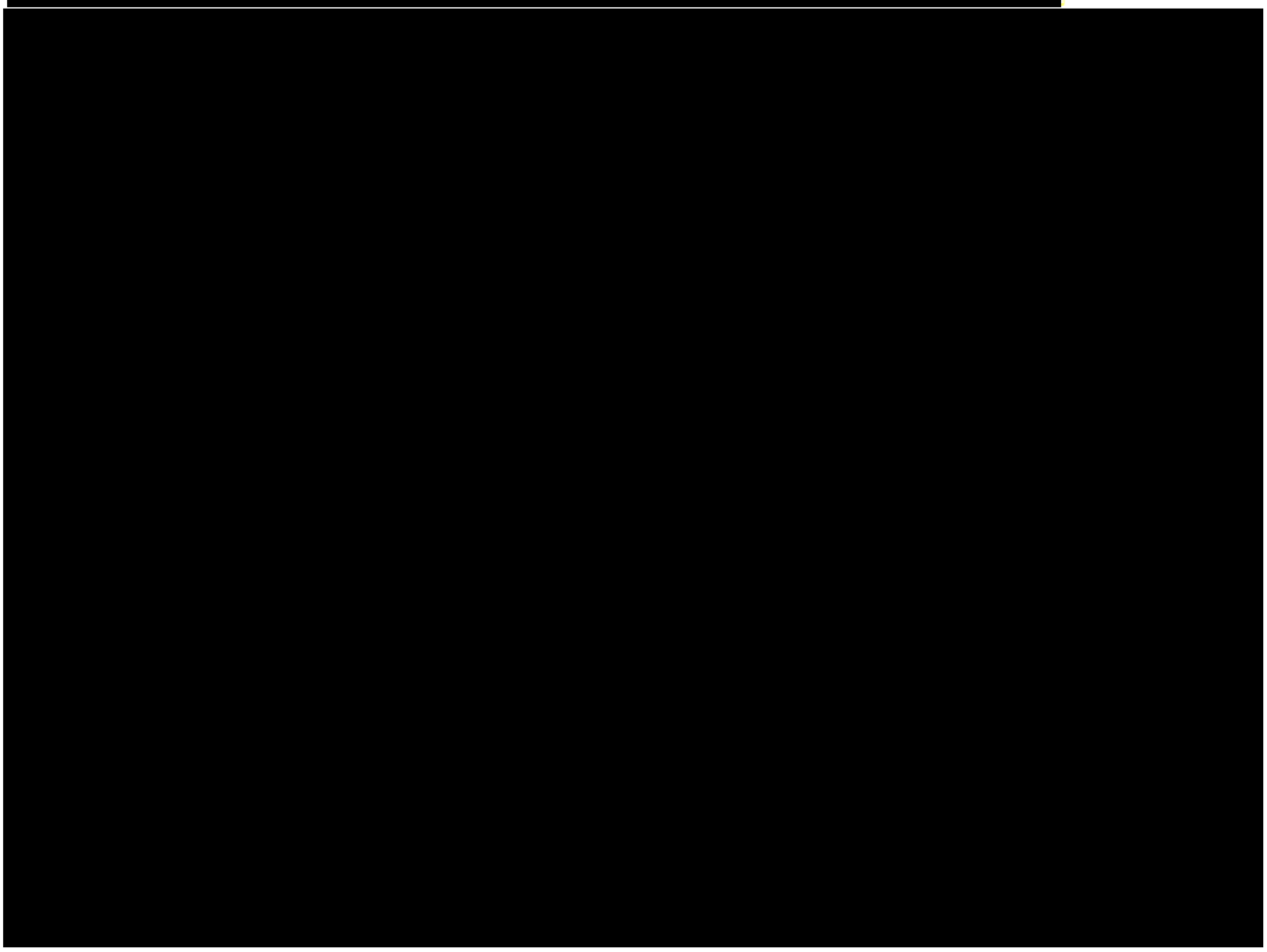

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Unadjusted results

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[redacted]

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[redacted]

Progression-free survival

Individual treatment classes

[redacted]

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[redacted]

[redacted]

PFS – EU cohort

IPW – ATT approach

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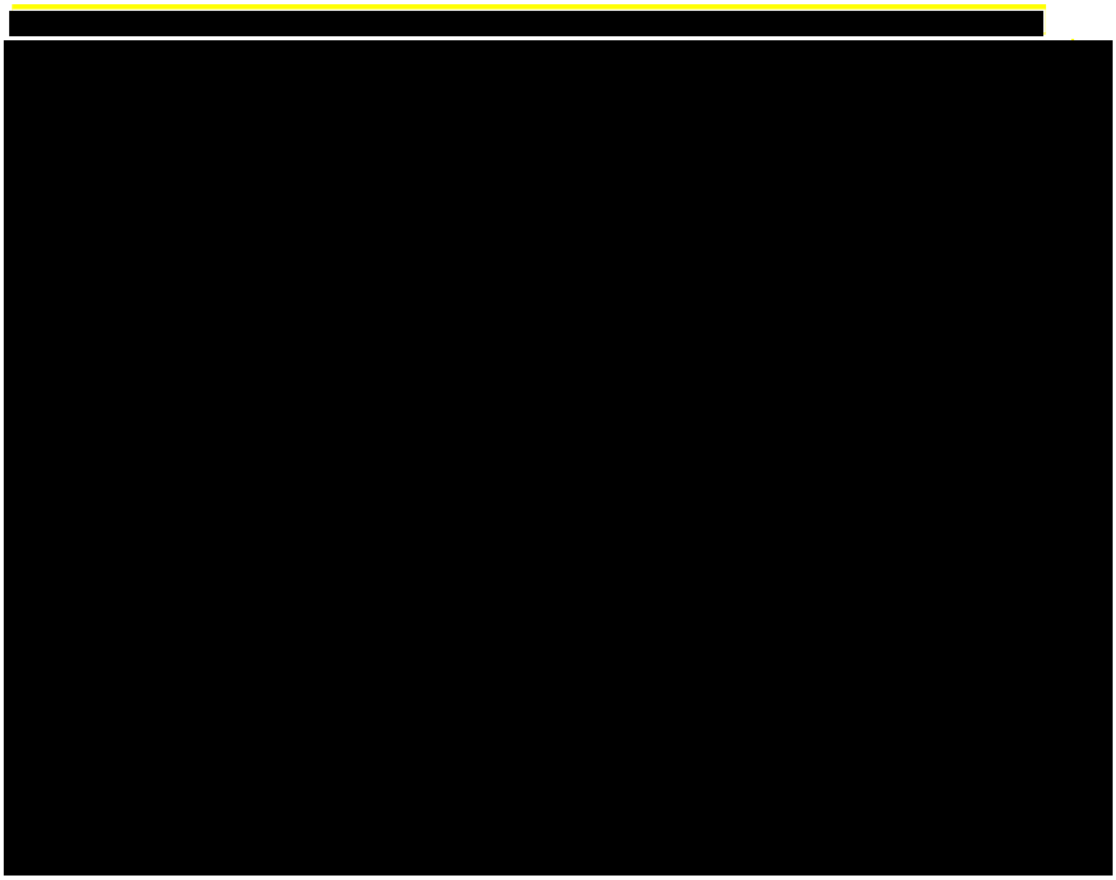

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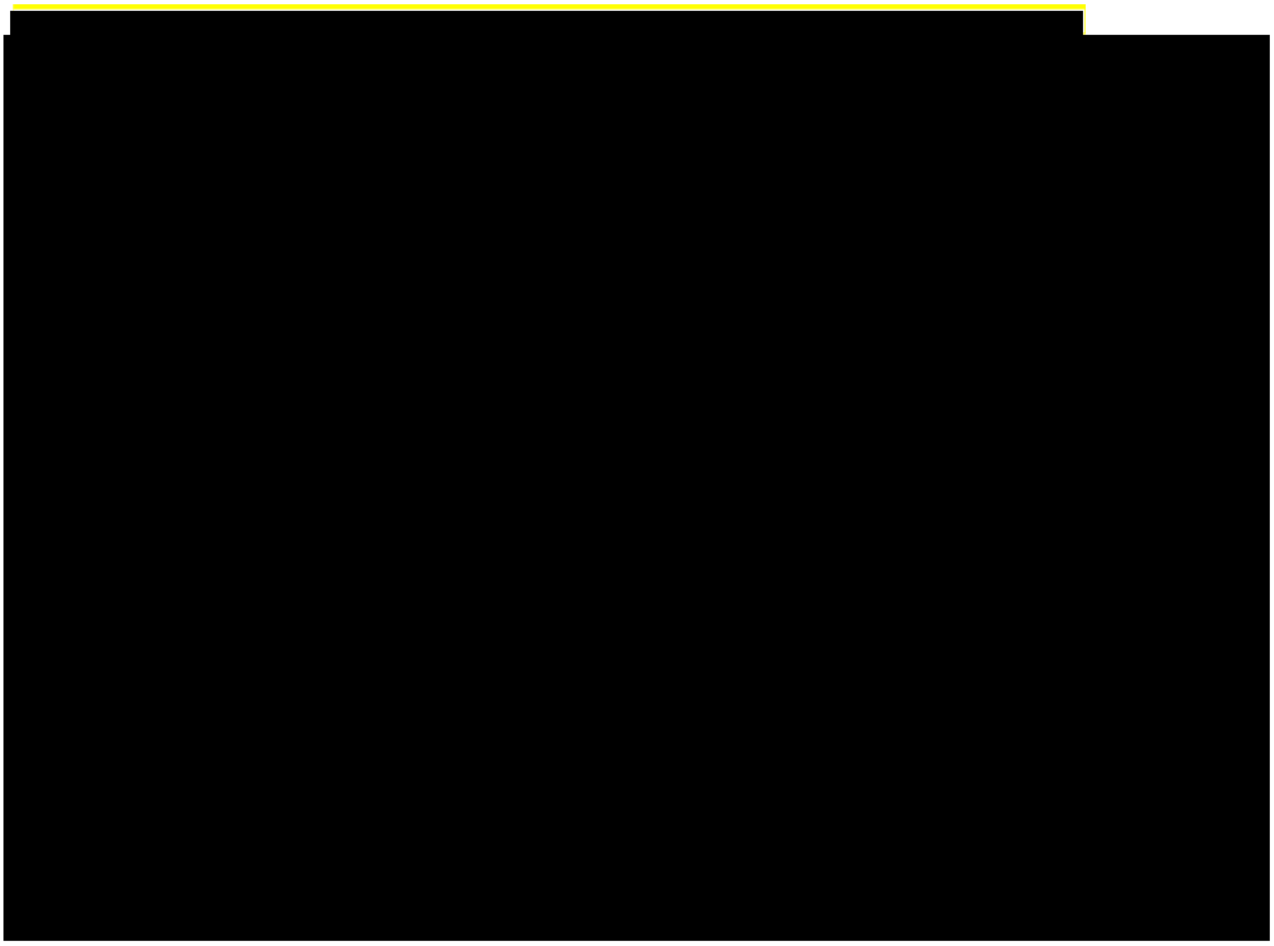

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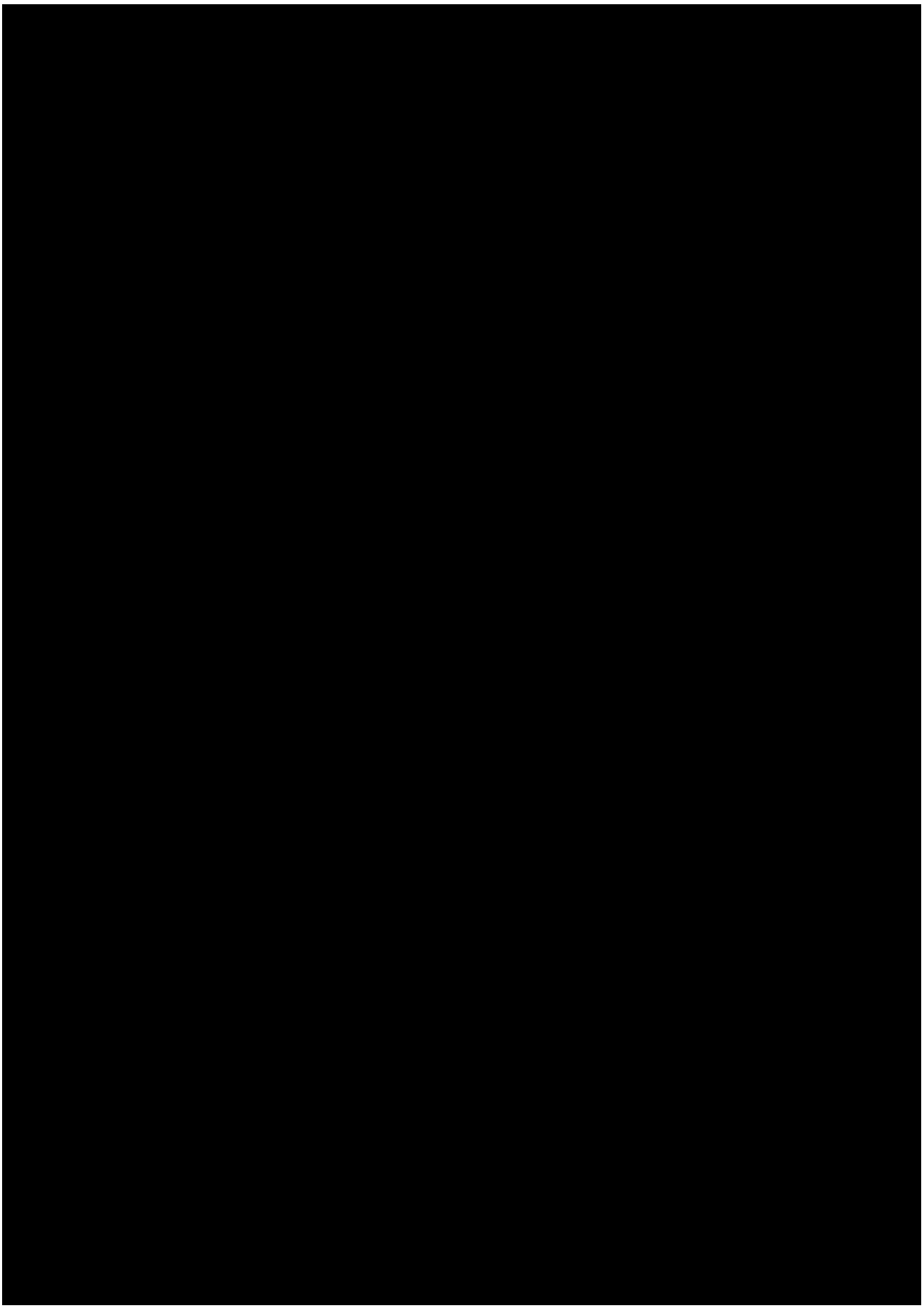

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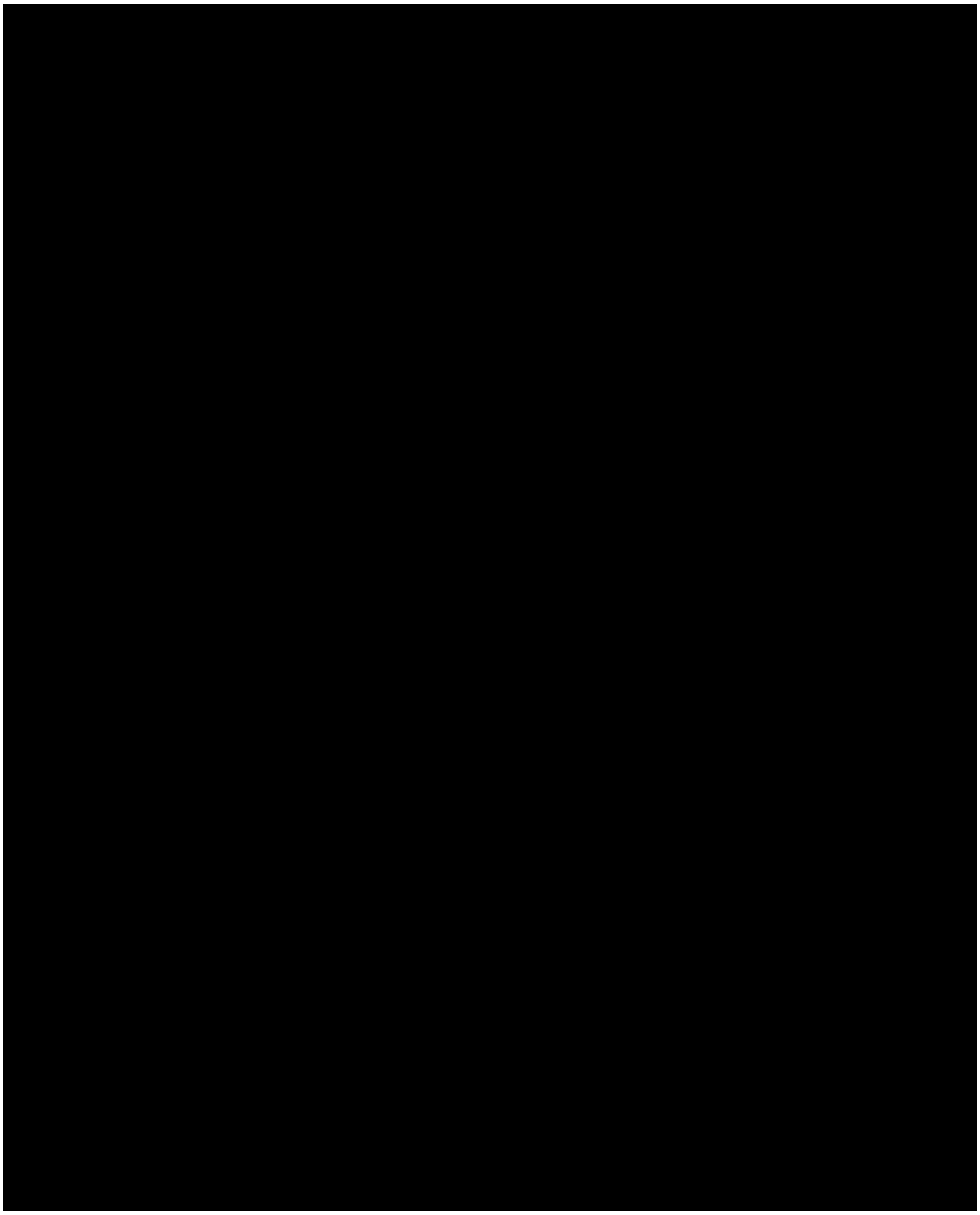

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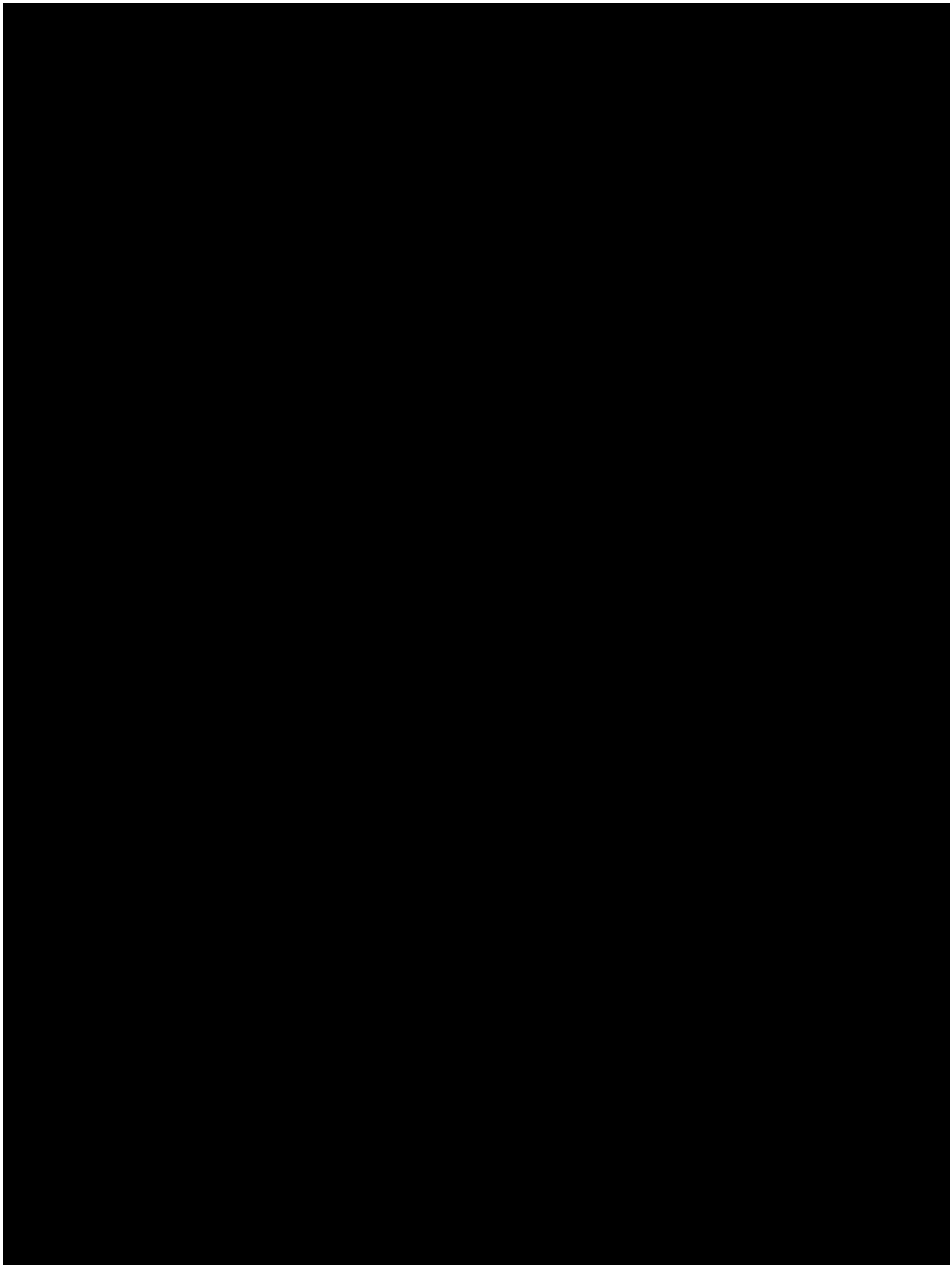

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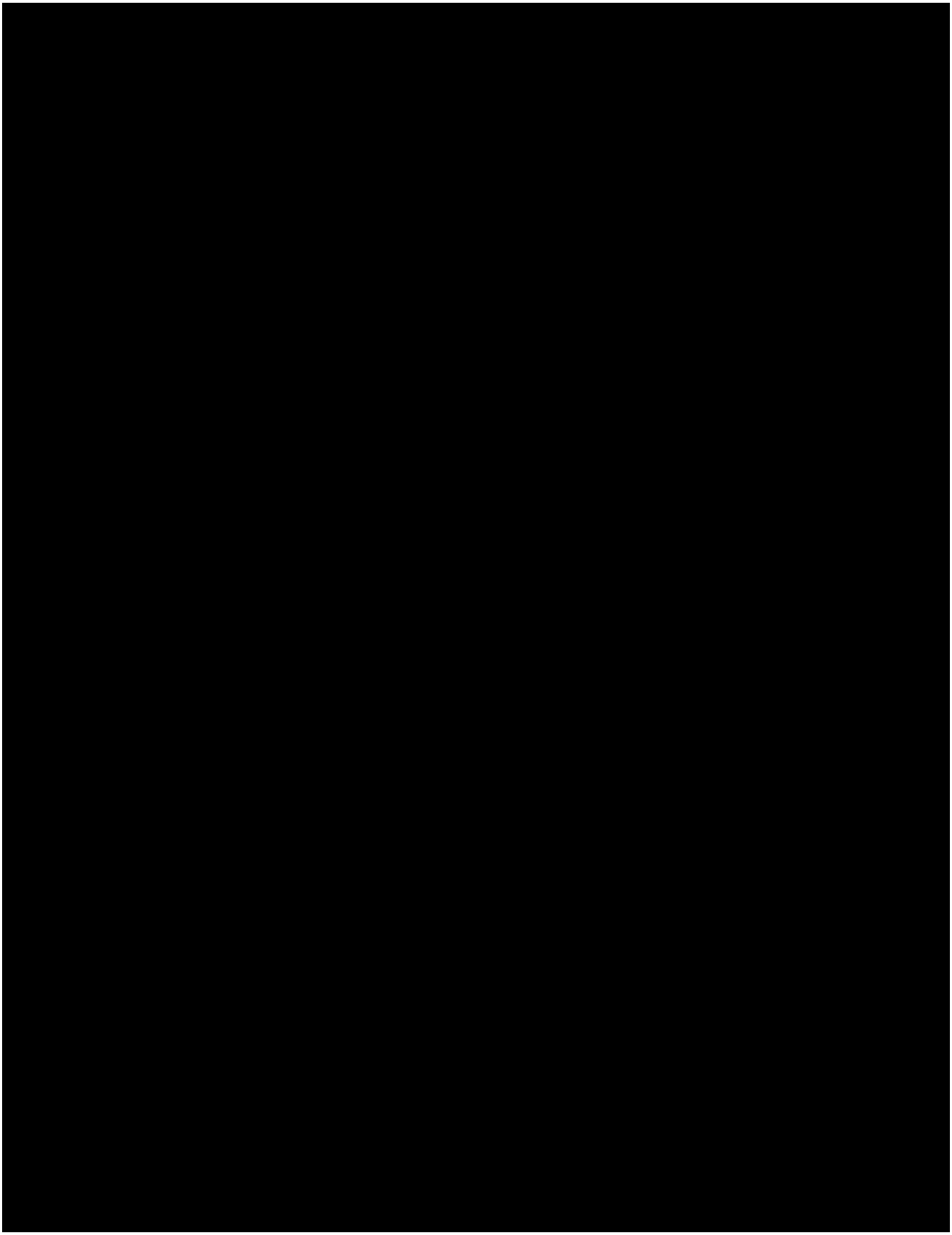

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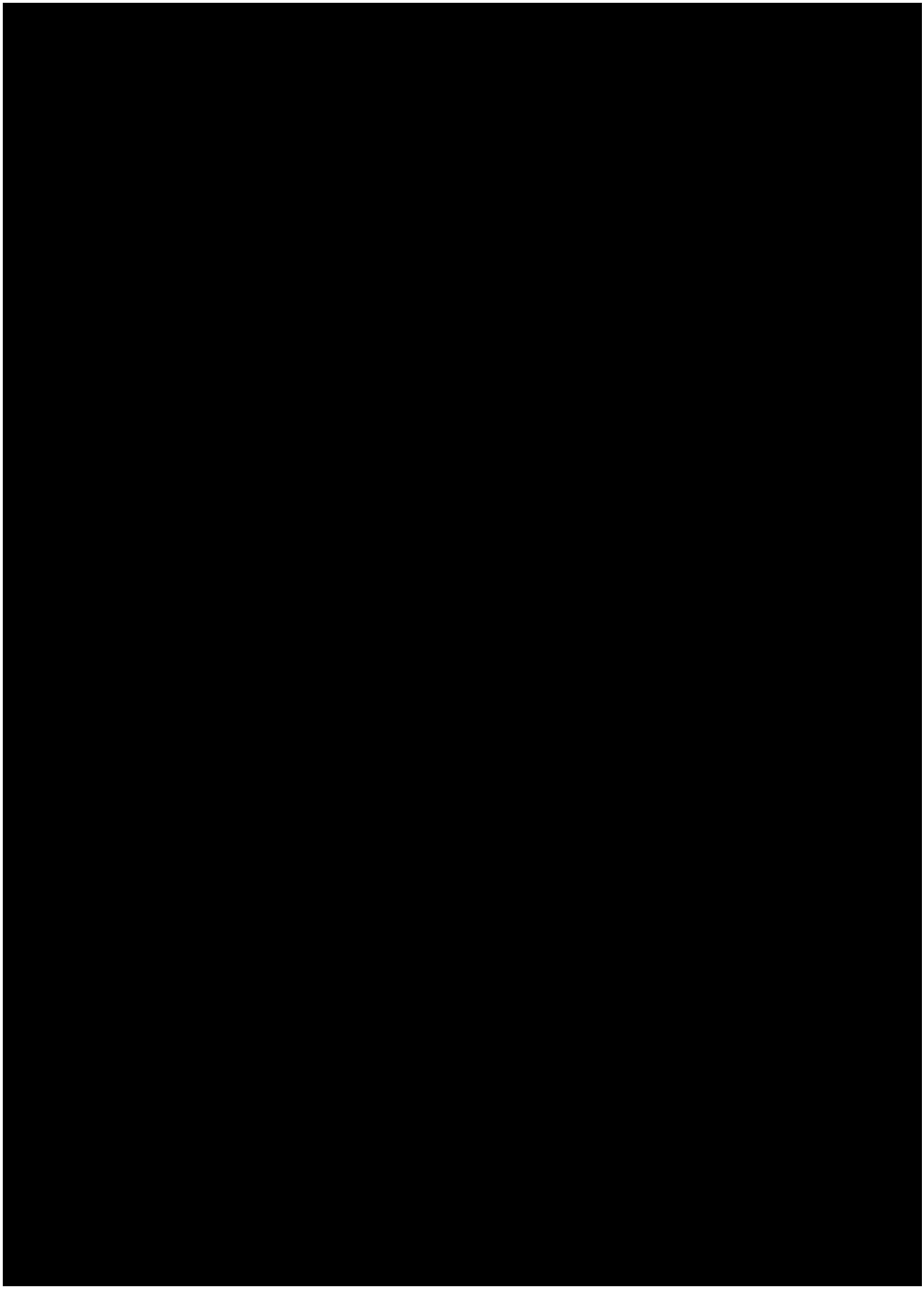

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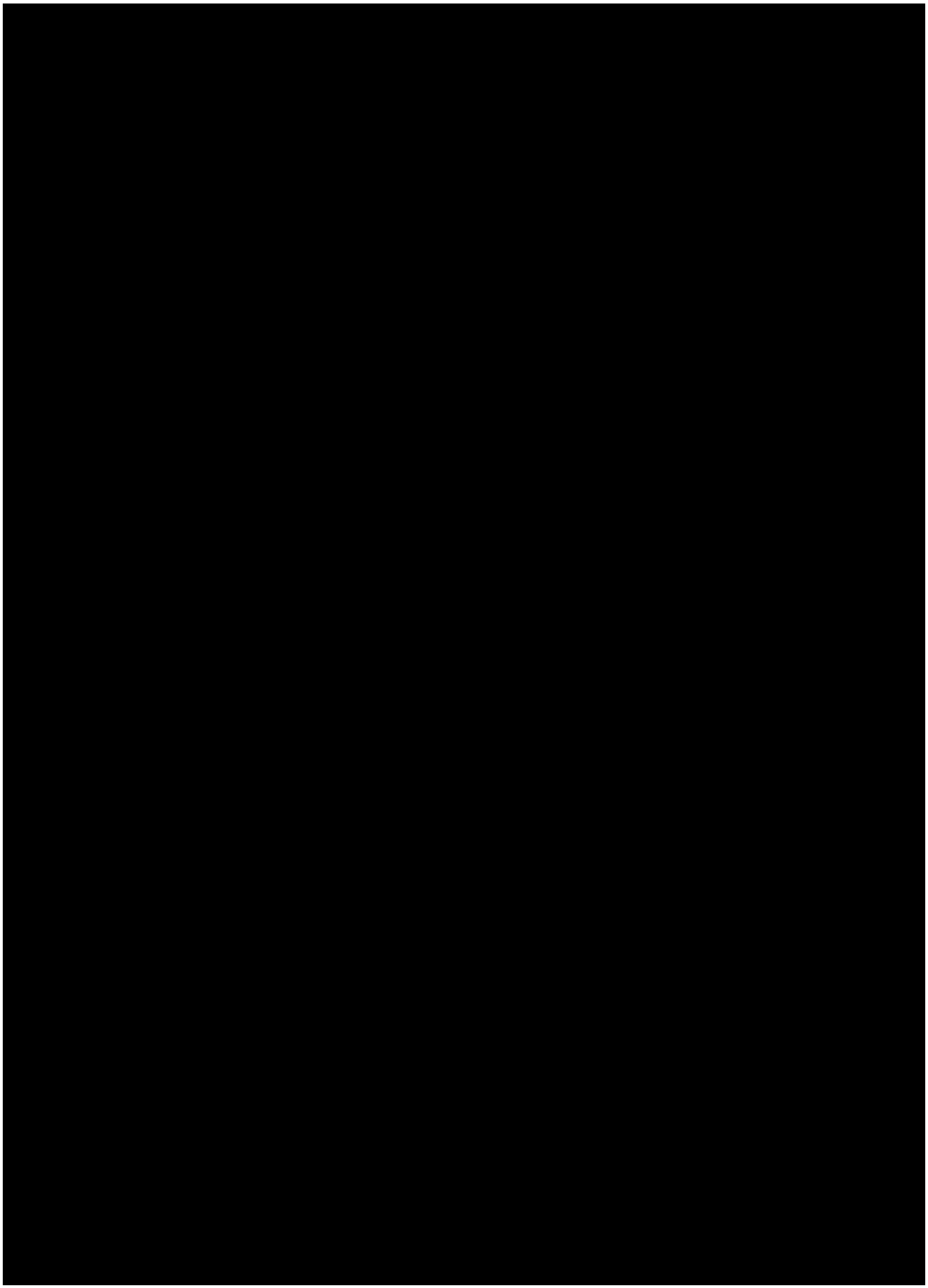

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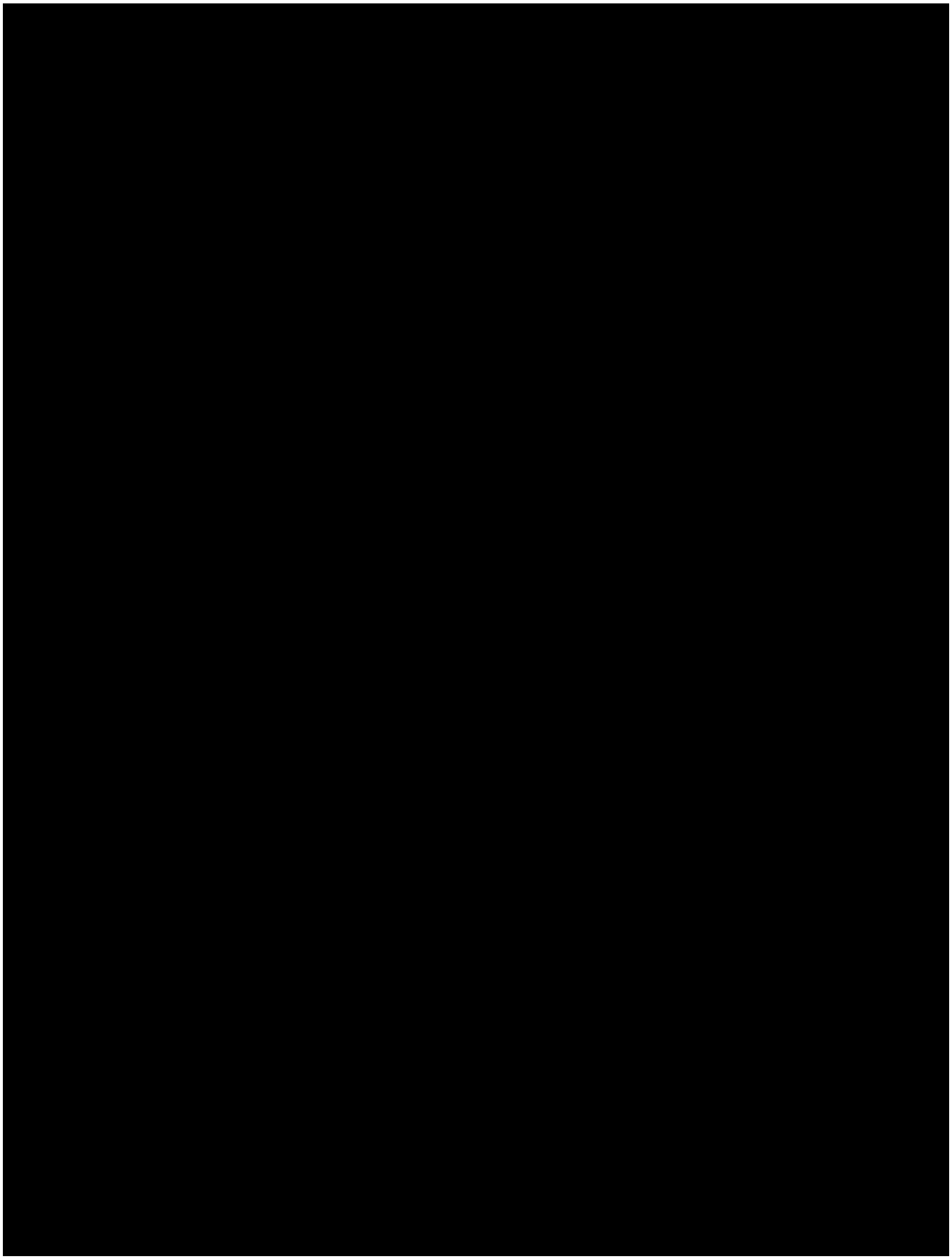

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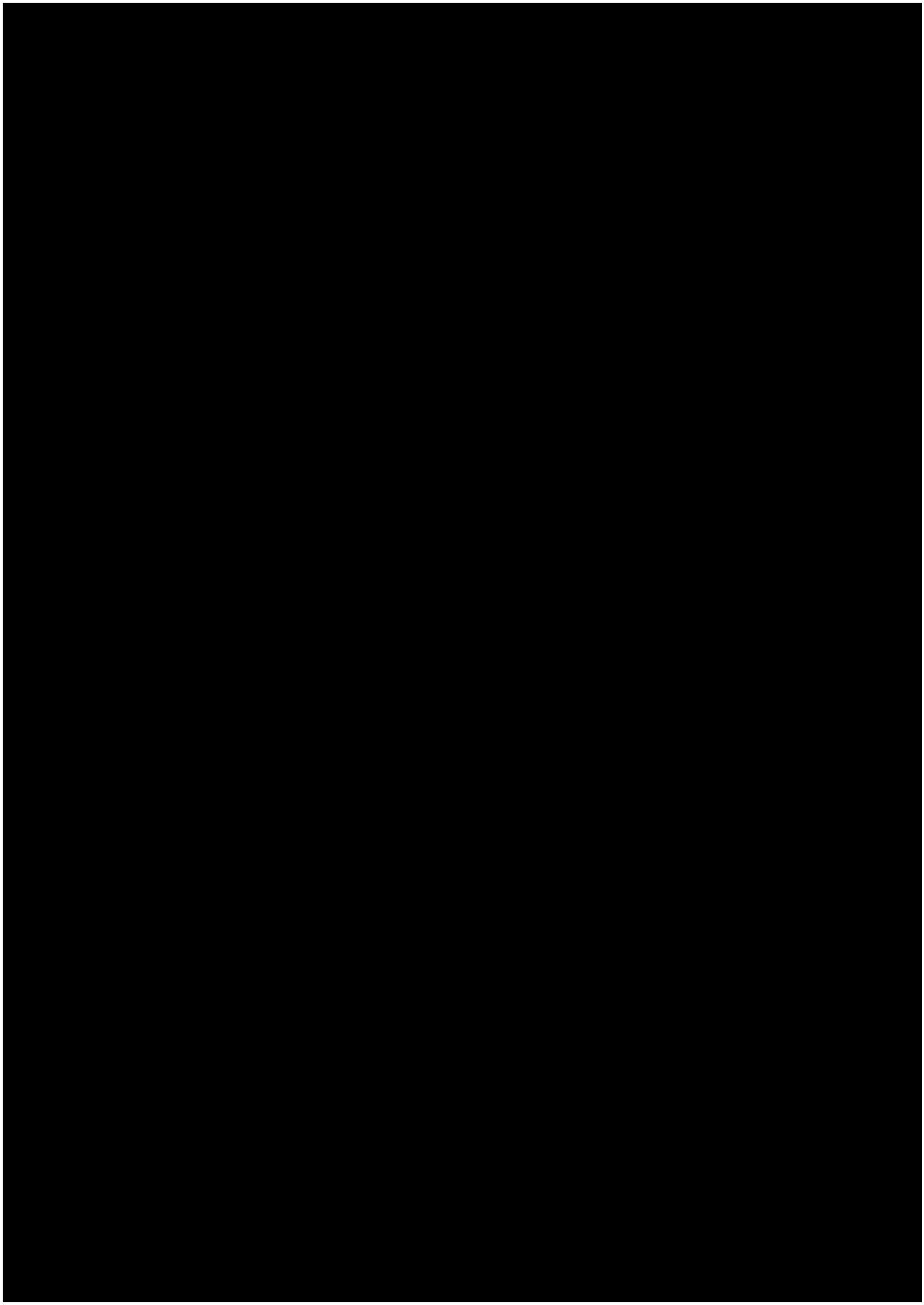

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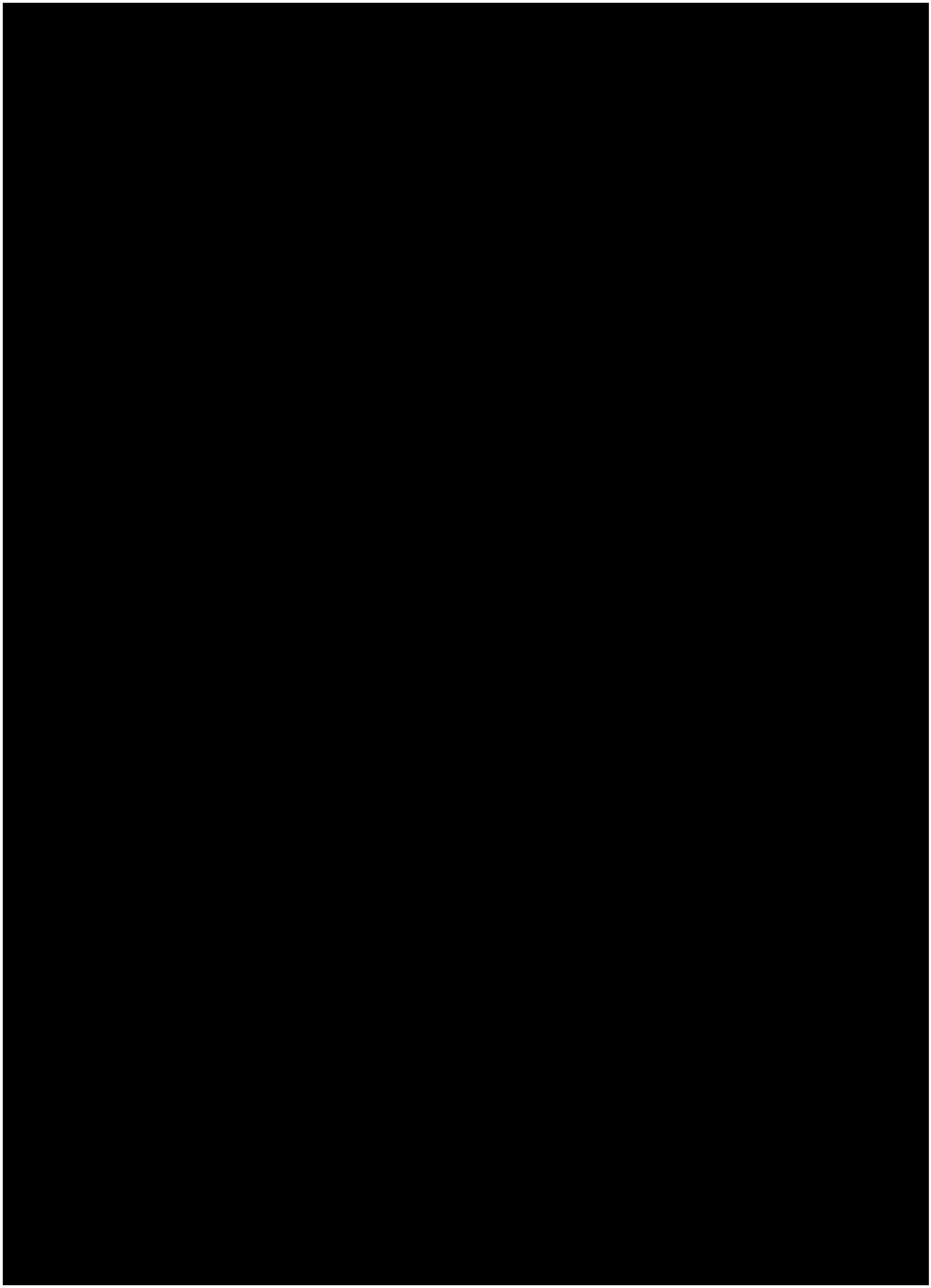

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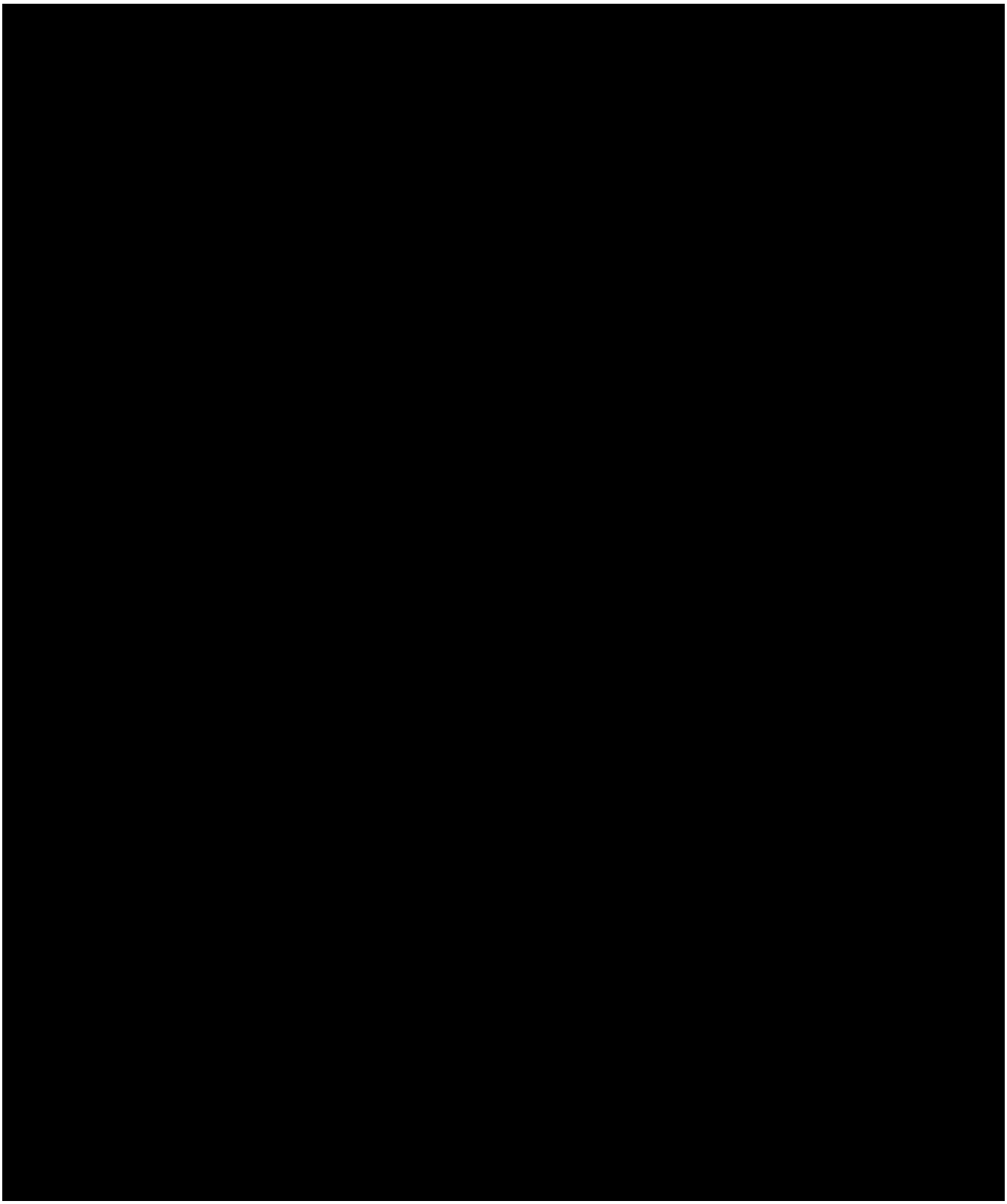

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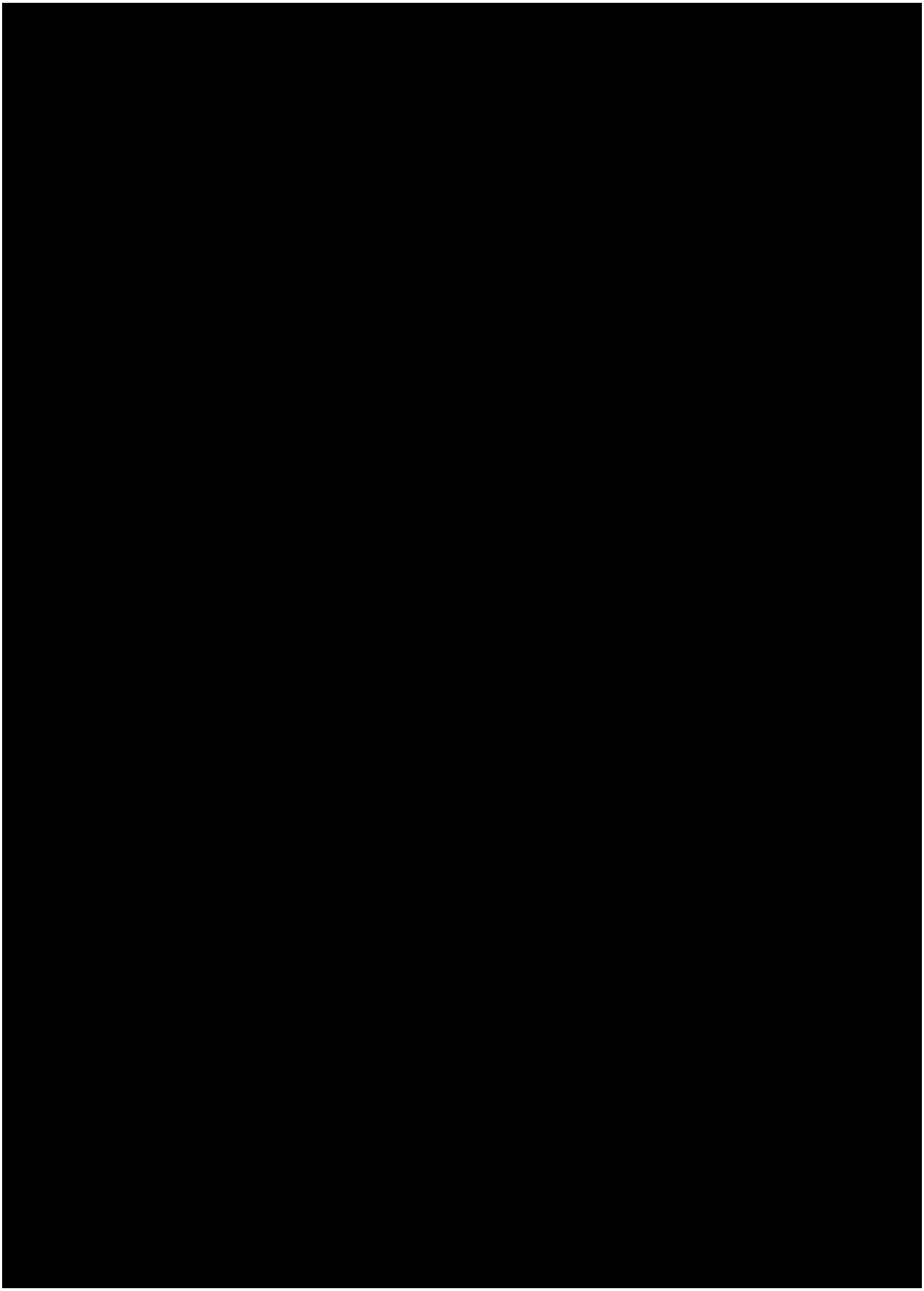

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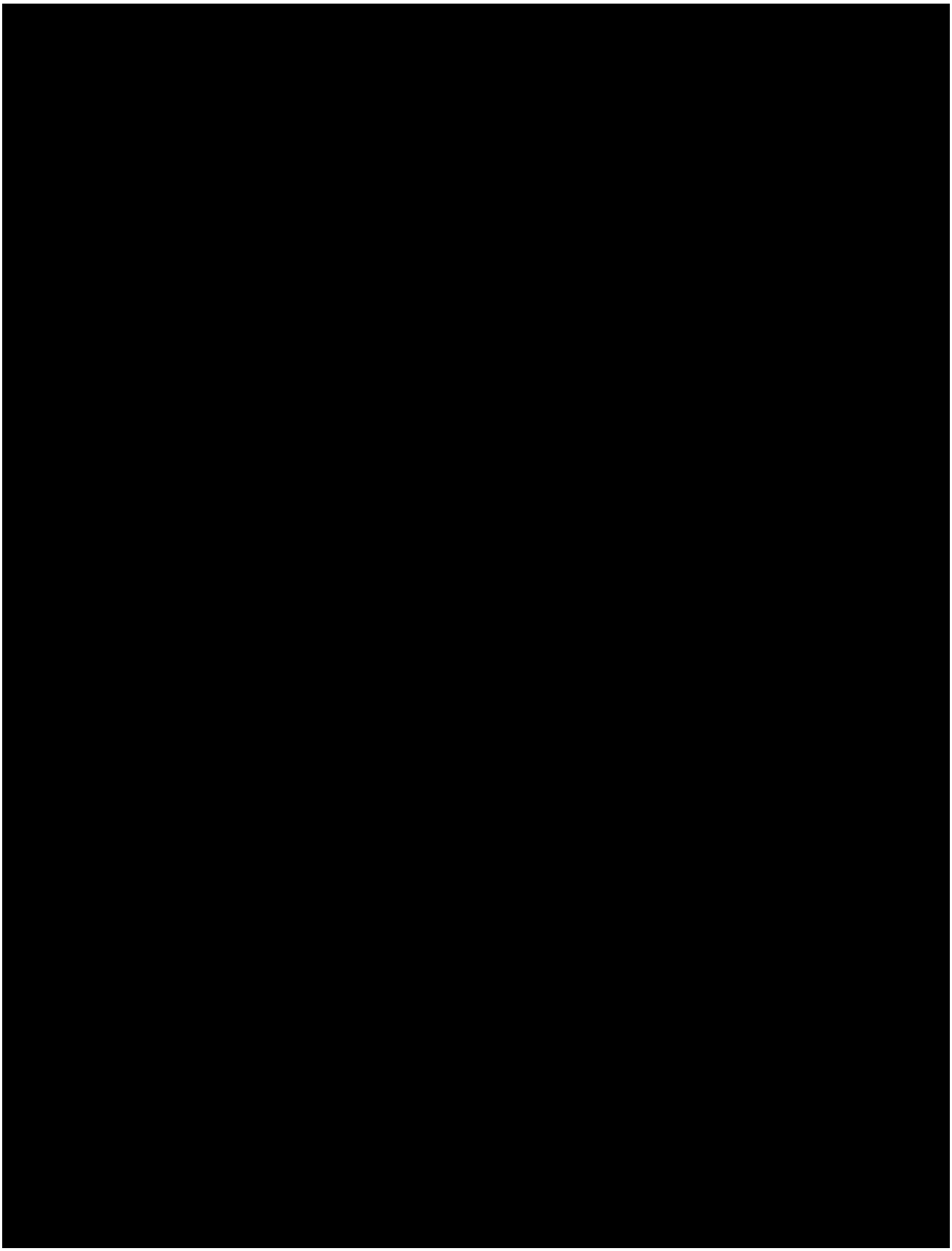

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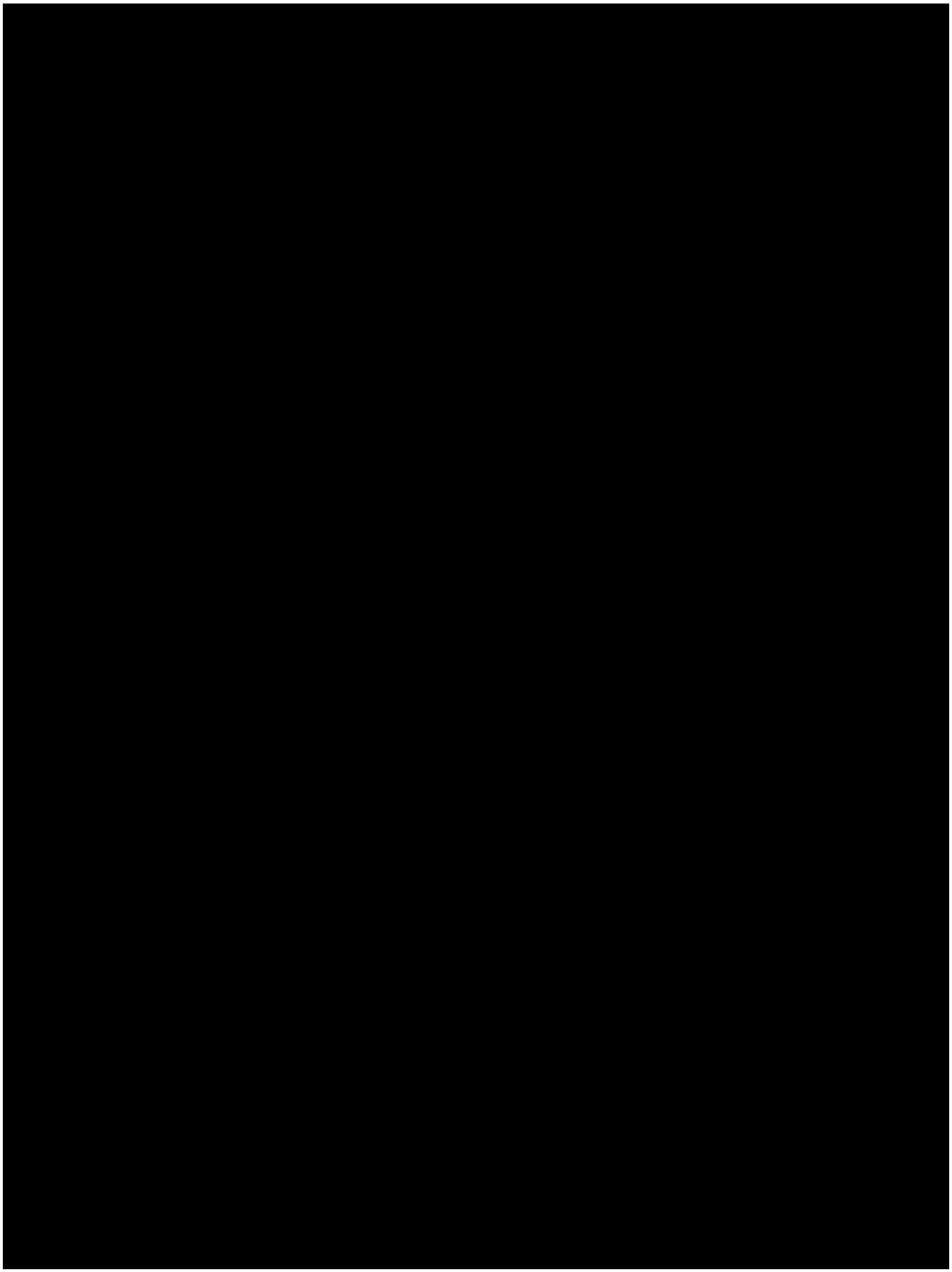

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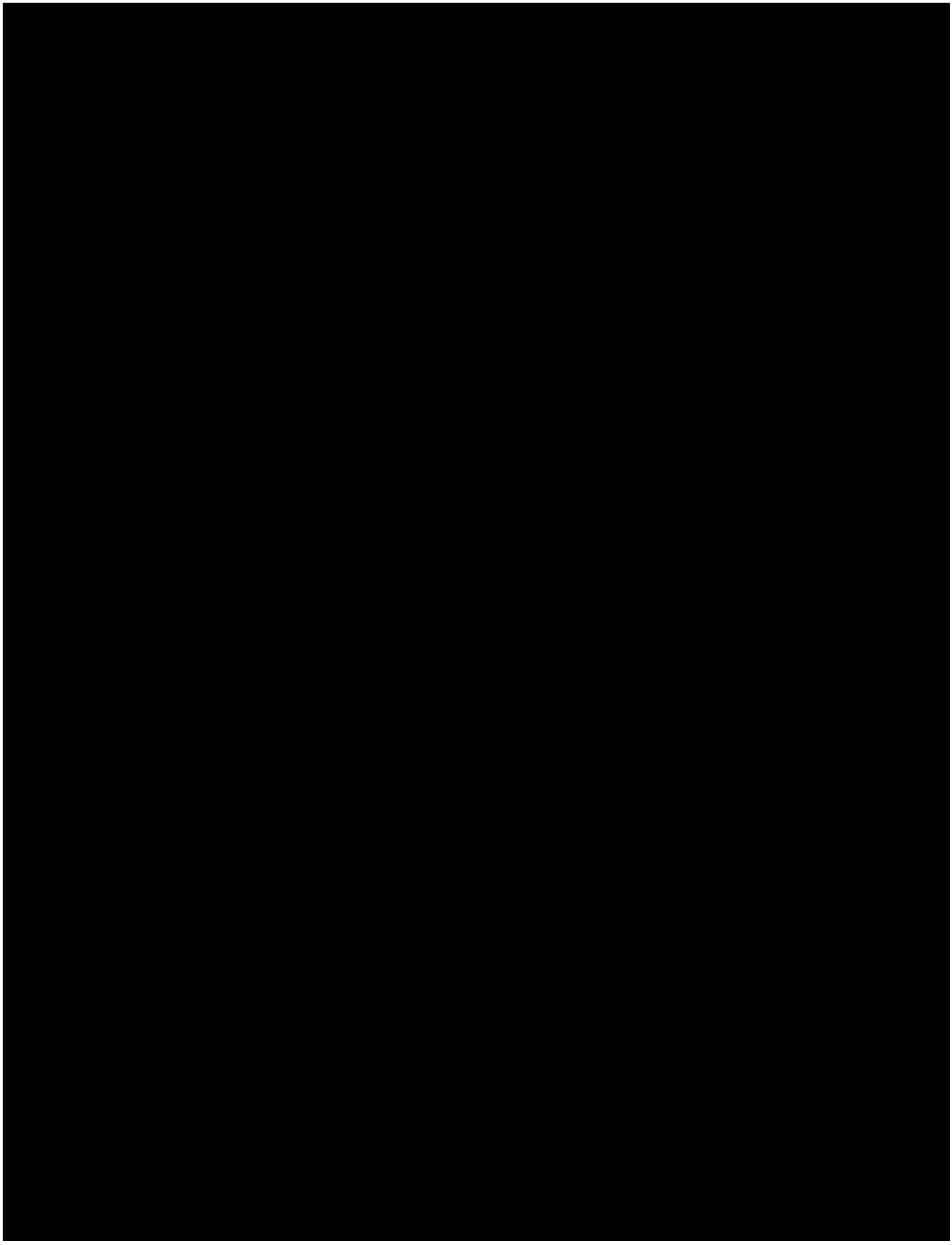

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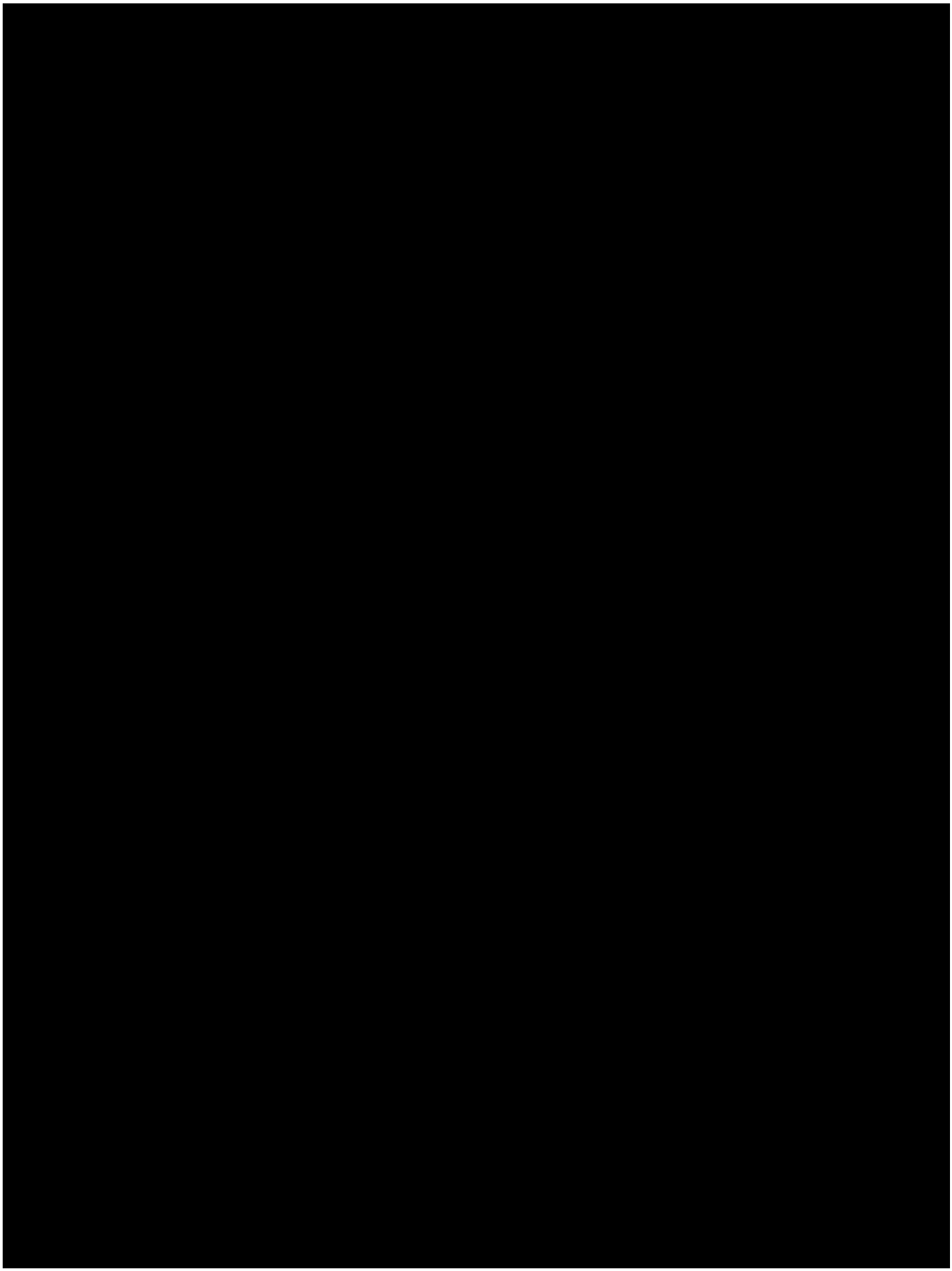

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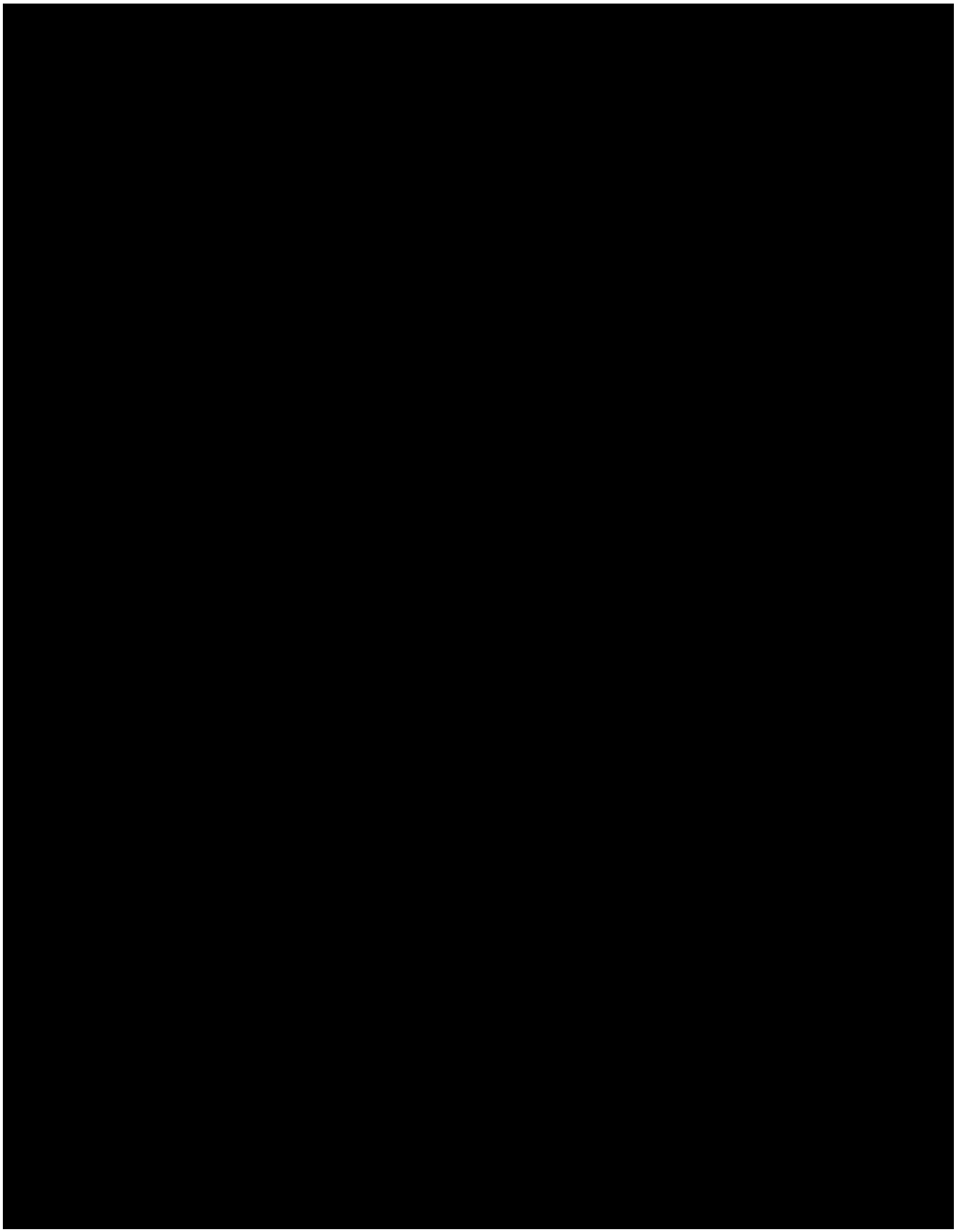

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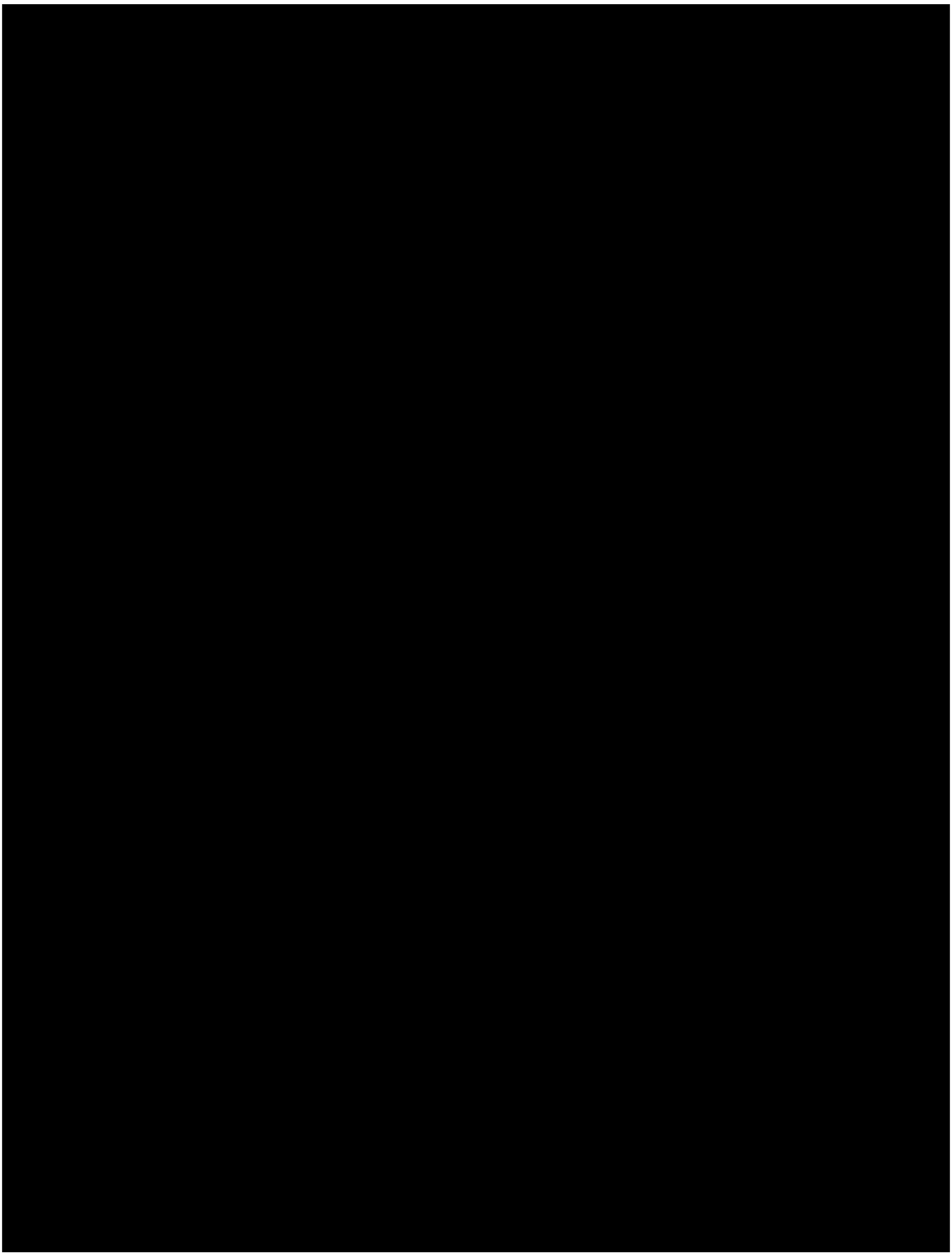

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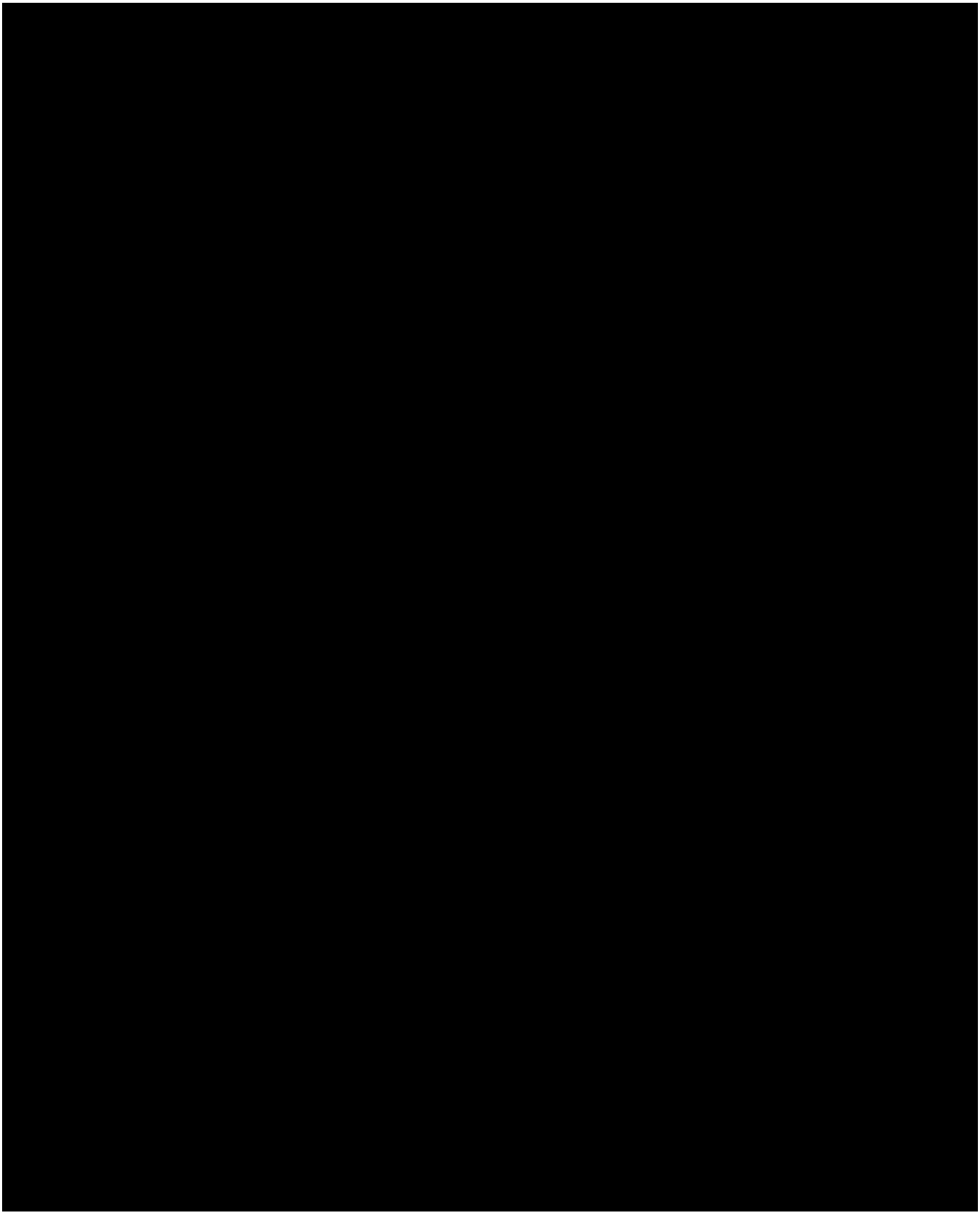

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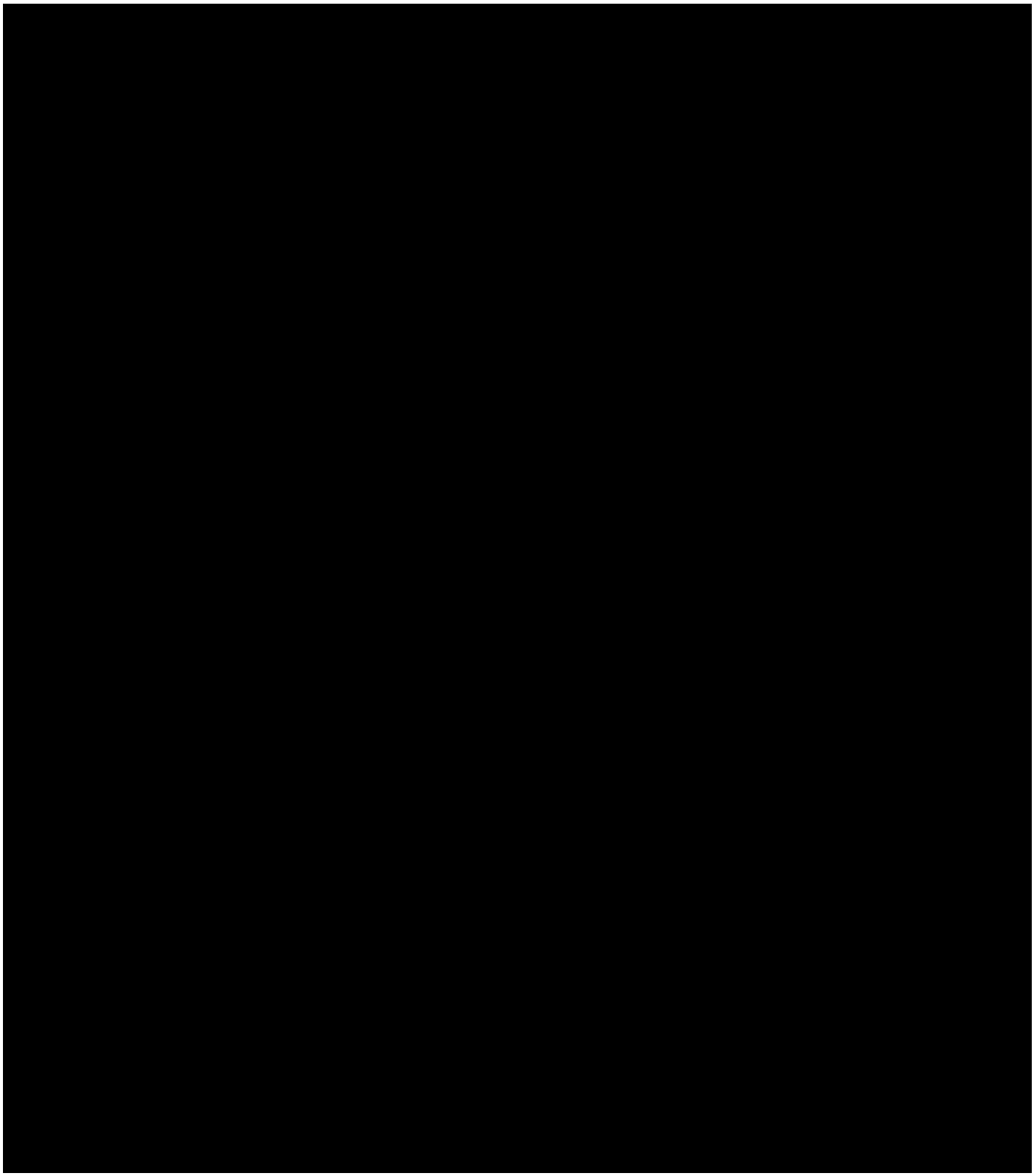

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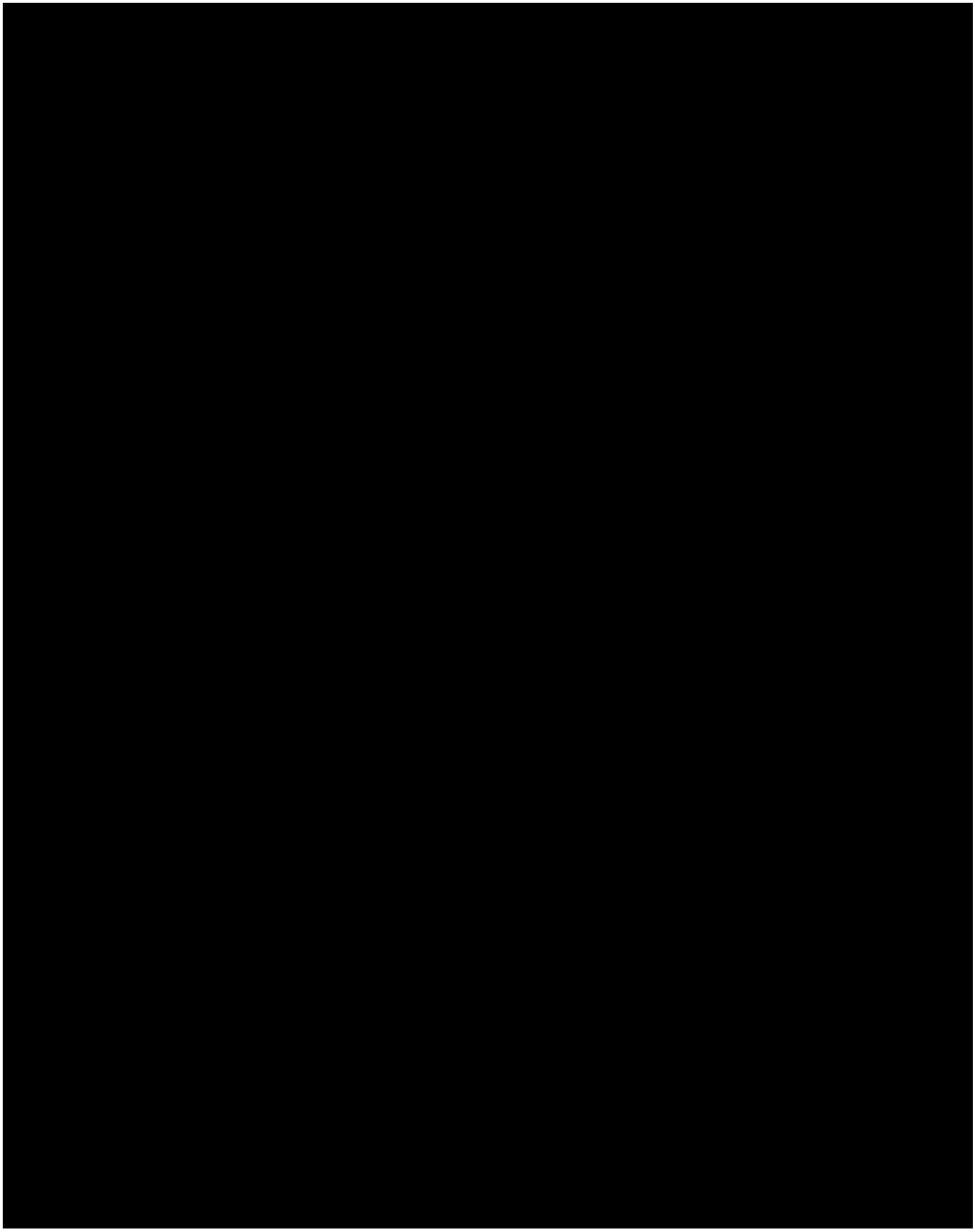

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Appendix G – Extrapolation

[redacted]

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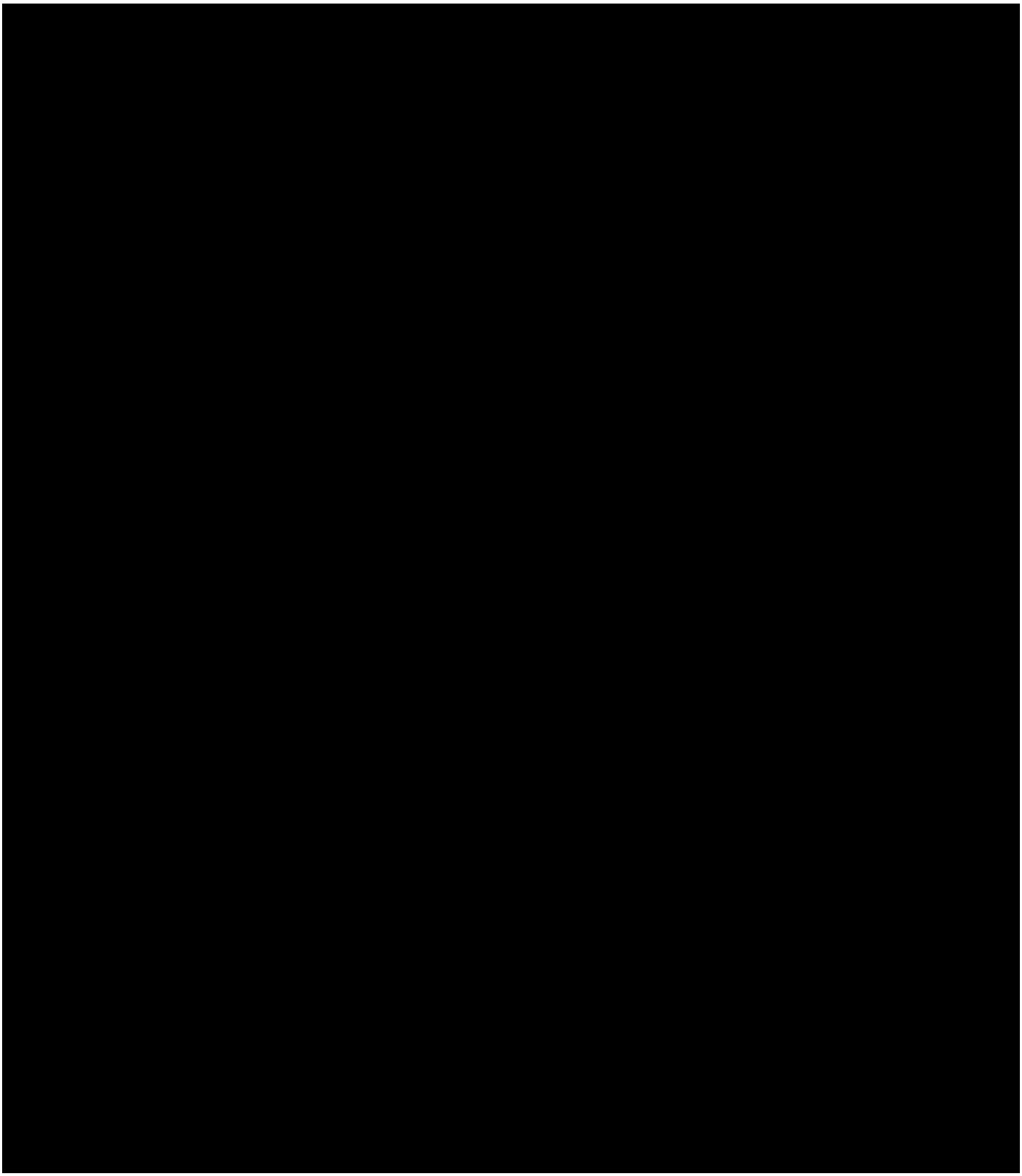

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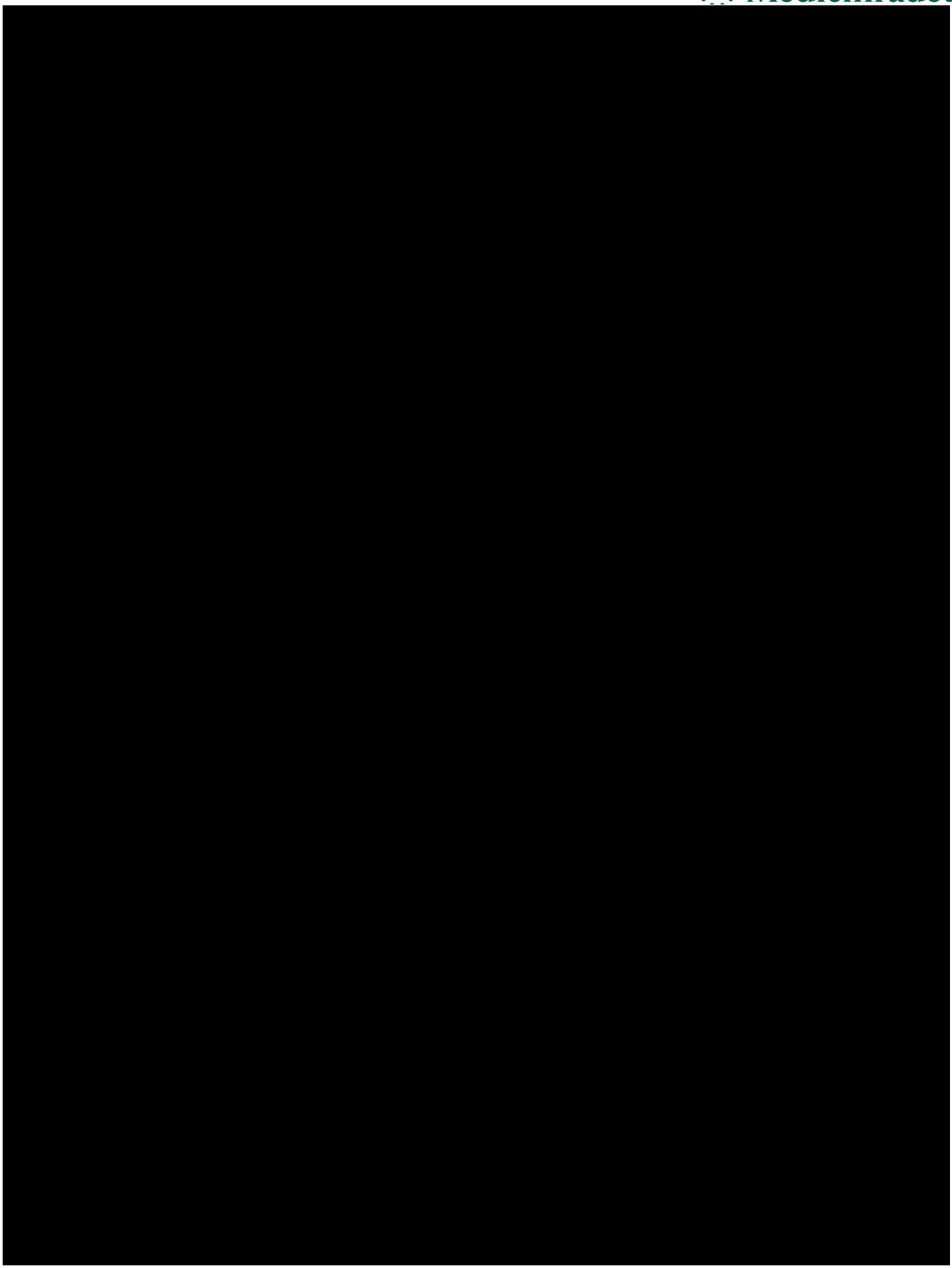

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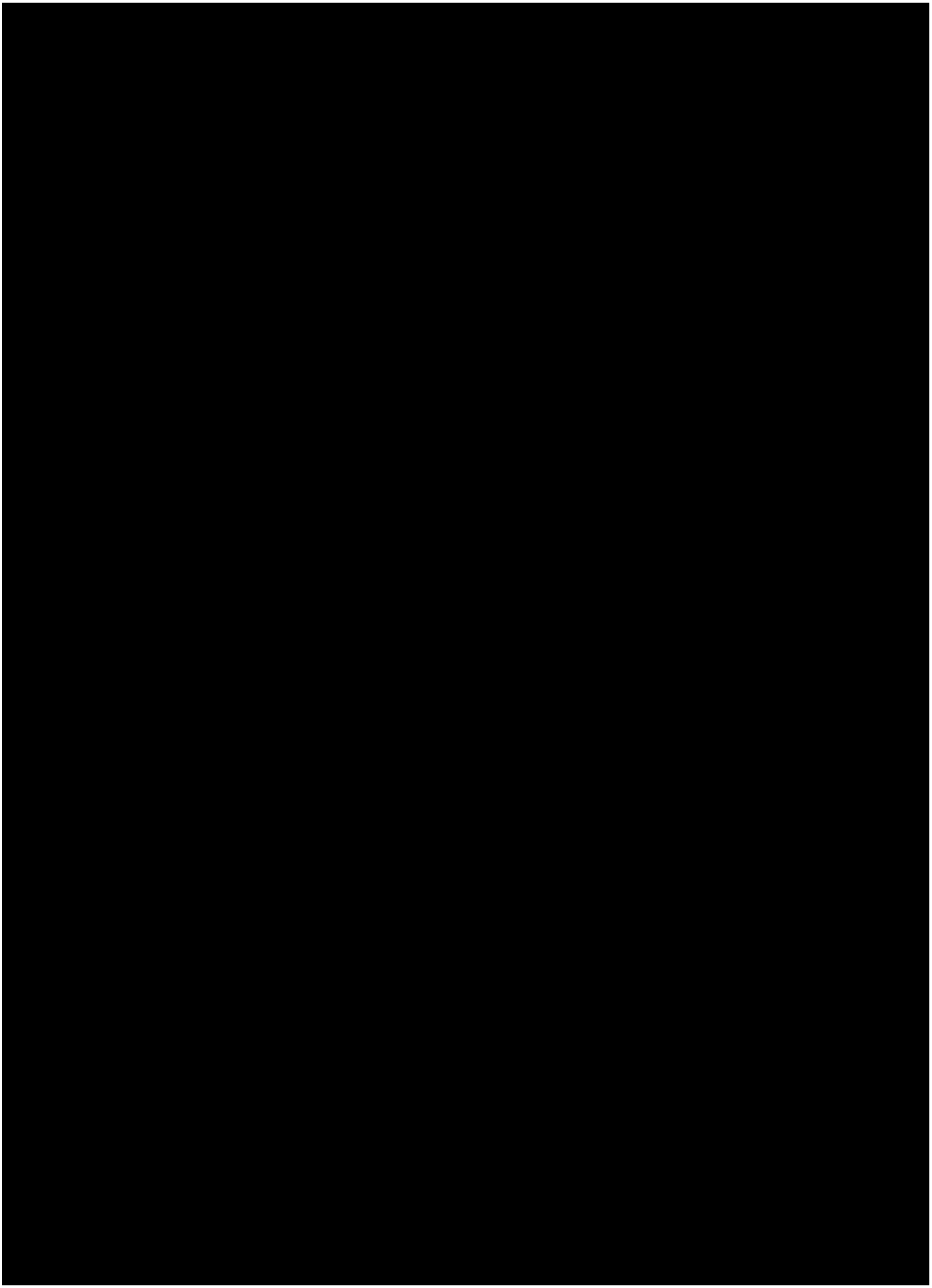

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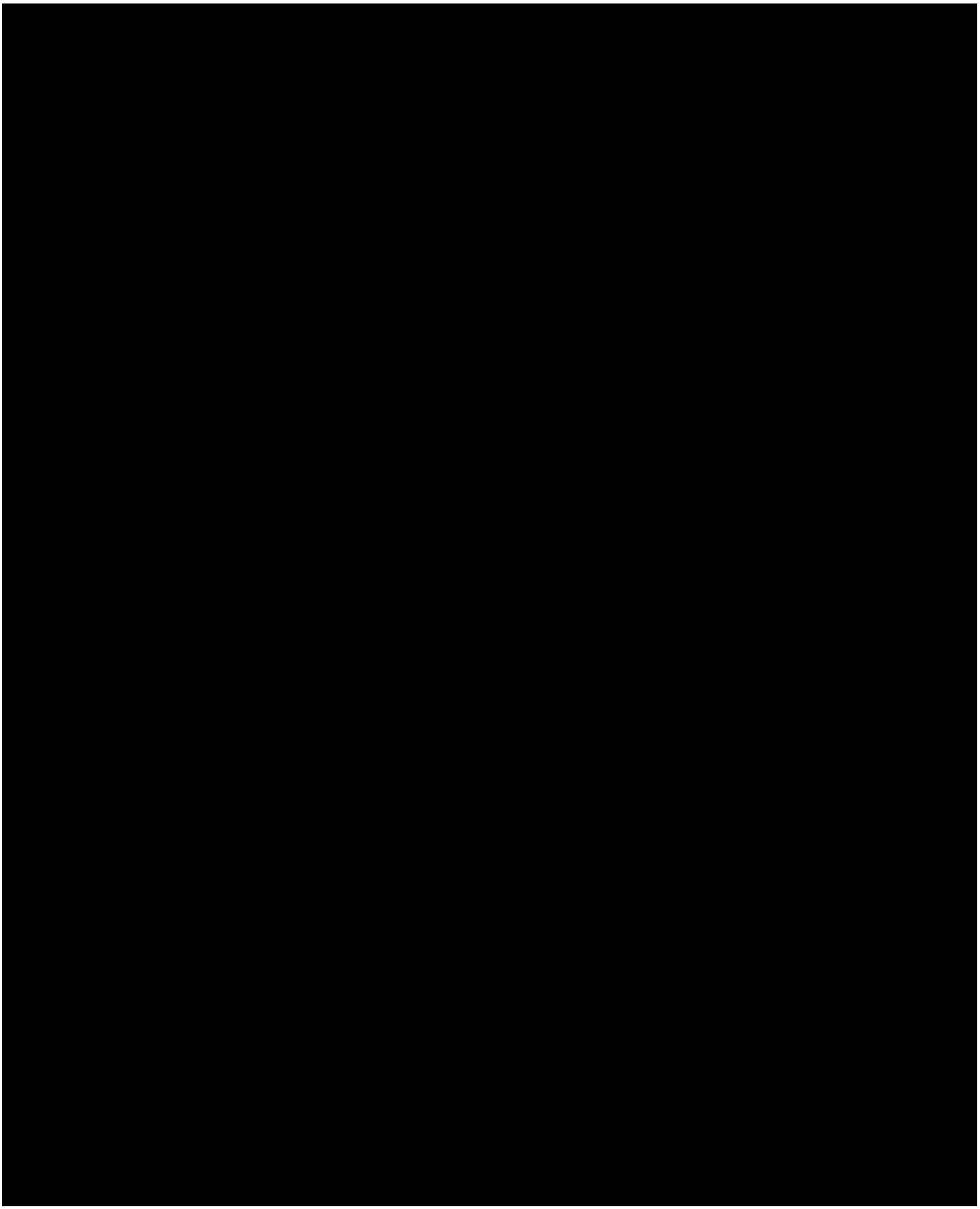

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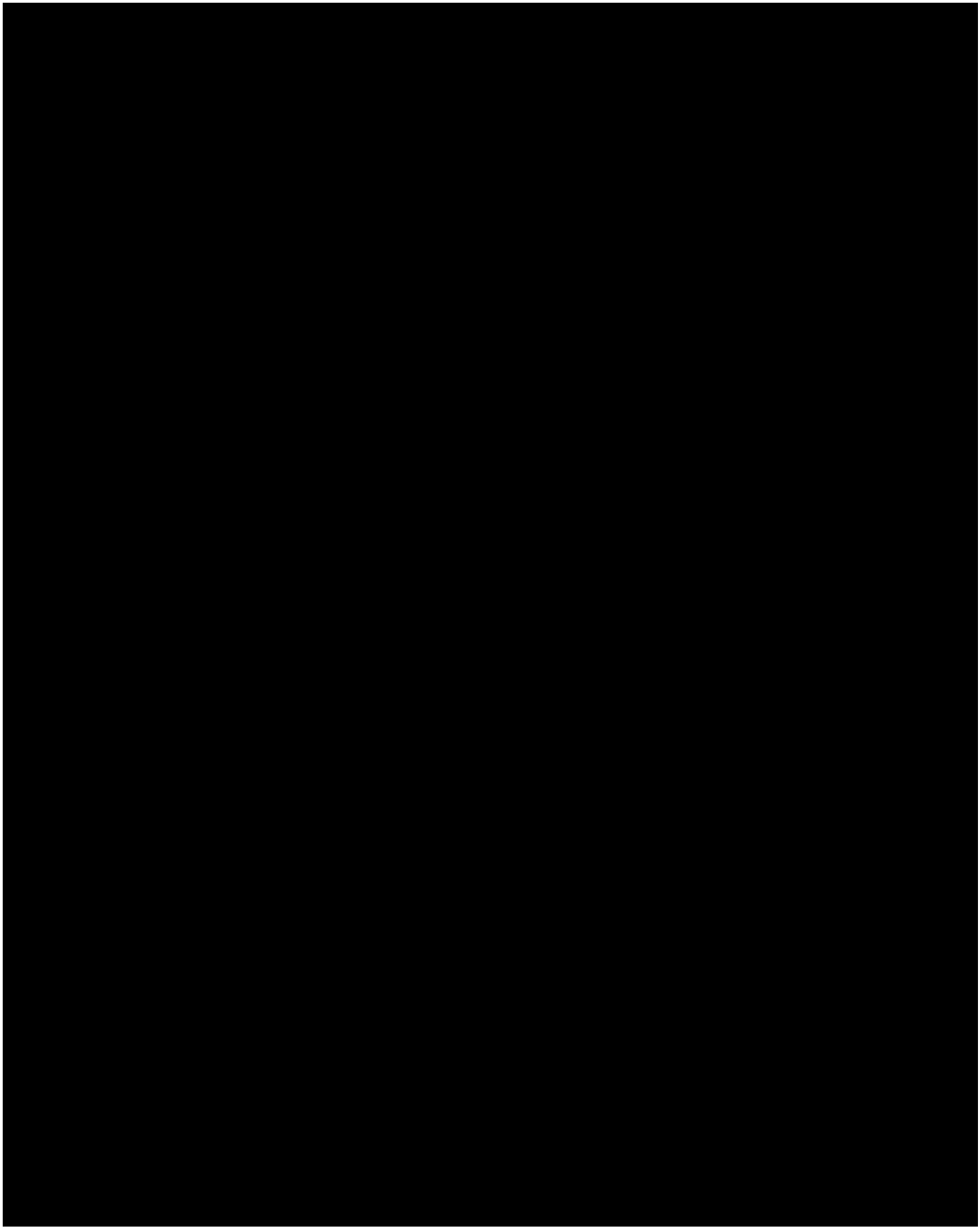
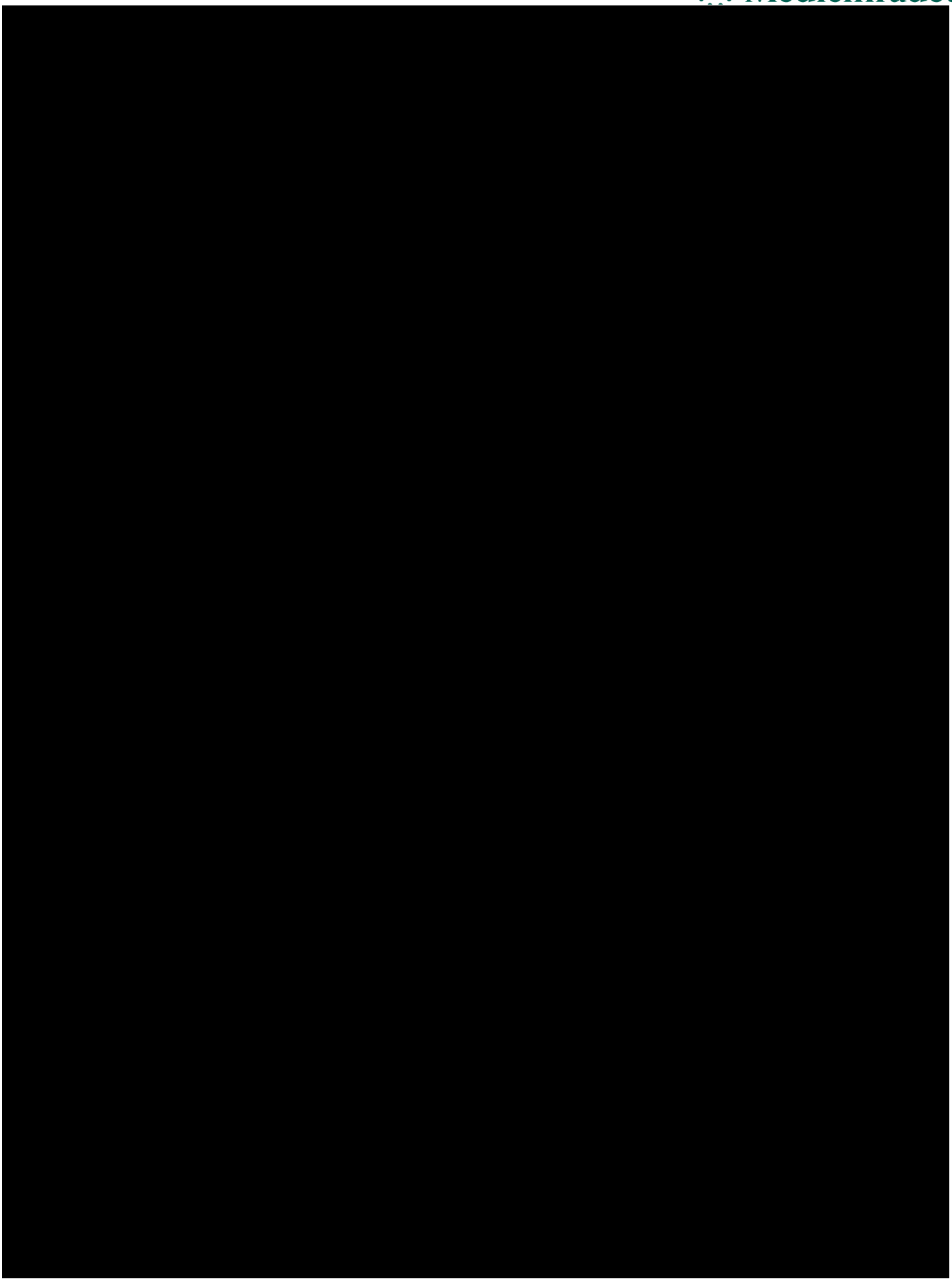


Medicinrådet Dampfærgevej 27-29, 3. th. DK-2100 København Ø +45 70 10 36 00 medicinraadet@medicinraadet.dk www.medicinraadet.dk



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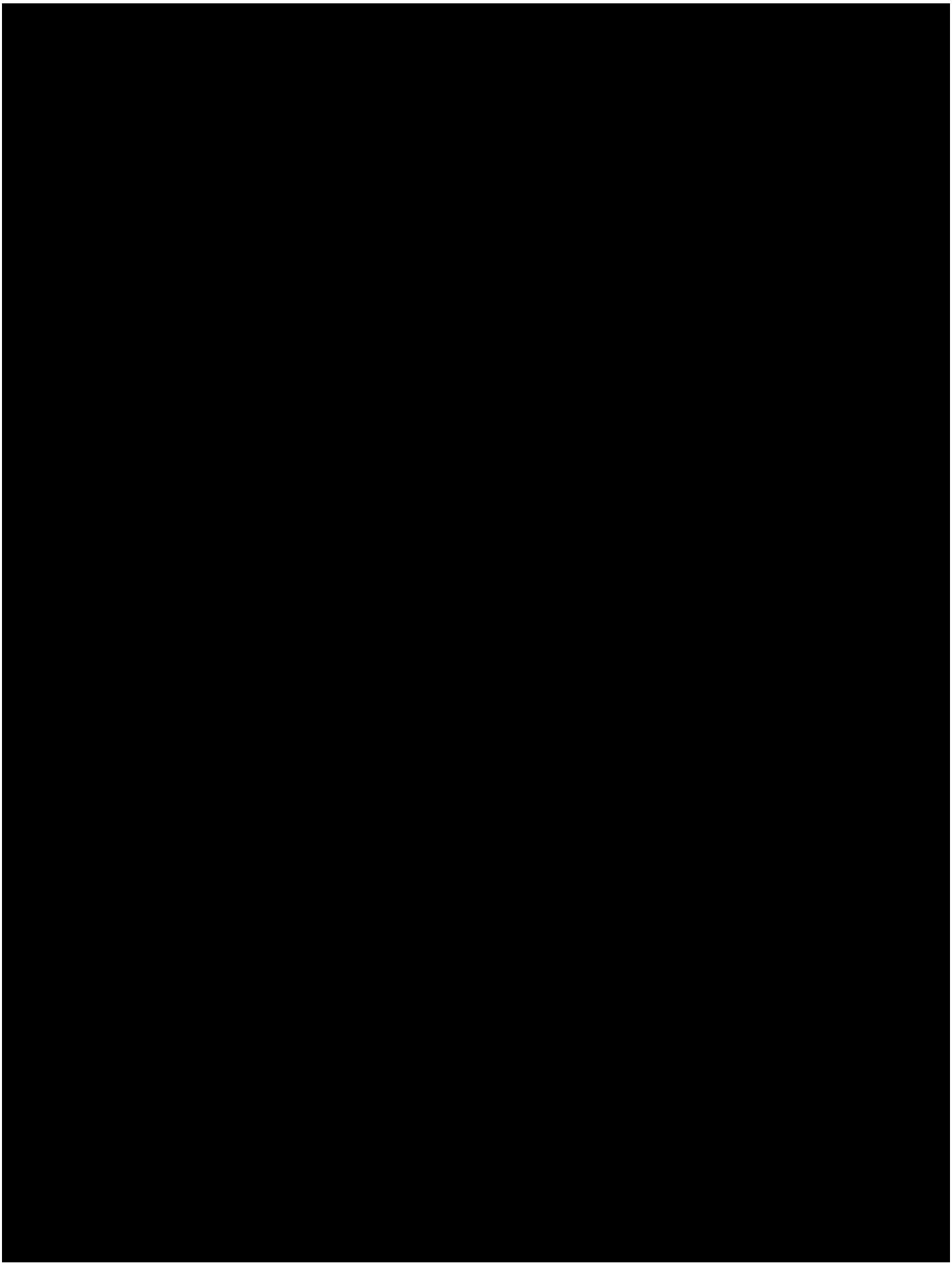

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Appendix H – Literature search for HRQoL data

The objective of the review was to support Janssen's continued investigation of amivantamab, as well as to understand the current evidence in metastatic or surgically unresectable EGFR-mutated NSCLC. A SLR was conducted to identify the available evidence on HRQoL, utilities, costs, medical resource use, and economic evaluations in this patient population. This section will focus on HRQoL. As no HRQoL data was available for Exon 20ins patients, the values found in this literature review were not used in the health economic model, please see section 8.4.2 for an overview of the values used instead.

Electronic database

The following databases (Table 83) were searched from database inception on 4th May 2020 using the search terms presented in Table 91.

Table 83. Bibliographic databases included in the literature search

Database	Platform	Relevant period for the search	Date of search completion
Embase	via Ovid SP	1946-May 1st, 2020	04.05.2020
Medline	Via Ovid SP	1974 – May 1st, 2020	04.05.2020
National Health Service Economic Evaluation Database (NHS-EED)	N/A	Issues 2 of 4, April 2015	04.05.2020
Health Technology Assessment Database (HTAD)	N/A	Issues 4 of 4, October 2016	04.05.2020

MEDLINE and Embase were searched separately via the Ovid SP platform. NHS-EED and HTAD were searched simultaneously via the University of York Centre for Reviews and Dissemination (CRD) platform.

Search terms

Where the database allowed, search terms included combinations of free text and Medical Subject Heading (MeSH) or Emtree terms, grouped into the following categories:

- Disease area: metastatic NSCLC
- Study design: economic evaluations, utilities and HRQoL studies, and cost and resource use studies
- Exclusion terms: studies indexed as including animals only, case reports, case studies, comments, editorials and Phase I clinical trials (MEDLINE/Embase only)
- Limits: conference abstracts from the last two years (Embase only)

Full details of the search strategies for the electronic database searches are presented below (Table 84, Table 85, Table 86, Table 87, Table 88 and Table 89).

Table 84. Search terms for MEDLINE, MEDLINE In-Process, MEDLINE Daily and MEDLINE Epub Ahead of Print (via Ovid)

Term Group	#	Search Terms	Results 04.05.2020
Disease area: Metastatic NSCLC	1	NSCLC.ti,ab,kw,kf.	42,328
	2	exp Lung/ and (exp Neoplasms/ or exp Neoplasms, squamous cell/ or exp Adenocarcinoma/ or exp Carcinoma, squamous cell/ or exp Carcinoma, large cell/)	31,682
	3	(lung$ and (non small cell or nonsmall cell) and (carcinoma$ or adenocarcinoma$ or cancer$ or tumo?r$ or neoplasm$)).ti,ab,kw,kf.	65,008
	4	exp Neoplasm metastasis/ or (metastat$ or metastas$ or advanced or stage IIIb or stage 3b or stage IIIc or stage 3c or	1,204,898

		stage IV or stage 4 or unresectable or non-resectable or nonresectable or inoperable or progressive).ti,ab,kw,kf.	
	5	1 or 2 or 3	97,266
	6	4 and 5	38,296
Study design: Economic evaluations	7	Cost-benefit analysis/	80,282
	8	"Costs and cost analysis"/	48,438
	9	Economics/	27,175
	10	(cost$ adj (effective$ or utilit$ or consequence$ or benefit$ or minimi$)).tw.	144,247
	11	(economic evaluation$ or economic analysis or life year$ gained or ICER or QALY$ or DALY$ or quality adjusted or adjusted life year$ or disability adjusted life or qald$ or qale$ or qtime$).tw.	33,137
	12	Quality-adjusted life years/	11,998
	13	Value of life/	5,697
	14	or/7-13	266,201
Study design: Utilities and HRQoL	15	(health utilit$ or health state$1 or illness state$1 or HSUV or HSUVs or health state$ value$ or health state$ preference$ or utility assessment$ or utility measure$ or preference based or utility based).tw.	9,440
	16	((index adj3 wellbeing) or (quality adj3 wellbeing) or qwb).tw.	721
	17	(multiattribute$ or multi attribute$).ti,ab.	863
	18	utility.ab. /freq=2	17,233
	19	(utilities or disutilit$).tw.	7,303
	20	(euro qual or euro qual5d or euro qol5d or eq-5d or eq5-d or eq5d or eq 5d or euroqual or euroqol or euro qol or euroqual5d or euroqol5d or eq-sdq or eqsdq).tw.	10,795
	21	(short form$ or shortform$).ti,ab.	32,878
	22	(sf36$ or sf 36$ or sf thirtysix or sf thirty six).tw.	21,685
	23	(sf6 or sf 6 or sf6d or sf 6d or sf six D or sfsixD or sf six or sfsix or sf8 or sf 8 or sf eight or sfeight).tw.	3,237
	24	(sf12 or sf 12 or sf twelve or sftwelve).tw.	4,611
	25	(sf16 or sf 16 or sf sixteen or sfsixteen).tw.	29
	26	(sf20 or sf 20 or sf twenty or sftwenty).tw.	334
	27	(15D or 15-D or 15 dimension).tw.	5,191
	28	visual analog$ scale$.tw.	54,082
	29	(standard gamble$ or sg).tw.	10,530

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	30	(time trade off$1 or time tradeoff$1 or tto or timetradeoff$1).tw.	1,872
	31	(health$1 year$1 equivalent$1 or hye or hyes).tw.	78
	32	(hui or hui1 or hui2 or hui3 or rosser).tw.	1,592
	33	*quality of life/ and (quality of life or qol or hrqol).tw.	71,162
	34	quality of life/ and ((quality of life or qol or hrqol) adj (score$1 or measure$1)).tw.	13,658
	35	quality of life/ and health-related quality of life.tw.	30,912
	36	quality of life/ and ec.fs.	9,953
	37	quality of life/ and (health adj3 status).tw.	8,785
	38	((qol or hrqol or quality of life).ti,kf. or *quality of life/) and ((qol or hrqol$ or quality of life) adj2 (increas$ or decrease$ or improv$ or declin$ or reduc$ or high$ or low$ or effect or effects or worse or score or scores or change$1 or impact$1 or impacted or deteriorat$)).ab.	36,924
	39	or/15-38	223,953
Study design: Cost or resource use studies	40	Cost allocation/	2,004
	41	Cost control/	21,471
	42	Cost savings/	11,740
	43	Cost of illness/	26,823
	44	Cost sharing/	2,497
	45	"Deductibles and coinsurance"/	1,746
	46	Medical savings accounts/	534
	47	Health care costs/	39,045
	48	Direct service costs/	1,189
	49	Drug costs/	15,932
	50	Employer health costs/	1,090
	51	Hospital costs/	10,943
	52	Health expenditures/	20,025
	53	Capital expenditures/	1,989
	54	exp economics, Hospital/	24,393
	55	exp economics, Medical/	14,180
	56	Economics, nursing/	3,997
	57	Economics, pharmaceutical/	2,927
	58	exp Budgets/	13,667
	59	Financial management/	16,507
	60	exp "Fees and charges"/	30,208
	61	(low adj cost).mp.	57,064
	62	(high adj cost).mp.	14,407
	63	((health?care) adj cost$).mp.	11,444
	64	(fiscal or funding or financial or finance).tw.	144,313
	65	(cost adj estimate$).mp.	2,254
	66	(cost adj variable$).mp.	161
	67	(unit adj cost$).mp.	2,484
	68	(economic$ or pharmacoeconomic$ or price$ or pricing).tw.	295,858

	69	((resource$ or healthcare$ or service$) adj3 (use$ or utilis$ or utiliz$ or consume$ or consuming or consumption$)).tw.	100,930
	70	((patient$ or caregiver$ or carer$ or social$ or society$ or family$) adj2 (burden$ or productiv$)).tw.	15,158
	71	("length of stay" or utili?ation or "economic burden" or "cost-of-illness" or nursing cost$ or physician cost$ or physician visit$ or "out of pocket").tw.	266,156
	72	(absenteeism or presenteeism or employment or unemployment).tw. or exp presenteeism/ or exp absenteeism/ or exp unemployment/ or exp employment/	139,805
	73	or/40-72	1,036,809
	74	limit 73 to yr="2015-2020"	339,069
Exclusion terms	75	exp animals/ not exp humans/	4,695,034
	76	(comment or editorial or "case reports" or "clinical trial, phase I").pt.	3,304,506
	77	(case stud$ or case report$).ti.	291,814
	78	or/75-77	7,996,043
Combination	79	6 and (14 or 39 or 74)	1,379
	80	79 not 78	1,321

Database: Ovid MEDLINE(R) and Epub Ahead of Print, In-Process & Other Non-Indexed Citations and Daily 1946 to May 01, 2020

Table 85. Search terms for Embase (via Ovid)

Term Group	#	Search Terms	Results 30.04.2020
Disease area: Metastatic NSCLC	1	NSCLC.ti,ab,kw.	81,003
	2	exp Lung/ and (exp Neoplasm/ or exp squamous cell carcinoma/ or exp Adenocarcinoma/ or exp large cell carcinoma/)	66,534
	3	(lung$ and (non small cell or nonsmall cell) and (carcinoma$ or adenocarcinoma$ or cancer$ or tumo?r$ or neoplasm$)).ti,ab,kw.	104,930
	4	exp Metastasis/ or exp Advanced cancer/ or (metastat$ or metastas$ or advanced or stage IIIb or stage 3b or stage IIIc or stage 3c or stage IV or stage 4 or unresectable or non-resectable or nonresectable or inoperable or progressive).ti,ab,kw.	1,791,865
	5	1 or 2 or 3	177,029
	6	4 and 5	88,298
Study design: Economic evaluations	7	Cost benefit analysis/ or exp economic evaluation/ or cost effectiveness analysis/ or cost minimization analysis/	303,435
	8	Economics/ or health economics/ or socioeconomics/ or economic aspect/	486,779
	9	(cost$ adj (effective$ or utilit$ or consequence$ or benefit$ or minimi$)).tw.	199,469
	10	(economic evaluation$ or economic analysis or life year$ gained or ICER or QALY$ or DALY$ or quality adjusted or adjusted life year$ or disability adjusted life or qald$ or qale$ or qtime$).tw.	50,848
	11	quality adjusted life year/	26,129
	12	or/7-11	823,304
Study design: Utilities and HRQoL	13	(health utilit$ or health state$1 or illness state$1 or HSUV or HSUVs or health state$ value$ or health state$ preference$ or utility assessment$ or utility measure$ or preference based or utility based).tw.	15,785
	14	((index adj3 wellbeing) or (quality adj3 wellbeing) or qwb).tw.	1,139
	15	(multiattribute$ or multi attribute$).ti,ab.	1,105

	16	utility.ab. /freq=2	26,942
	17	(utilities or disutilit$).tw.	11,956
	18	(euro qual or euro qual5d or euro qol5d or eq-5d or eq5-d or eq5d or eq 5d or euroqual or euroqol or euro qol or euroqual5d or euroqol5d or eq-sdq or eqsdq).tw.	20,158
	19	(short form$ or shortform$).ti,ab.	44,797
	20	(sf36$ or sf 36$ or sf thirtysix or sf thirty six).tw.	37,196
	21	(sf6 or sf 6 or sf6d or sf 6d or sf six D or sfsixD or sf six or sfsix or sf8 or sf 8 or sf eight or sfeight).tw.	4,444
	22	(sf12 or sf 12 or sf twelve or sftwelve).tw.	7,971
	23	(sf16 or sf 16 or sf sixteen or sfsixteen).tw.	55
	24	(sf20 or sf 20 or sf twenty or sftwenty).tw.	339
	25	(15D or 15-D or 15 dimension).tw.	6,556
	26	visual analog$ scale$.tw.	77,073
	27	(standard gamble$ or sg).tw.	15,939
	28	(time trade off$1 or time tradeoff$1 or tto or timetradeoff$1).tw.	2,729
	29	(health$1 year$1 equivalent$1 or hye or hyes).tw.	151
	30	(hui or hui1 or hui2 or hui3 or rosser).tw.	2,369
	31	*quality of life/ and (quality of life or qol or hrqol).tw.	93,710
	32	quality of life/ and ((quality of life or qol or hrqol) adj (score$1 or measure$1)).tw.	28,988
	33	quality of life/ and health-related quality of life.tw.	55,917
	34	quality of life/ and ec.fs.	41,876
	35	quality of life/ and (health adj3 status).tw.	15,303
	36	((qol or hrqol or quality of life).ti. or *quality of life/) and ((qol or hrqol$ or quality of life) adj2 (increas$ or decrease$ or improv$ or declin$ or reduc$ or high$ or low$ or effect or effects or worse or score or scores or change$1 or impact$1 or impacted or deteriorat$)).ab.	49,333
	37	or/13-36	360,679
Study design: Cost or resource use studies	38	Cost control/	67,800
	39	Cost of illness/	19,052
	40	Drug cost/	76,863
	41	Hospital cost/	21,232
	42	exp Budget/	28,786
	43	Financial management/	112,403
	44	health care cost/	187,668
	45	health care financing/	13,232
	46	health expenditure/	169,305
	47	(low adj cost).mp.	64,946
	48	(high adj cost).mp.	18,850
	49	((health?care) adj cost$).mp.	20,011
	50	(fiscal or funding or financial or finance).tw.	194,350
	51	(cost adj estimate$).mp.	3,374
	52	(cost adj variable$).mp.	260
	53	(unit adj cost$).mp.	4,446
	54	(economic$ or pharmacoeconomic$ or price$ or pricing).tw.	382,371
	55	((resource$ or healthcare$ or service$) adj3 (use$ or utilis$ or utiliz$ or consume$ or consuming or consumption$)).tw.	141,176
	56	((patient$ or caregiver$ or carer$ or social$ or society$ or family$) adj2 (burden$ or productiv$)).tw.	25,438
	57	("length of stay" or utili?ation or "economic burden" or "cost-of-illness" or nursing cost$ or physician cost$ or physician visit$ or "out of pocket").tw.	383,728
	58	(absenteeism or presenteeism or employment or unemployment).tw. or exp presenteeism/ or exp absenteeism/ or exp unemployment/ or exp employment/	143,634
	59	or/38-58	1,470,365
	60	limit 59 to yr="2015-2020"	505,524
Exclusion terms	61	(conference abstract or conference review).pt.	3,779,855
	62	limit 61 to yr="1946-2017"	3,030,409
	63	exp animals/ not exp humans/	4,623,263
	64	(comment or editorial or "case reports" or "clinical trial, phase I").pt.	650,801
	65	(case stud$ or case report$).ti.	355,781

	66	or/62-65	8,334,193
Combination	67	6 and (12 or 37 or 60)	4,695
	68	67 not 66	3,048

Database: Embase 1974 to 2020 May 01

Table 86. Search terms for the NHS-EED and HTAD (via the University of York CRD platform)

Term Group	#	Search Terms	Results 04.05.2020
Disease area:	1	NSCLC	257
Metastatic NSCLC	2	MeSH DESCRIPTOR Lung EXPLODE ALL TREES	146
	3	MeSH DESCRIPTOR Neoplasms EXPLODE ALL TREES	11,971
	4	MeSH DESCRIPTOR Neoplasms, squamous cell EXPLODE ALL TREES	250
	5	MeSH DESCRIPTOR Adenocarcinoma EXPLODE ALL TREES	872
	6	MeSH DESCRIPTOR Carcinoma, squamous cell EXPLODE ALL TREES	214
	7	MeSH DESCRIPTOR Carcinoma, large cell EXPLODE ALL TREES	2
	8	#3 or #4 or #5 or #5 or #7	11,971
	9	#2 and #8	31
	10	(lung* and (non small cell or nonsmall cell) and (carcinoma* or adenocarcinoma* or cancer* or tumor* or tumour* or neoplasm*))	821
	11	#1 or #9 or #10	855
	12	MeSH DESCRIPTOR Neoplasm metastasis EXPLODE ALL TREES	705
	13	(metastat* or metastas* or advanced or stage IIIb or stage 3b or stage IIIc or stage 3c or stage IV or stage 4 or unresectable or non-resectable or nonresectable or inoperable or progressive)	5,136
	14	#12 or #13	5,161
	15	#11 and #14	483
	16	#15 in NHS EED, HTAD	227

Database: Health Technology Assessment Database: Issue 4 of 4, October 2016; NHS Economic Evaluation Database: Issue 2 of 4, April 2015

Table 87. Search strategies for hand-searching of relevant congresses

Conference	Link	Search strategy	Total hits	Relevant hits
American Association for Cancer Research (AACR) Annual Meeting AACR 2020 AACR 2019 AACR 2018	2020: https://www.abstractsonline.com/pp8/#!/9045 2019: https://cancerres.aacrjournals.org/content/79/13_Supplement 2018: https://www.abstractsonline.com/pp8/#!/4562	**2020 and 2018:** (NSCLC "non-small" "non small")+(cost economic resource) (NSCLC "non-small" "non small")+(quality utili*) Click the presentations tab **2019:** Use advanced search function, enter Volume: 79, Issue: 13 supplement, untick exclude meeting abstracts, select "Cancer Research" from the dropdown menu of "Include articles in journal", and in the search bar "Full text to Abstract or Title", enter: "non small cell" NSCLC Select 'Phrase' and search And check records from: Clinical Research (Excluding Clinical Trials) Clinical Trials Epidemiology Experimental and Molecular Therapeutics	2020: 80 2019: 238 2018: 97	2020: 0 2019: 0 2018: 0

ESMO Lung Cancer Annual Congress (ELCC) ELCC 2019 ELCC 2018	2019: https://oncologypro.esmo.org/meeting-resources/european-lung-cancer-congress-2019 2018: https://oncologypro.esmo.org/meeting-resources/elcc-2018-european-lung-cancer-congress	**2019 and 2018:** Filter by topic "Non-small cell lung cancer". Filter by format: Select "abstract"	2019: 28 2018: 8	2019: 0 2018: 0
European Society for Medical Oncology (ESMO) ESMO 2019 ESMO 2018	2019: https://oncologypro.esmo.org/meeting-resources/esmo-2019-congress 2018: https://oncologypro.esmo.org/meeting-resources/esmo-2018-congress	**2019:** Filter by topic "Non-small cell lung cancer". Filter by format: Select "abstract" Use the search term: cost* OR economic OR utili* OR resource OR "quality of life" **2018:** Use the search term: (NSCLC OR "non-small" OR "non small") AND (cost* OR economic OR utili* OR resource OR "quality of life")	2019: 30 2018: 89	2019: 0 2018: 0
The American Society of Clinical Oncology (ASCO) ASCO 2019 ASCO 2018	2019 and 2018: https://meetinglibrary.asco.org/	**2019 and 2018:** Paste the following strategy into the search bar and search: (cost* OR economic OR utili* OR resource OR "quality of life") Ensure only the "ASCO Annual Meeting" option is selected under the "Meeting" filter, then select 2019 and 2018 in the "Year" filter section. Media: Abstracts, Slides, Posters Type: Publication only + Poster Session + Oral Abstract Session Topic: Cancers -> Lung Cancer -> Non small cell lung carcinoma Screen all hits by title first, clicking only those abstracts that may be relevant from the title alone. Screen any potentially relevant abstracts and record only relevant ones in the tracker, ensuring the year of the congress (right hand-side of the abstract) is recorded.	2019 and 2018: 180	2019 and 2018: 0
The International Society for Pharmacoeconomics and Outcomes Research (ISPOR) Annual International and	2020, 2019 and 2018: https://www.ispor.org/heor-resources/presentations-database/search	**2020, 2019 and 2018:** Under Conference, click on each congress in turn. Enter in the keyword search bar: (NSCLC OR "non-small" OR "non small") AND (advance* OR metasta* OR unresectable OR	ISPOR International 2020: 16 ISPOR International 2019: 2 ISPOR International 2018: 17	ISPOR International 2020: 4, of which 1 deprioritised ISPOR International 2019: 1

European Meetings ISPOR International 2020 ISPOR International 2019 ISPOR International 2018 ISPOR Europe 2019 ISPOR Europe 2018	"stage 3*" OR "stage 4*" OR "stage III*" OR "stage IV*")	ISPOR Europe 2019: 25 ISPOR Europe 2018: 30	ISPOR International 2018: 2 ISPOR Europe 2019: 0 ISPOR Europe 2018: 0

Abbreviations: AACR, American Association for Cancer Research; ASCO, The American Society of Clinical Oncology; EGFR, epidermal growth factor receptor; ELCC, ESMO Lung Cancer Annual Congress; ESMO, European Society for Medical Oncology; ISPOR, International Society for Pharmacoeconomics and Outcomes Research; NSCLC, non-small cell lung cancer.

Table 88. Search strategies for hand-searching of HTA body websites

HTA Body	Link	Search Strategy	Total hits	Relevant hits
Agencia Española de Medicamentos y Productos Sanitarios (AEMPS)	https://www.aemps.gob.es/home.htm	Change to the English language version of the site using the toggle at the top of the homepage. Type each of the following search terms in turn into the search box: metastatic non small cell lung cancer metastatic NSCLC advanced non small cell lung cancer advanced NSCLC	0	0
Agenzia Italiana del Farmaco (AIFA)	http://www.agenziafarmaco.gov.it	Type each of the following search terms in turn into the search box, tick 'Documenti' under file type, and then only consider results that have the search term in the title (using ctrl+F function on each page): metastatic non small cell lung cancer metastatic NSCLC advanced non small cell lung cancer advanced NSCLC	60 pages	0
All Wales Medicines Strategy Group (AWMSG)	http://www.awmsg.org/	Type each of the following search terms in turn into the search box, and then review the 'Appraisals' tab and 'Appraisal documents' tab: metastatic non small cell lung cancer metastatic NSCLC advanced non small cell lung cancer advanced NSCLC In the results, look for AWMSG Secretariat Appraisal Report documents.	146	0
Bundesamt für Gesundheit (BAG)	https://www.bag.admin.ch/bag/de/home.html	Type each of the following search terms in turn into the search box and search hits under the 'Documents' tab: metastatic non small cell lung cancer metastatic NSCLC advanced non small cell lung cancer advanced NSCLC	8	0
Danish Medicine Council	https://medicinraadet.dk/igangvaerende-vurderinger	Use Google Translate function to translate website to English. Type each of the following search terms in turn into the free text search box and select 'Drugs and indications extensions' under Category: metastatic non small cell lung cancer metastatic NSCLC advanced non small cell lung cancer advanced NSCLC	48	0

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Finnish Coordinating Center for Health Technology Assessment (FinCCHTA)	https://www.ppshp.fi/Tutkimus-ja-opetus/FinCCHTA/Sivut/default.aspx	Use Google Translate function to translate website to English. Type each of the following search terms in turn into the search box: metastatic non small cell lung cancer metastatic NSCLC advanced non small cell lung cancer advanced NSCLC	0	0
Gemeinsamer Bundesausschuss (G-BA)	https://www.g-ba.de/	Type each of the following search terms in turn into the search box and then click on 'Beschlusse' (Decisions): metastatic non small cell lung cancer metastatic NSCLC advanced non small cell lung cancer advanced NSCLC	381	0
Haute Autorité de Santé (HAS)	https://www.has-sante.fr/portail/	Change to the English language version of the site using the toggle at the top of the homepage. Type each of the following search terms in turn into the search box: metastatic non small cell lung cancer metastatic NSCLC advanced non small cell lung cancer advanced NSCLC	10	0
Ministerio de Sanidad, Consumo y Bienestar Social (MSCBS)	http://www.mscbs.gob.es/home.htm	Download list of HTA reports in Excel file format and search with Ctrl + F function for 'metastatic non small cell lung cancer', 'metastatic NSCLC', 'advanced non small cell lung cancer' and 'advanced NSCLC'	0	0
National Centre for Pharmacoeconomics (NCPE)	http://www.ncpe.ie/	Type each of the following search terms in turn into the search box: metastatic non small cell lung cancer metastatic NSCLC advanced non small cell lung cancer advanced NSCLC Review the “Summary” document (where available) for relevance	46	9, of which 8 deprioritised
National Institute for Health and Care Excellence (NICE)	https://www.nice.org.uk/	Type each of the following search terms in turn into the search box and then tick the boxes for ‘Guidance’ and ‘NICE advice’ under Document Type: metastatic non small cell lung cancer metastatic NSCLC advanced non small cell lung cancer advanced NSCLC For relevant results, click these and look for the “History” tab on the right-hand side of the screen. Download the “Final Appraisal Document” and “Committee papers” for each result. Within the “Committee papers” document, double click the “Submission from manufacturer” document and screen this for relevance.	159	30
Norwegian Institute of Public Health (NIPH)	https://www.fhi.no/en/	Type each of the following search terms in turn into the search box then click on 'Health Technology Assessment': metastatic non small cell lung cancer metastatic NSCLC advanced non small cell lung cancer advanced NSCLC	133	1, which was deprioritised

Scottish Medicines Consortium (SMC)	https://www.scottishmedicines.org.uk/	In the 'Medicines Advice' tab, search for each of the following search terms in turn: metastatic non small cell lung cancer metastatic NSCLC advanced non small cell lung cancer advanced NSCLC Under submission type, only consider 'Full submissions' and 'resubmissions' and review the 'detailed advice' PDF.	119	27, of which 16 deprioritised
Swedish Agency for Health Technology Assessment and Assessment of Social Services (SBU)	https://www.sbu.se/en/	Type each of the following search terms in turn into the search box: metastatic non small cell lung cancer metastatic NSCLC advanced non small cell lung cancer advanced NSCLC	3	0
Zorginstituut Nederland	https://www.zorginstituutnederland.nl/	Change to the English language version of the site using the toggle at the bottom of the homepage. Type each of the following search terms in turn into the search box: metastatic non small cell lung cancer metastatic NSCLC advanced non small cell lung cancer advanced NSCLC	16	1

Abbreviations: AEMPS, Agencia Española de Medicamentos y Productos Sanitarios; AIFA, Agenzia Italiana del Farmaco; AWMSG, All Wales Medicines Strategy Group; BAG, Bundesamt für Gesundheit; FinCCHTA, Finnish Coordinating Center for Health Technology Assessment; G-BA, Gemeinsamer Bundesausschuss; HAS, Haute Autorité de Santé; HTA, Health Technology Assessment; MSCBS, Ministerio de Sanidad, Consumo y Bienestar Social; NCPE, National Centre for Pharmacoeconomics; NICE, National Institute for Health and Care Excellence; NIPH, Norwegian Institute of Public Health; NSCLC, non-small cell lung cancer; SMC, Scottish Medicines Consortium; SBU, Swedish Agency for Health Technology Assessment and Assessment of Social Services.

Table 89. Search strategies for hand-searching of economic websites

Website	Link	Search Strategy	Total hits	Relevant hits
Health Economics Research Centre (HERC) Database of Mapping Studies	https://www.herc.ox.ac.uk/downloads/herc-database-of-mapping-studies	Filter by 'Non small cell lung cancer', 'lung cancer', 'non small cell lung cancer-cachexia' under 'disease or patient group'	5	0
The Cost-effectiveness Analysis (CEA) Registry, managed by Tufts Medical Center	http://healtheconomicsdev.tuftsmedicalcenter.org/cear2/search/search.aspx	Click on the yellow box titled 'View the CEA Registry'. In the search bar, paste in the first search term in the list below, with 'Methods' selected and hit search. advanced non-small cell lung cancer advanced NSCLC metastatic non-small cell lung cancer metastatic NSCLC Repeat with 'Ratios' selected and then with 'Utility Weights' selected. Then repeat for each subsequent search term in the list.	60	0
The EQ-5D Publications Database	http://eq-5dpublications.euroqol.org/?noheader=true	Ensure the advanced search is presented. In the 'type' dropdown, select 'abstract' and in the 'abstract' box enter the following: non-small cell lung cancer NSCLC Click the [+] button to the right of the abstract. This will add a new search line. In this search line in the 'type' dropdown, select 'And' in the operator box and	116	0

		'abstract' in the Type box. Search the following in the "abstract" box: Cost Once the results of [disease] AND cost have been searched, delete 'cost' from the abstract box and replace it with the following terms one by one: Economic Utility Utilities Quality of life Resource Repeat for the second disease term.		
The School of Health and Related Research Health Utilities Database (ScHARRHUD), University of Sheffield	http://www.scharrhud.org/	Select 'search' in the menu at the top. In the first search bar, search for the following (in Abstract [AB]): non-small cell lung cancer NSCLC	8	0

Abbreviations: CEA, Cost-effectiveness Analysis; HERC, Health Economics Research Centre; NSCLC, non-small cell lung cancer; ScHARRHUD, School of Health and Related Research Health Utilities Database

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Grey Literature Searching – Conference Proceedings

Manual searches of abstract books from conference proceedings of relevant major congresses that took place in the last two years were conducted to identify any relevant abstracts. The following conferences were hand-searched:

- American Association for Cancer Research (AACR) Annual Meeting
- American Society of Clinical Oncology (ASCO) Annual Meeting
- ESMO Lung Cancer Annual Congress (ELCC)
- European Society for Medical Oncology (ESMO) Congress
- The International Society for Pharmacoeconomics and Outcomes Research (ISPOR) Annual International and European Meetings

The rationale for limiting these searches to the last two years (i.e. 2018 to 2020) was that it was anticipated that any relevant, high-quality conference research published prior to this date would have since been developed into a full manuscript and would therefore have been found in the electronic database searches.

Where no poster or presentation was available, the abstract was reviewed in its own right. Any relevant results were cross-checked against the bibliographic database searches to ensure no duplicate records were included.

Full details of the search strategy for the conference searches are presented in Table 91.

Grey Literature Searching – HTA Body Websites

Searches of the following HTA body websites were also conducted to identify relevant HTAs from the last 10 years:

- Agencia Española de Medicamentos y Productos Sanitarios (AEMPS) – https://www.aemps.gob.es/home.htm
- Agenzia Italiana del Farmaco (AIFA) – http://www.agenziafarmaco.gov.it
- All Wales Medicines Strategy Group (AWMSG) – http://www.awmsg.org/
- Bundesamt für Gesundheit (BAG) – https://www.bag.admin.ch/bag/de/home.html
- Danish Medicine Council – https://medicinraadet.dk/igangvaerende-vurderinger
- Finnish Coordinating Center for Health Technology Assessment (FinCCHTA) – https://www.ppshp.fi/Tutkimus-ja-opetus/FinCCHTA/Sivut/default.aspx
- Gemeinsamer Bundesausschuss (G-BA) – https://www.g-ba.de/
- Haute Autorité de Santé (HAS) – https://www.has-sante.fr/portail/
- Ministerio de Sanidad, Consumo y Bienestar Social (MSCBS) – http://www.mscbs.gob.es/home.htm
- National Centre for Pharmacoeconomics (NCPE) – http://www.ncpe.ie/
- National Institute for Health and Care Excellence (NICE) – https://www.nice.org.uk/
- Norwegian Institute of Public Health (NIPH) – https://www.fhi.no/en/
- Scottish Medicines Consortium (SMC) – https://www.scottishmedicines.org.uk/
- Swedish Agency for Health Technology Assessment and Assessment of Social Services (SBU) – https://www.sbu.se/en/
- Zorginstituut Nederland – https://www.zorginstituutnederland.nl/

Full details of the search strategy for the HTA body searches are presented in Table 91.

Grey Literature Searching – Economic Websites

In line with current best practice guidelines for identifying inputs relevant to cost-effectiveness modelling, the following economic databases/registries were also hand-searched:

- The Cost-Effectiveness Analysis Registry, managed by Tufts Medical Center (available at http://healtheconomics.tuftsmedicalcenter.org/cear2n/search/search.aspx)
- The EQ-5D Publications Database (available at https://euroqol.org/search-for-eq-5d-publications/)

- The University of Sheffield Health Utilities Database (ScHARRHUD; available at https://www.scharrhud.org/index.php?recordsN1&m=search)
- The Nuffield Department of Population Health, Health Economics Research Center (HERC) Database of Mapping Studies (available at https://www.herc.ox.ac.uk/downloads/herc-database-of-mapping-studies)

Search strategy

The SLR was performed in accordance with a pre-specified protocol. This involved searching electronic databases, manual hand-searching of key conference proceedings from the last two years, manual hand-searching of key health technology assessment (HTA) body websites and health economics databases, and manual hand-searching of the bibliographies of any relevant SLRs, economic evaluations or HTAs identified during the review.

As the volume of the evidence base reporting specifically on EGFR-mutated patients was unclear, the review initially focused on all patients with metastatic or unresectable NSCLC. Inclusion and exclusion criteria for the search is presented below in Table 91.

Data extraction

HRQoL/utilities stream:

- Studies conducted in an OECD country, or international studies including an at least one OECD country, were prioritised for extraction, in order to focus on the most comparable settings in terms of economic development and most relevant to the UK healthcare setting.
- Studies which reported on three prioritised HRQoL/utility instruments (EORTC QLQ-C30, EORTC QLQ-LC13, and EQ-5D) underwent full extractions.
- Only top-level data (citation, study design, population, sample size, QoL instrument used) were extracted from the remaining studies which reported on other HRQoL/utility instruments.

Table 90. Summary of extracted data

HRQoL/Utilities (Priority instruments)	HRQoL/Utilities (Other instruments)
Top-level publication details, including study setting, population, presence of EGFR/other mutations and the questionnaire/tool used to elicit QoL or utility data Study details, including study design, recruitment method, intervention(s), comparator(s), sample size, response rate, and health states/adverse events Study results, including utility values and/or QoL scores, and the corresponding patient cohort, timepoint of data collection and instrument/ questionnaire used	Top-level publication details, including study setting, population, presence of EGFR/other mutations and the questionnaire/tool used to elicit quality of life or utility data

Abbreviations: EGFR, epidermal growth factor receptor; QoL, quality of life; ICER, incremental cost-effectiveness ratio.

Data extraction was performed by a single individual for each included study. When the initial extractions were completed, a second individual independently verified the extracted information and checked that no relevant information was missed for 10% of the extracted studies. For those studies which were checked, any discrepancies or missing information identified by the second individual were discussed by both individuals until a consensus was reached on the information that should be presented in the extraction grid. If necessary, a third individual arbitrated the final decision

Quality assessment and generalizability of estimates

The quality of all included economic evaluations was assessed using an abbreviated form of the Drummond checklist [124]. Quality assessments were completed by one reviewer, and checks of 10% of these were verified by a second independent reviewer. As HTA bodies such as NICE typically do not require critical appraisals of cost, resource use and

HRQoL/utility studies as part of manufacturers' evidence submissions, formal quality assessments were not conducted for these types of study. In the SLR, no Danish studies on HRQoL for NSCLC patients were identified. Therefore, the results should be interpreted with caution when applied to the Danish setting. However, the best available evidence for utilities have previously been accepted by NICE.

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Table 91. Eligibility criteria for the SLR

Category	Economic Evaluations		HRQoL/Utilities		Cost and Resource Use	
	Inclusion Criteria	Exclusion Criteria	Inclusion Criteria	Exclusion Criteria	Inclusion Criteria	Exclusion Criteria
Population	Inclusion criteria: Patients with metastatic or surgically unresectable NSCLCa Patients with stage IIIB, IIIC or IV disease. Studies with patients only specified as "advanced" or "stage III" were considered eligible if they received an intervention commonly used in stage IV/metastatic patients, or if stage IV patients were also included within the study population. Patients receiving an EGFR-targeted TKI but not specified as EGFR-mutated were considered EGFR-mutated Exclusion criteria: Patients without metastatic or unresectable NSCLC or studies where outcomes are not presented separately for the patients of interest Patients with locally advanced disease Patients with stage 3 disease					
Intervention	Any therapeutic or palliative intervention	Non-therapeutic or palliative interventions, e.g. mutation testing	Any or none	–	Any or none	–
Comparators	Any comparator (or none)	–	Any comparator (or none)	–	Any comparator (or none)	–
Outcomes	Cost-effectiveness outcomes, including but not limited to: ICERs Cost per clinical outcome Total QALYs Total LYGs Total costs Incremental costs and QALYs	Studies not presenting relevant outcomes	Any utilities or HRQoL data, including but not limited to: EQ-5D-5L Standard gamble Time trade-off SF-36 NSCLC-SAQ PGIS PGIC EORTC QLQ C-30 PROMIS-PF Studies reporting data collected using the EQ-5D, EORTC QLQ-C30 or EORTC QLQ-LC13 instruments were prioritised for full extraction, studies using any other	Studies not presenting relevant outcomes for the population of interest	Direct costs Direct resource use	Studies not presenting relevant outcomes for the population of interest

Category	Economic Evaluations		HRQoL/Utilities		Cost and Resource Use	
	Inclusion Criteria	Exclusion Criteria	Inclusion Criteria	Exclusion Criteria	Inclusion Criteria	Exclusion Criteria
			instrument were included but had topline details extracted only			
Study design	Any of the following analysis types: Cost-utility Cost-effectiveness Cost-consequence Cost-benefit Cost-minimisation	Any other types of analysis	Any	–	Any	–
	SLRs of relevant primary publications were considered relevant at the title/abstract review stage and hand searched for relevant primary studies, but were excluded during the full text review stage unless they themselves presented primary research					
Publication type	Original research studies including economic evaluations HTAs Congress abstracts published in or after 2018	Any other publication type, including studies not reporting any original research Congress abstracts published before 2018	Original research studies including economic evaluations HTAs Congress abstracts published in or after 2018	Any other publication type, including studies not reporting any original research Congress abstracts published before 2018	Original research studies including economic evaluations HTAs Congress abstracts published in or after 2018	Any other publication type, including studies not reporting any original research Congress abstracts published before 2018
Other considerations	Human subjects English language abstract/full text Studies conducted from a European perspective were prioritised	Non-human subjects Non-English language abstract/full text Studies conducted from a non-European perspective were deprioritised	Human subjects English language abstract/full text Studies that reported data from at least one OECD country were prioritised	Non-human subjects Non-English language abstract/full text Studies that reported data from countries outside the OECD only were deprioritised	Human subjects English language abstract/full text Data must be reported for the year 2015 or later to ensure the inclusion of the latest data that are most reflective of current clinical practice Studies that reported data from at least one	Non-human subjects Non-English language abstract/full text Data reported for the year 2014 or previous Studies that reported data from countries outside the OECD only were deprioritised

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Category	Economic Evaluations		HRQoL/Utilities		Cost and Resource Use	
	Inclusion Criteria	Exclusion Criteria	Inclusion Criteria	Exclusion Criteria	Inclusion Criteria	Exclusion Criteria
					OECD country were prioritised	

Abbreviations: EGFR, epidermal growth factor receptor; EORTC QLQ C-30, European Organization for Research and Treatment of Cancer Quality-of-life Questionnaire Core 30; EQ-5D-5L, EuroQol five dimensions five levels; HRQoL, health-related quality of life; HTA, health technology assessment; ICER, incremental cost-effectiveness ratio; LYG, life years gained; NSCLC, non-small cell lung cancer; NSCLS-SAQ, Non-Small Cell Lung Cancer Symptom Assessment Questionnaire; OECD, Organisation for Economic Co-operation and Development; PGIC, Patient Global Impression of Change Scale; PGIS, Patient's Global Impression of Severity; PROMIS-PF, PROMIS Physical Function; QALY, quality-adjusted life years; SF-36, 36-Item Short Form Survey; SLR, systematic literature review

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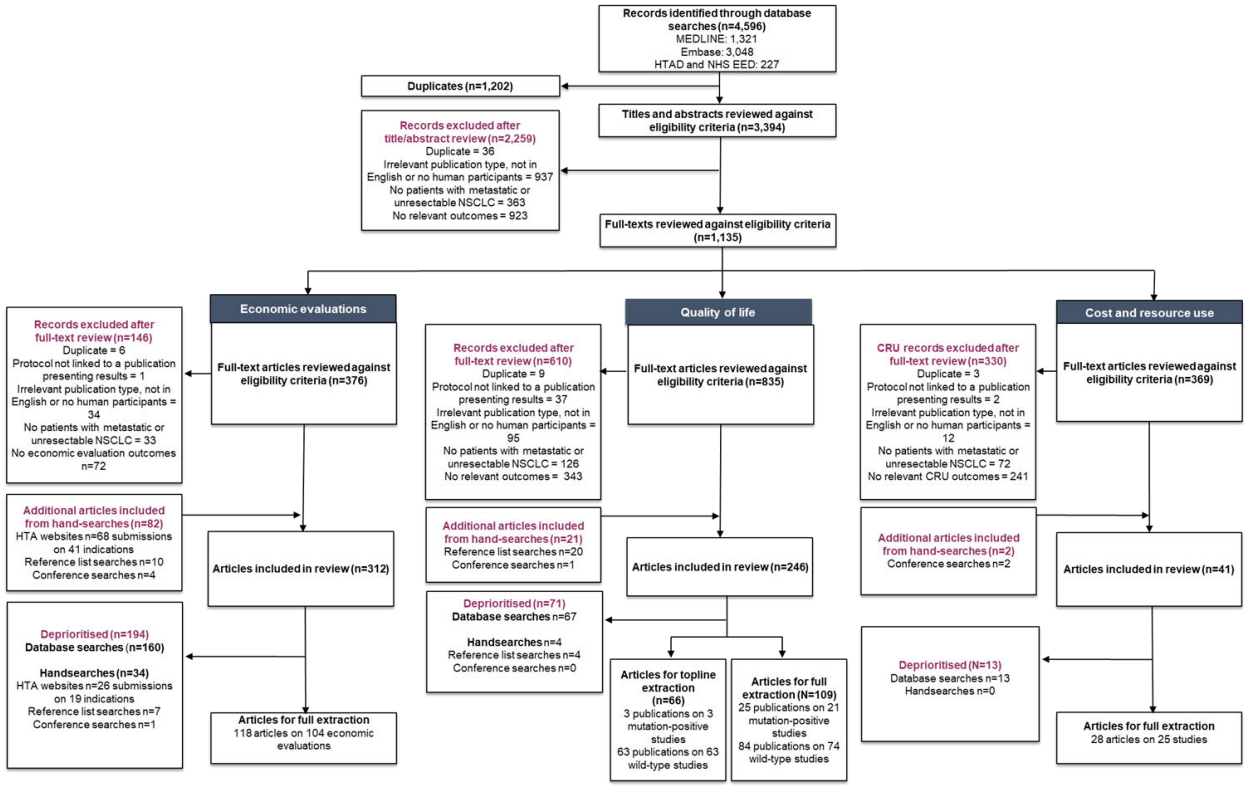
In total, 835 full texts were reviewed for relevant QoL data, of which 225 were found to fulfil the inclusion criteria. As part of the supplementary searching, 21 records were identified from reference list searches and one from the conference searches. In total, 246 publications reporting QoL data in unresectable or metastatic NSCLC were initially included in this SLR. Studies reporting health state utility values (HSUV) or QoL data were divided into two categories: studies in patients with mutation-positive NSCLC including EGFR, anaplastic lymphoma kinase (ALK) and other mutations, and those without mutations or mixed populations. Inclusion of QoL studies in patients with wild type NSCLC allowed for exploration of the effect that the presence of driver mutations could have on QoL.

In mutation-positive NSCLC populations, a total of 28 records reporting on 24 studies were included in the SLR and their top-line details were extracted. Of these, 25 publications reporting on 21 unique studies were fully extracted according to the criteria laid out above in the section Data extraction and are the focus of this SLR report. In wild type NSCLC populations, a total of 147 records reporting on 137 studies were included in the SLR and their top-line details were extracted. Of these, 84 publications reporting on 74 unique studies were selected for full extraction.

Figure 100. PRISMA diagram



Abbreviations: HTA, Health Technology Assessment; HTAD, Health Technology Assessment Database; NHS EED, National Health Service Economic Evaluations Database; NSCLC, non-small cell lung cancer.

Summary of Included Studies

This section includes a summary of the results from the included studies. A list of all included studies can be found in Table 93.

Quality of Life

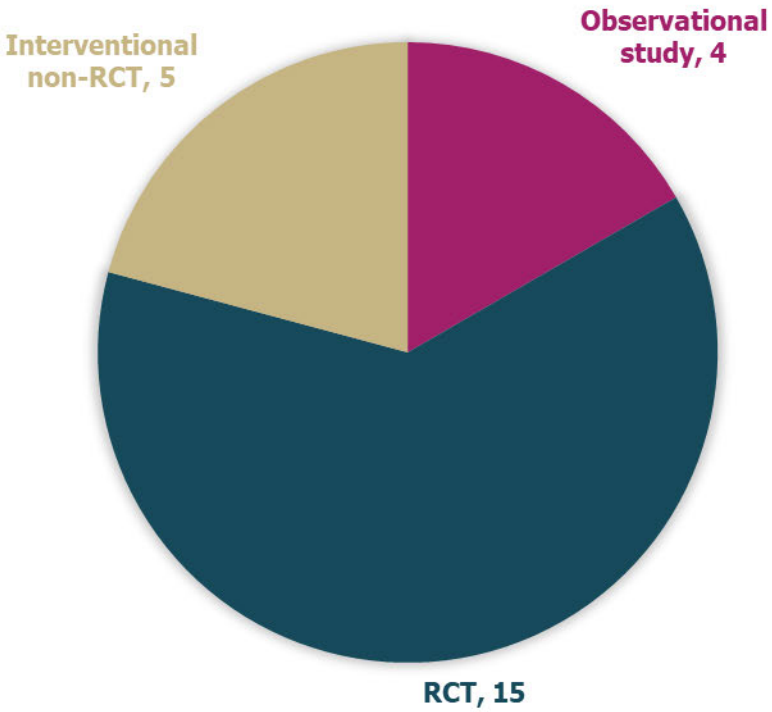
A total of 28 publications reporting 24 unique studies were identified which included data on mutation-positive populations. The remaining 148 publications reporting 138 studies identified in this stream included data on wild type populations.

Mutation-Positive Populations – Overview of Included Evidence

Study Characteristics

Of the 28 included publications on 24 unique studies, 15 were RCTs, five were single-arm trials and four were observational studies (Figure 101).

Figure 101. Included quality of life studies by study design

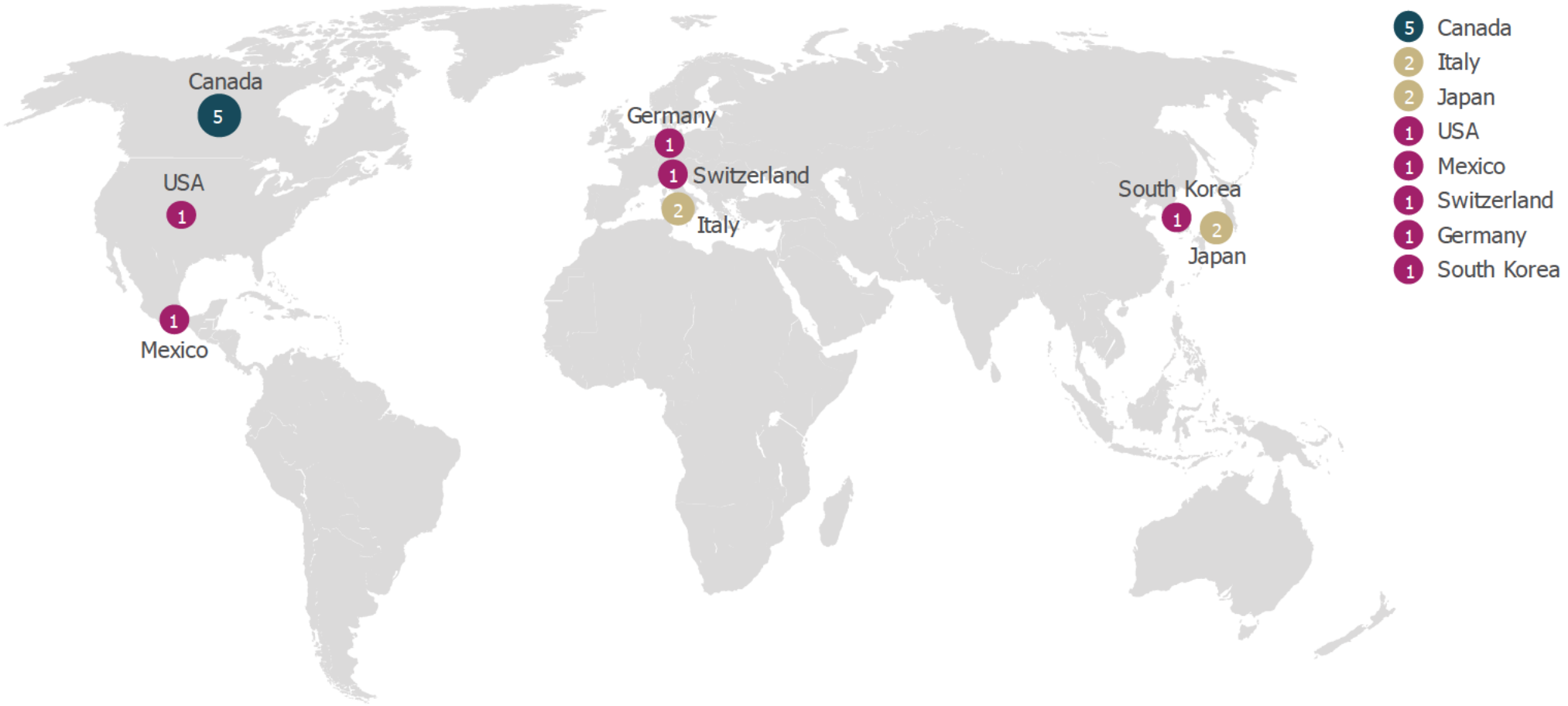


Abbreviations: RCT= randomised controlled trial.

Region and Country

Of the 24 unique studies, half were conducted in an international setting. Of the remaining 12, the country from which the highest number of publications was identified was Canada, with five studies identified. The other seven studies identified were spread across the USA and Central America, Europe, and Asia. Figure 102 presents the countries where QoL and utilities studies were conducted, excluding the larger international studies.

Figure 102. Geographical distribution of studies assessing QoL or HSUV in patients with EGFR mutation-



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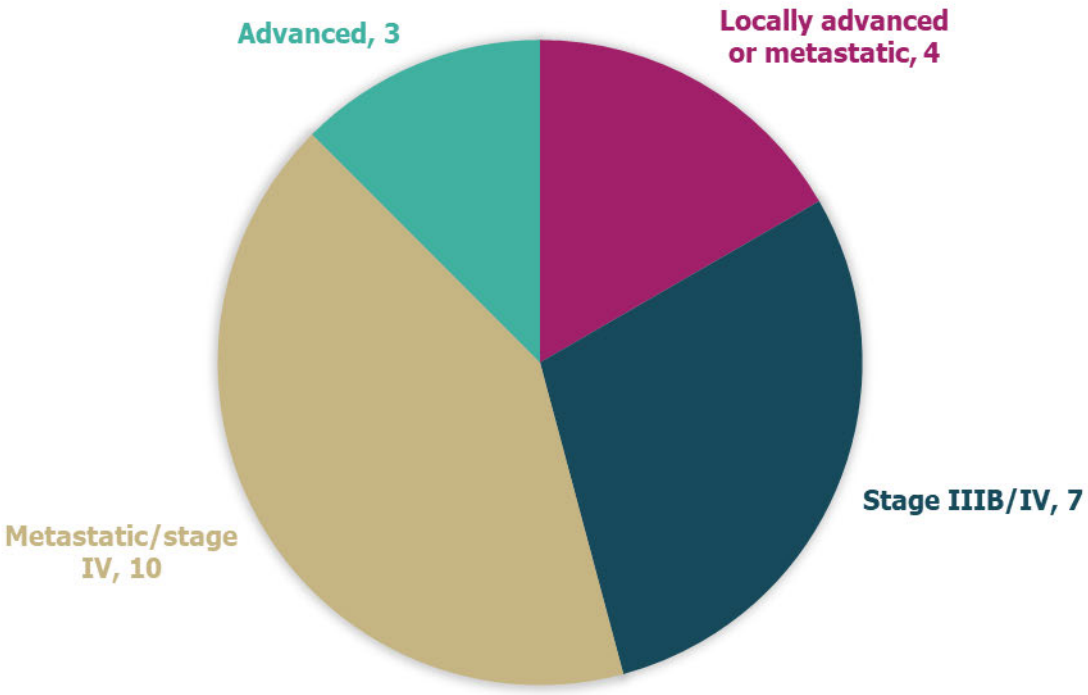
Population: Disease Stage

Of the included studies, the majority were classified by the publication as including patients with locally advanced or metastatic NSCLC (N=11), of which most specified the numerical stage as IIIB or IV (N=7) (Figure 103). Ten studies exclusively included NSCLC patients with metastatic NSCLC, while the remaining three studies classified patients as having advanced NSCLC.

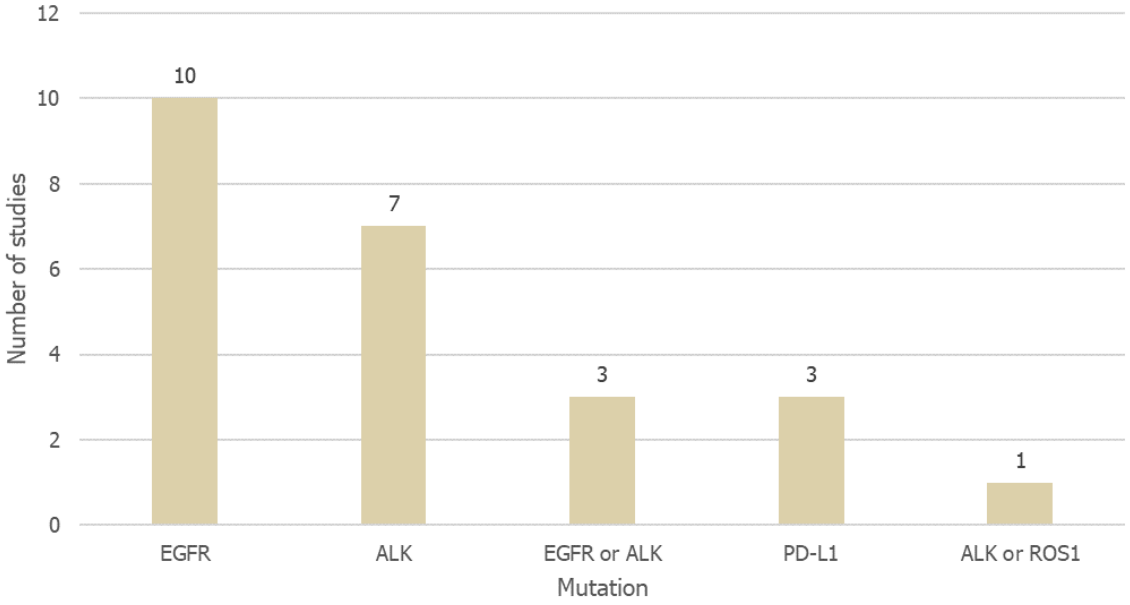
Figure 103. Included studies by disease stage



Population: Mutation Status

Of the included studies, 10 studies included patients with EGFR mutations, eight with ALK mutations (of which one additionally included patients with mutations in the ROS-1 proto-oncogene tyrosine-protein kinase gene), three which included patients with EGFR or ALK mutations, and three with PD-L1 positive NSCLC (Figure 104).

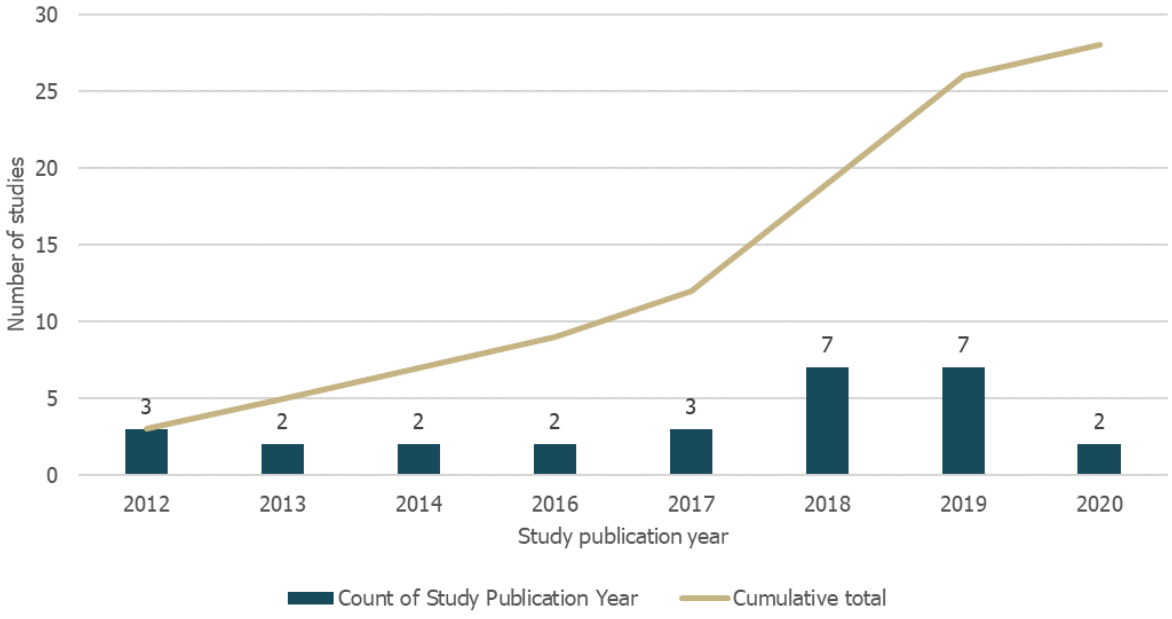
Figure 104. Included studies by EGFR mutation status



Publication Timeframe

In terms of the timeframe of publication of the included records, all 28 included publications were published in the last eight years between 2012–2020. The majority were published in the last five years, with notable spikes in 2018 and 2019, attributed to a large number of clinical trials published at that time. A summary is provided in Figure 105.

Figure 105. Included studies by publication

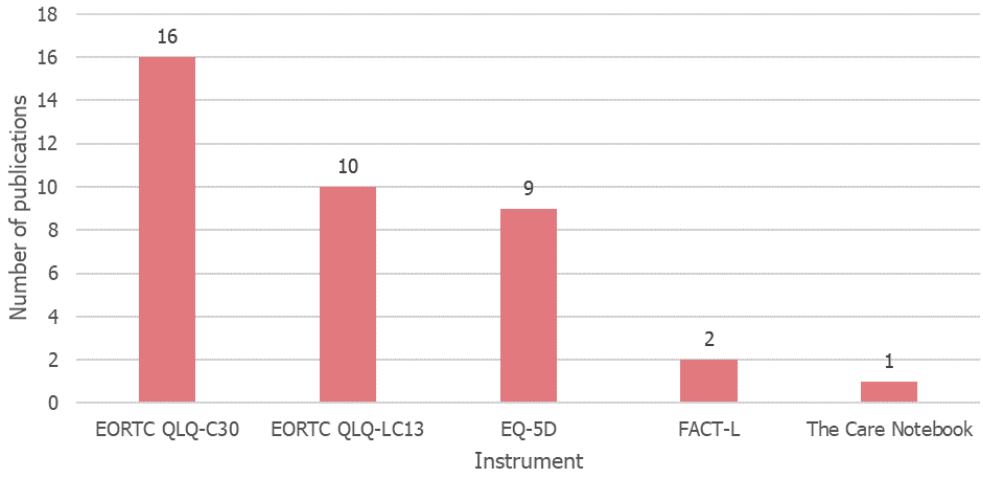


Data Collection

In terms of the instruments used, the majority of publications reported QoL data measured by the EORTC QLQ-C30 (16/28), of which 11 additionally reported data from the EORTC QLQ-LC13 (Figure 106). Of the publications selected for top-line extraction, all but one study used the Functional Assessment of Cancer Therapy - Lung instrument (FACT-L), with the remaining study collecting QoL data using 'The Care Notebook' in Japan.

Of the included publications that presented HSUV data, all of them reported EQ-5D; three publications further specified reporting on the EQ-5D-3L version whereas six publications did not report whether the 3L or 5L version was used.

Figure 106. Included studies by instrument used



Abbreviations: EORTC QLQ-C30, European Organization for the Research and Treatment of Cancer Quality of Life Questionnaire C30; EORTC QLQ-LC13, European Organization for the Research and Treatment of Cancer Quality of Life Questionnaire Lung Cancer Module; FACT-L, Functional Assessment of Cancer Therapy - Lung.

Exon 20 Insertions

No publications reporting on quality of life data included in this review specifically assessed populations with EGFR Exon 20ins.

Mutation-Positive Populations – Results of Prioritised Studies

HSUV Results

Four studies reported EQ-5D scores in patients with activating mutations during or post-treatment with targeted therapy. Two studies, which may have overlapping but not identical cohorts, presented mean EQ-5D scores that were measured in advanced EGFR-mutated patients at any point during the disease course, in patients being treated with osimertinib (0.80–0.85), gefitinib (range 0.79–0.80), chemotherapy (0.72–0.73) and other TKIs (0.79–0.80) [125, 126]. Utility scores reported by Labbe (2017)[127], ranged from 0.78 to 0.81 across the TKIs. In ALK-mutated patients, patients treated with ceritinib had a utility of 0.83, in patients treated with crizotinib 0.81, and patients treated with brigatinib had a utility of 0.77, although sample sizes were small.

Two studies compared EQ-5D scores following treatment. In patients with ALK mutations, crizotinib demonstrated greater improvement in EQ-5D (+0.09 change from baseline) compared with chemotherapy (+0.03 change from baseline) ($p<0.001$), however the median duration of treatment was longer in the crizotinib arm (31 weeks) than in the chemotherapy arm (12 weeks) [128]. Results of the LUX-LUNG 1 trial found that EQ-5D scores were higher in patients treated with afatinib (0.71) compared with placebo (0.67) at 13 weeks ($p<0.05$)[129].

Mutation-Positive Populations – Quality of Life Results

Of the studies that used the EORTC QLQ-C30 and EORTC QLQ-LC13, seven studies included patients treated with ALK inhibitors (crizotinib N=3, brigatinib N=2, ceritinib, alectinib, lorlatinib N=1 each) [128, 130-136], six included patients treated with EGFR TKIs (osimertinib N=2, afatinib N=2, other N=3)[129, 137-142], six included patients treated with chemotherapy (platinum based chemotherapy [N=3] non-platinum chemotherapy [N=2])[128, 137, 138, 140-143], one included patients treated with immunotherapy (pembrolizumab)[143] and one included patients treated with therapeutic cranial radiation [144].

In terms of when measures were taken with the EORTC QLQ-C30 and EORTC QLQ-LC13, 13 studies collected data at baseline [128-134, 136, 138, 140-145] and 10 collected data during/post-treatment initiation in addition to baseline [128-131, 134, 136, 137, 139, 140, 143-145].

Of studies that reported the EORTC QLQ-C30 Global Health Status (GHS, otherwise known as global QoL), eight reported scores at baseline, whereby a higher score represents better QoL. GHS scores in patients with metastatic or unresectable NSCLC at baseline generally lay between 50 and 70, with scores ranging from 53.0 (standard deviation [SD] 21.7) to 56.2 in EGFR-mutated cohorts [140], and from 57.6 to 62.2 in ALK-mutated NSCLC cohorts [128]. Patients with either EGFR or ALK mutations in the Gonzalez-Ling (2018) study had a baseline global QoL score of 66.7 (N=84) [144]. Role and social functioning were associated with the lowest QoL scores before treatment, with fatigue, dyspnoea and appetite loss representing symptoms with higher burden scores. Whilst higher scores indicate better QoL in the GHS and functioning domains of the C30, higher scores in the symptom subdomains of both the C30 and LC13 instruments represent higher symptom burden (lower QoL). At baseline, QoL scores for the cough, dyspnoea and pain subdomains of the EORTC QLQ-LC13 questionnaire were consistently highest across the included studies where reported [128, 129, 136, 138, 145], demonstrating substantial symptom burden, with multiple treatment trials therefore focussing their analyses on these specific symptoms.

Treatment-Related QoL

Five trials compared the impact of different interventions on QoL in EGFR mutations, and four in patients with ALK mutations. The AURA-3 trial in patients with EGFR T790M mutations specifically demonstrated that time to worsening of chest pain, dyspnoea and cough as measured by the LC13 (Table 92), and fatigue and appetite loss measured by the C30, were significantly longer on treatment with 2L osimertinib than with chemotherapy ($p<0.01$ for all comparisons). A higher proportion of patients also had improved C30 GHS with osimertinib, demonstrating a key treatment benefit [138]. By contrast, in the large, international FLAURA trial of 1L osimertinib compared with standard of care in patients with any EGFR mutation, both treatments improved QoL scores with no significant differences between them for all reported subdomains, which included the C30 appetite loss and fatigue subdomains, and cough, dyspnoea and pain subdomains of the LC13 [139].

Three RCTs in EGFR-mutated populations demonstrated that afatinib significantly improved cough, chest pain and dyspnoea subdomain scores, in comparison with placebo (LUX-Lung 1) and chemotherapy (LUX-Lung 3 and LUX-Lung 6 (Table 92) [129, 146]. Interestingly, Wu (2018) performed analyses of trial data to explore the potential influence of common EGFR mutation type on treatment outcomes; finding that the mean treatment difference in GHS improvement between afatinib and chemotherapy as 1L treatment was larger in patients with Del19 mutations (6.59) than L858 mutations (0.71) in both the LUX-Lung 3 and LUX-Lung 6 trials [141].

In ALK-mutated NSCLC, the ALTA trial found a substantial improved with brigatinib in overall EORTC QLQ-C30 GHS compared with crizotinib as 1L therapy (mean difference in change from baseline 4.1, $p<0.05$), as well as an improvement in several functional domains and symptoms [130, 131]. In one single-arm trial, alectinib was shown to improve several LC13 subdomain scores, by up to 16.67 points in the pain subdomain [145]. Loratinib was reported to have improved (42.7%) or maintained (43.5%) QoL associated with coughing in the majority of patients with ALK-1 or ROS-1 mutations, in the Peters (2020) study [136].

Table 92. Treatment comparisons in HRQoL in mutation

Study	EORTC QLQ-LC13 Subdomain	Timepoint	Intervention and comparator	Outcome description	Outcome value
EGFR mutations					
Lee 2018 (AURA-3)[138]	**Cough**	On-treatment (mean of 6 months)	Osimertinib (N=279)	Median TTD, months (95% CI)	8.3 (6.1 to not calculable)
			Chemotherapy (N=140)		6.1 (1.1 to 11.0)
			Osimertinib vs chemotherapy	Mean treatment difference (95% CI)	-5.53 (-8.89 to -2.17)**
	Chest pain	On-treatment (mean of 6 months)	Osimertinib (N=279)	Median TTD, months (95% CI)	12.4 (8.2 to not calculable)
			Chemotherapy (N=140)		2.1 (0.8 to 4.8)
			Osimertinib vs chemotherapy	Mean treatment difference (95% CI)	-5.36 (-8.20 to -2.53)***
	Dyspnoea	On-treatment (mean of 6 months)	Osimertinib (N=279)	Median TTD, months (95% CI)	6.1 (4.1 to 8.9)
			Chemotherapy (N=140)		0.6 (0.4 to 1.0)
			Osimertinib vs chemotherapy	Mean treatment difference (95% CI)	-7.09 (-9.86 to -4.33)***
Di Maio 2012[137]	**Cough**	Based on patients with at least one questionnaire at 3, 6, or 9 weeks after baseline	Erlotinib (N=16)	Improved, n (%)	7 (44)
				Stable, n (%)	3 (19)
				Worse, n (%)	4 (25)
			Cisplatin and gemcitabine (N=15)	Improved, n (%)	7 (47)
				Stable, n (%)	5 (33)
				Worse, n (%)	3 (20)

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Study	EORTC QLQ-LC13 Subdomain	Timepoint	Intervention and comparator	Outcome description	Outcome value
Hirsh 2013 (LUX-Lung 1)[129]	**Cough**	Week 13	Afatinib (N=380) vs placebo (N=195)	Mean difference between afatinib and placebo (95% CI)	-6.99 (-9.71 to -4.27)
	Pain in chest				-5.60 (-8.03 to -3.17)
	Dyspnoea				-2.68 (-4.86 to -0.49)
Leighl 2018 (FLAURA)[139]	**Cough**	9 months	Osimertinib	Adjusted least-squares mean (95% CI); estimated treatment difference, SoC as reference (95% CI)	-11.0 (-12.8 to -9.2); 0.7 (-1.9 to 3.2)
			Standard of care	Adjusted least-squares mean (95% CI)	-11.7 (-13.5 to -9.8)
	Pain in chest	9 months	Osimertinib	Mean (95% CI); estimated treatment difference (95% CI)	-6.6 (-8.2 to -5.0), -0.2 (-2.5 to 2.1)
			Standard of care		-6.4 (-8.0 to -4.8)
	Dyspnoea	9 months	Osimertinib	Mean (95% CI); estimated treatment difference (95% CI)	-4.0 (-5.6 to -2.5), 0.1 (-2.2 to 2.4)
			Standard of care		-4.1 (-5.7 to -2.5)
Wu 2018 (LUX-Lung 3 and 6)[141]	**Cough**	Post-treatment	LUX-Lung 3, exon 19 deletion (N=166)	Mean treatment difference between afatinib and chemotherapy (95% CI)	-7.18 (-11.06 to -3.30)*
	Dyspnoea				-7.86 (-11.14 to -4.57)*
	Pain				0.66 (-3.16 to 4.49)
	Cough	Post-treatment	LUX-Lung 3, L858R (N=135	Mean treatment difference between afatinib and chemotherapy (95% CI)	-5.21 (-9.39 to -1.03)*
	Dyspnoea				-6.44 (-9.69 to -3.19)*
	Pain				-0.62 (-5.13 to 3.88)
	Cough	Post-treatment			-6.62 (-10.39 to –2.85)*

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Study	EORTC QLQ-LC13 Subdomain	Timepoint	Intervention and comparator	Outcome description	Outcome value
	Dyspnoea		LUX-Lung 6, exon 19 deletion mutation (N=183)	Mean treatment difference between afatinib and chemotherapy (95% CI)	-11.41 (-14.26 to -8.57)*
	Pain				-7.50 (-10.84 to -4.17)*
	Cough	Post-treatment	LUX-Lung 6, L858R mutation (N=133)	Mean treatment difference between afatinib and chemotherapy (95% CI)	-4.78 (-9.24 to -0.32)*
	Dyspnoea				-6.61 (-10.54 to -2.69)*
	Pain				-4.70 (-9.37 to -0.03)*
ALK mutations					
Ou 2018 (NP28761 study)[135]	**Cough**	Baseline	Alectinib (N=84)	Mean (SD); median	33.76 (27.47); 33.33
		Week 6			19.58 (21.28); 33.33
		Change from baseline			-13.89 (31.47); 0
	Dyspnoea	Baseline	Alectinib (N=84)	Mean (SD); median	30.85 (27.13); 22.22
		Week 6			23.28 (21.56); 22.22
		Change from baseline			-8.24 (22.57); 0
	Pain in chest	Baseline	Alectinib (N=84)	Mean (SD); median	21.52 (28.6); 0
		Week 6			5.82 (17.50); 0
		Change from baseline			-16.67 (29.75); 0
Peters 2020[136]	**Cough**	Baseline	Patients treated with loratinib (N=255)	Mean (SD)	29.26 (28.06)
		Clinically meaningful change from baseline	Patients treated with loratinib (N=255)	Improved, n (%)	109 (42.7)
				Stable, n (%)	111 (43.5)
				Worse, n (%)	34 (13.3)
	Dyspnoea	Baseline	Patients treated with loratinib (N=255)	Mean (SD)	23.1 (22.9)
		Clinically meaningful change from baseline	Patients treated with loratinib (N=255)	Improved, n (%)	70 (27.5)
				Stable, n (%)	140 (54.9)

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Study	EORTC QLQ-LC13 Subdomain	Timepoint	Intervention and comparator	Outcome description	Outcome value
				Worse, n (%)	44 (17.3)
	Pain in chest	Baseline	Patients treated with loratinib (N=255)	Mean (SD)	16.34 (25.31)
		Clinically meaningful change from baseline	Patients treated with loratinib (N=255)	Improved, n (%)	76 (29.8)
				Stable, n (%)	152 (59.6)
				Worse, n (%)	25 (9.8)

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Table 93. List of included studies.

Short Reference	Reference
Blackhall 2014	Blackhall F, Kim DW, Besse B, et al. Patient-reported outcomes and quality of life in PROFILE 1007: A randomised trial of crizotinib compared with chemotherapy in previously treated patients with ALK-positive advanced non-small-cell lung cancer. Journal of Thoracic Oncology 2014;9:1625-1633.
Chouhaid 2013	Chouaid C, Agulnik J, Goker E, et al. Health-related quality of life and utility in patients with advanced non-small-cell lung cancer: A prospective cross-sectional patient survey in a real-world setting. Journal of Thoracic Oncology 2013;8:997-1003.
Doyle 2008	Doyle S, Lloyd A, Walker M. Health state utility scores in advanced non-small cell lung cancer. Lung Cancer 2008;62:374-80.
Galetta 2015	Galetta D, Cinieri S, Pisconti S, et al. Cisplatin/Pemetrexed Followed by Maintenance Pemetrexed Versus Carboplatin/Paclitaxel/Bevacizumab Followed by Maintenance Bevacizumab in Advanced Nonsquamous Lung Cancer: The GOIM (Gruppo Oncologico Italia Meridionale) ERACLE Phase III Randomised Trial. Clinical Lung Cancer 2015;16:262-73.
Gridelli 2012	Gridelli C, de Marinis F, Pujol JL, et al. Safety, resource use, and quality of life in paramount: a phase III study of maintenance pemetrexed versus placebo after induction pemetrexed plus cisplatin for advanced nonsquamous non-small-cell lung cancer. Journal of Thoracic Oncology: Official Publication of the International Association for the Study of Lung Cancer 2012;7:1713-21.
Ha 2020	Ha TV, Hoang MV, Vu MQ, et al. Willingness to pay for a quality-adjusted life year among advanced non-small cell lung cancer patients in Viet Nam, 2018. Medicine (United States) 2020;99 (9) (no pagination).
Hirsh 2013	Hirsh V, Cadranel J, Cong XJ, et al. Symptom and quality of life benefit of afatinib in advanced non-small-cell lung cancer patients previously treated with erlotinib or gefitinib: results of a randomised phase IIb/III trial (LUX-Lung 1). Journal of Thoracic Oncology: Official Publication of the International Association for the Study of Lung Cancer 2013;8:229-37.
Huang 2018a (Jiang 2020, from SLR update)	Huang M, Chandwani S, Insinga R, et al. Health State Utilities in Metastatic Nsclc: A Study of Multiple Immuno-Oncology Trials. Value in Health 2018;21 (Supplement 3):S72-S73.
	Jiang Y, Wang X. Cost-effectiveness analysis of pembrolizumab plus standard chemotherapy versus chemotherapy alone for first-line treatment of metastatic non-squamous non-small-cell lung cancer in China. European Journal of Hospital Pharmacy Science & Practice 2020;31:31.
Huang 2018b (Huang 2019)	Huang M, Pietanza MC, Samkari A, et al. Q-TWiST analysis to assess benefit-risk of pembrolizumab in patients with PD-L1-positive advanced or metastatic NSCLC. Annals of Oncology 2018;29 (Supplement 8):viii434.
	Huang M, Pietanza MC, Samkari A, et al. Q-TWiST Analysis to Assess Benefit-Risk of Pembrolizumab in Patients with PD-L1-Positive Advanced or Metastatic Non-small Cell Lung Cancer. Pharmacoeconomics 2019;37:105-116.
Hui 2019	Hui R, Ozguroglu M, Villegas A, et al. Patient-reported outcomes with durvalumab after chemoradiotherapy in stage III, unresectable non-small-cell lung cancer (PACIFIC): a randomised, controlled, phase 3 study. The Lancet Oncology 2019;20:1670-1680.
Iyer 2013	Iyer S, Taylor-Stokes G, Roughley A. Symptom burden and quality of life in advanced non-small cell lung cancer patients in France and Germany. Lung Cancer 2013;81:288-93.
Jiang 2018	Jiang SX, Walton RN, Hueniken K, et al. Real-world health utility scores and toxicities to tyrosine kinase inhibitors in epidermal growth factor receptor mutated advanced non-small cell lung cancer. Cancer Medicine 2019;8:7542-7555.
Jiang 2019	Jiang S, Hurry M, Hueniken K, et al. Predictors of Health Utility Scores (HUS) in Advanced EGFR-Mutated NSCLC. Journal of Thoracic Oncology 2018;13 (10 Supplement):S420-S421.

Khan 2015	Khan I, Morris S, Hackshaw A, et al. Cost-effectiveness of first-line erlotinib in patients with advanced non-small-cell lung cancer unsuitable for chemotherapy. BMJ Open 2015;5 (7) (no pagination).
Krivasi 2018	Krivasi T, Castro AY. Health state utilities in first line patients with non-squamous metastatic non-small cell lung cancer. The International Society for Pharmacoeconomics and Outcomes Research (ISPOR) Europe 2018.
Labbe 2017	Labbe C, Leung Y, Silva Lemes JG, et al. Real-World EQ5D Health Utility Scores for Patients With Metastatic Lung Cancer by Molecular Alteration and Response to Therapy. Clinical Lung Cancer 2017;18:388-395.e4.
Lamers 2007	Lamers LM, Uyl-de Groot CA, Buijt I. The Use of Disease-Specific Outcome Measures in Cost-Utility Analysis. Pharmacoeconomics 2007 Jul;25(7):591-603.
Nafees 2017	Nafees B, Lloyd AJ, Dewilde S, et al. Health state utilities in non-small cell lung cancer: An international study. Asia-Pacific Journal of Clinical Oncology 2017;13:e195-e203.
Nafees 2008	Nafees B, Stafford M, Gavriel S, et al. Health state utilities for non small cell lung cancer. Health and Quality of Life Outcomes 2008;6 (no pagination).
O'Kane 2019	O'Kane GM, Su J, Tse BC, et al. The Impact of Brain Metastases and Associated Neurocognitive Aspects on Health Utility Scores in EGFR Mutated and ALK Rearranged NSCLC: A Real World Evidence Analysis. Oncologist 2019;24:e501-e509.
Reck 2018a	Reck M, Brahmer J, Bennett B, et al. Evaluation of health-related quality of life and symptoms in patients with advanced non-squamous non-small cell lung cancer treated with nivolumab or docetaxel in CheckMate 057. European Journal of Cancer 2018;102:23-30.
Reck 2018b	Reck M, Taylor F, Penrod JR, et al. Impact of Nivolumab versus Docetaxel on Health-Related Quality of Life and Symptoms in Patients with Advanced Squamous Non-Small Cell Lung Cancer: Results from the CheckMate 017 Study. Journal of Thoracic Oncology 2018;13:194-204.
Schuette 2012	Schuette W, Tesch H, Buttner H, et al. Second-line Treatment of Stage III/IV Non-Small-Cell Lung Cancer (NSCLC) with pemetrexed in routine clinical practice: Evaluation of performance status and health-related quality of life. BMC Cancer 2012:14.
Shen 2018	Shen Y, Wu B, Wang X, et al. Health state utilities in patients with advanced non-small-cell lung cancer in China. Journal of Comparative Effectiveness Research 2018;7:443-452.
Trippoli 2001	Trippoli S, Vaiani M, Lucioni C, et al. Quality of life and utility in patients with non-small cell lung cancer. Quality-of-life Study Group of the Master 2 Project in Pharmacoeconomics. Pharmacoeconomics 2001;19:855-63.
Verduyn 2012	Verduyn SC, Biesma B, Schramel FM, et al. Estimating quality adjusted progression free survival of first-line treatments for EGFR mutation positive non small cell lung cancer patients in The Netherlands. Health & Quality of Life Outcomes 2012;10:108.
Wood 2019	Wood R, Taylor-Stokes G, Smith F, et al. The humanistic burden of advanced non-small cell lung cancer (NSCLC) in Europe: a real-world survey linking patient clinical factors to patient and caregiver burden. Quality of Life Research 2019;28:1849-1861.
Yang 2014	Yang SC, Lai WW, Chang HY, et al. Estimation of loss of quality-adjusted life expectancy (QALE) for patients with operable versus inoperable lung cancer: adjusting quality-of-life and lead-time bias for utility of surgery. Lung Cancer 2014;86:96-101.
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Appendix I Mapping of HRQoL data

N/A

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Appendix J Probabilistic sensitivity analyses

Table 94. Base Case Parameters Varied in the Sensitivity Analyses

Parameter	Mean Value/Base case value	DSA Values		PSA Variation		Source of Variation
		Lower	Upper	Distribution	SE	
Efficacy – KM curves						
When varying the KM curves a random number is sampled using the normal distribution which is then multiplied by the SE of each KM data point.						
PFS KM curve – Amivantamab	Raw KM data from the CHRYSALIS n=114 trial	-1.96	1.96	Normal	Derived for each point of the KM curve individually	The PSA values are generated using a random number between zero and one. The DSA values are the number of standard deviations in a normal distribution to provide a 95% confidence interval
PFS KM curve – SoC	Pooled European and US RWE, adjusted to n=114 CHRYSALIS	-1.96	1.96	Normal		
OS KM Curve – SoC	Pooled European and US RWE, adjusted to n=114 CHRYSALIS	-1.96	1.96	Normal		
Efficacy - Extrapolations						
OS Weibull – Parameter 1: Amivantamab	3.48	3.44	3.53	Cholesky /Normal	N/A – varied using covariance matrices	Pooled US and EU RWE ITC, adjusted to CHRYSALIS n=114
OS Weibull – Parameter 2: Amivantamab	0.77	0.75	0.79			
Patient Characteristics						
Starting Age	61.75	59.92	63.58	Normal	0.94	SE from CHRYSALIS n=114. DSA values are at 95% CI
Gender (% of male)	38.6%	31.2%	46.3%	Beta	3.9%	SE assumed 10% of mean value. DSA values calculated using the SE to estimate the 95% CI values
Utilities						
PF utility	0.71	0.56	0.84	Beta	0.07	SE assumed 10% of mean value. DSA values calculated using the SE to estimate the 95% CI values
PP utility	0.57	0.46	0.68	Beta	0.06	
AE disutility: Amivantamab	-0.00077	-0.00062	-0.00092	Beta	-0.00008	
AE disutility: SoC	-0.00258	-0.00210	-0.00311	Beta	-0.00026	
Costs						
Drug costs, initial cycle: Amivantamab	DKK 133,330	DKK 106,664	DKK 159,996	Gamma	DKK 13,605	SE is calculated as the DSA variance of ±20% divided by 1.96 (1 SE). DSA variation is ±20%
Drug costs, subsequent cycle: Amivantamab	DKK 66,665	DKK 53,332	DKK 79,998	Gamma	DKK 6,803	

Parameter	Mean Value/Base case value	DSA Values Lower	DSA Values Upper	PSA Variation Distribution	PSA Variation SE	Source of Variation
Drug costs, subsequent cycle: I-O Agents	DKK 35,931	DKK 28,745	DKK 43,117	Gamma	DKK 3,666	
Drug costs, subsequent cycle: EGFR TKIs	DKK 18,086	DKK 14,469	DKK 21,703	Gamma	DKK 1,846	
Drug costs, subsequent cycle: Non-platinum-based Chemotherapy Regimens	DKK 13,732	DKK 10,985	DKK 16,478	Gamma	DKK 1,401	
Administration costs, first cycle: Amivantamab	DKK 12,900	DKK 10,320	DKK 15,480	Gamma	DKK 1,316	
Administration costs, subsequent cycle: Amivantamab	DKK 6,450	DKK 5,160	DKK 7,740	Gamma	DKK 658	
Administration costs: I-O Agents	DKK 3,763	DKK 3,010	DKK 4,515	Gamma	DKK 384	
Administration costs: Non-platinum-based Chemotherapy Regimens	DKK 5,375	DKK 4,300	DKK 6,450	Gamma	DKK 548	
AE Mgmt Cost: Amivantamab	DKK 1,555	DKK 1,244	DKK 1,866	Gamma	DKK 159	
AE Mgmt Cost: SoC	DKK 7,446	DKK 5,956	DKK 8,935	Gamma	DKK 760	
Disease Mgmt Cost - PF: Amivantamab	DKK 5,999	DKK 4,799	DKK 7,199	Gamma	DKK 612	
Disease Mgmt Cost - PF: SoC	DKK 5,999	DKK 4,799	DKK 7,199	Gamma	DKK 612	
Disease Mgmt Cost - Progressed: Amivantamab	DKK 5,581	DKK 4,465	DKK 6,697	Gamma	DKK 569	
Disease Mgmt Cost - Progressed: SoC	DKK 5,581	DKK 4,465	DKK 6,697	Gamma	DKK 569	
Disease Mgmt Cost - One-off cost of mortality	DKK 71,612	DKK 57,290	DKK 85,934	Gamma	DKK 7,307	
Subsequent treatment cost: Amivantamab	DKK 86,971	DKK 69,577	DKK 104,366	Gamma	DKK 8,875	
Subsequent treatment cost: SoC	DKK 95,589	DKK 76,471	DKK 114,706	Gamma	DKK 9,754	
Indirect cost PF: Amivantamab	DKK 1,219	DKK 975	DKK 1,463	Gamma	DKK 124	

Parameter	Mean Value/Base case value	DSA Values		PSA Variation		Source of Variation
		Lower	Upper	Distribution	SE	
Indirect cost PF: SoC	DKK 3,356	DKK 2,685	DKK 4,027	Gamma	DKK 342	
Indirect cost Progressed: Amivantamab	DKK 456	DKK 365	DKK 547	Gamma	DKK 47	
Indirect cost Progressed: SoC	DKK 456	DKK 365	DKK 547	Gamma	DKK 47	

Abbreviations: AE = adverse event, DKK = Danish krone, DSA = deterministic sensitivity analysis, EGFR = epidermal growth factor receptor, I-O = immuno-oncology, KM = Kaplan-Meier, Mgmt = management, OS = overall survival, PF = progression-free, PFS = progression-free survival, PP = post-progression, SoC = standard of care, TKI = tyrosine kinase inhibitor

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Appendix K Email from DMC regarding choice of comparator

Tak for detaljerne i præsentation.

Vi har været i dialog med fagudvalget omkring fordelinger af behandlinger i komparatorarmen på baggrund af dansk klinisk praksis. Og her er meldingen, at patienter bliver behandlet iht. alm. retningslinjer for behandling af NSCLC. Rækkefølgen og hvilke præparater patienterne får er bl.a. afhængig af PD-L1-status, sygdomsudbredning og almen tilstand. Nogle gange bliver der forsøgt med osimertinib som 2. linje men det kan også være yderligere kemoterapi eller immunterapi. Der er derfor ikke en standardiseret praksis så umiddelbart må I komme med jeres bud, som fagudvalget vil så forholde sig til. Det samme gælder for antal patienter, her er meldingen en håndfuld patienter om året i hver region.

Hvad angår jeres spørgsmål om at udelade at lave en cost-utility analyse, så vil det som udgangspunkt gælde i helt særlige tilfælde. Vi har ikke nogle konkrete eksempler endnu, men hvis jeres lægemiddel hverken viser effekt på overlevelse eller livskvalitet, er en cost-utility analyse selvfølgelig ikke meningsfuld. Men tænker det ikke er tilfældet for amivantamab. På baggrund af den information vi har nu, er det svært for os at vurdere hvilken analyse er mest hensigtsmæssigt. Det er jeres valg og derfor vigtigt at I argumenterer for jeres valg. Her refererer vi til afsnit 6.2.1 i vores metodehåndbog:

Der kan være tilfælde, hvor data er for sparsomt til, at der kan udføres en cost-utility analyse. Det kan for eksempel være i forbindelse med nogle lægemidler til sjældne sygdomme. I tilfælde, hvor virksomheden vurderer, at det ikke er muligt at udføre en cost-utility analyse, skal virksomheden præsentere det tilgængelige data vedrørende effekt, sikkerhed og omkostninger. På baggrund af det indsendte data skal virksomheden desuden begrunde, hvorfor en cost-utility analyse ikke er mulig. I de tilfælde, hvor en ansøgning ikke omfatter en cost-utility analyse, vil det tilgængelige data vedrørende det nye lægemiddels effekt, sikkerhed og omkostninger blive vurderet, som beskrevet under de relevante afsnit i metodevejledningen. Fagudvalg og sekretariat vurderer data og virksomhedens rationale for ikke at udføre en cost-utility analyse.

På baggrund af ovenstående, synes vi ikke der er anledning til at holde et dialogmøde. Du er selvfølgelig altid velkommen at skrive igen eller ringe.

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Appendix L Patient reported outcomes in CHRYSALIS

[redacted]

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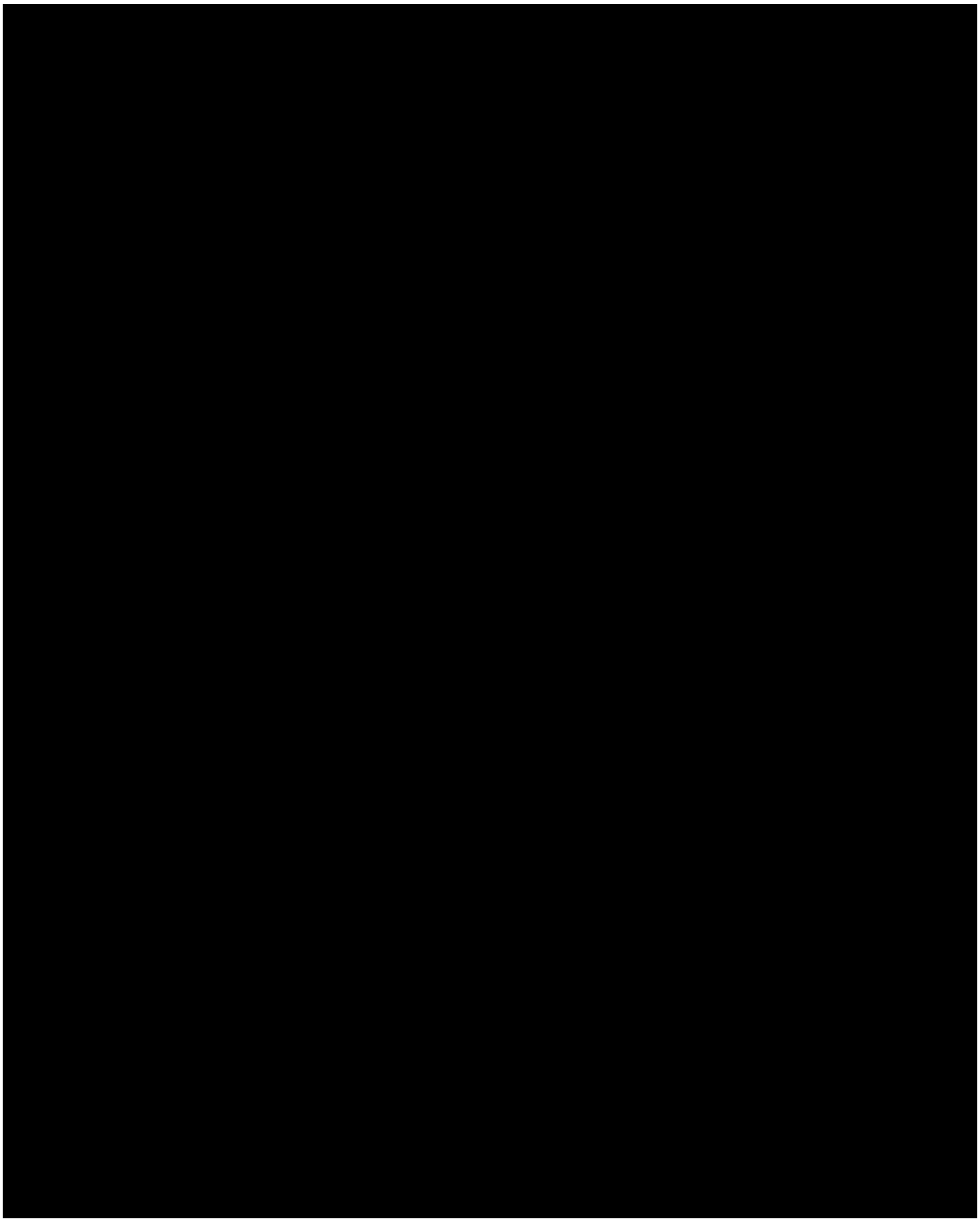

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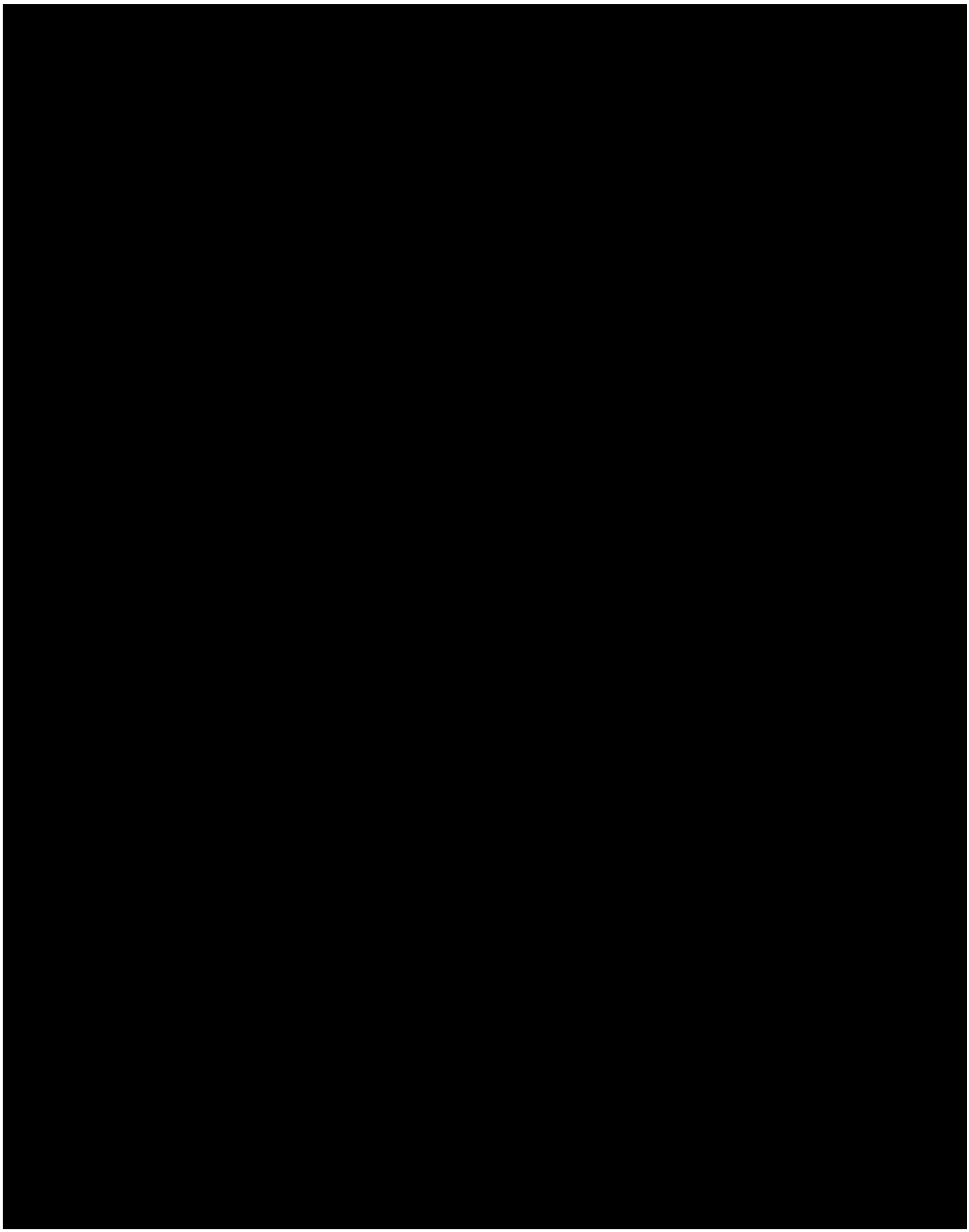

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Appendix M – Treatments included in the RWE study

Table 97. Distribution of treatments in the RWE study (per treatment group)

Treatment group	Treatment Regimen	Total	Percentage of the group
TKI (17%)	Afatinib	26	43%
	Erlotinib	11	18%
	Osimertinib	20	33%
	Afatinib, Carboplatin, Pemetrexed	1	2%
	Afatinib, Paclitaxel	1	2%
	Erlotinib, Pemetrexed	1	2%
	Subtotal	60	
IO (26%)	Atezolizumab	4	4%
	Carboplatin/Gemcitabin/Nivolumab	1	1%
	Carboplatin/Paclitaxel/Atezolizumab	1	1%
	Nivolumab	53	59%
	Nivolumab/Ipilimumab	2	2%
	Pembrolizumab	15	17%
	Pembrolizumab/Pemetrexed	3	3%
	Carboplatin, Nivolumab	1	1%
	Carboplatin, Pembrolizumab, Pemetrexed	7	8%
	Durvalumab	2	2%
	Nivolumab, Paclitaxel, Ramucirumab	1	1%
	Subtotal	90	
Non-platinum chemotherapy (22%)	Docetaxel	18	24%
	Gemcitabin	15	20%
	Pemtrexed	15	20%
	Vinorelbin	1	1%
	Docetaxel, Paclitaxel	1	1%
	Gemcitabine, Paclitaxel	1	1%
	Gemcitabine, Vinorelbine	3	4%
	Mitomycin	1	1%
	Paclitaxel	13	17%
	Paclitaxel Protein-Bound	2	3%
	Vinorelbine	6	8%
	Subtotal	76	
VEGFi (17%)	Carboplatin/Pemetrexed/Bevacizumab	2	3%
	Carboplatin/Nab-Paclitaxel/Bevacizumab	1	2%
	Docetaxel/Nintedanib	20	34%
	Docetaxel/Ramucirumab	14	24%
	Pemetrexed/Bevacizumab	1	2%
	Bevacizumab, Carboplatin, Paclitaxel	3	5%
	Bevacizumab, Carboplatin, Pemetrexed	8	14%
	Bevacizumab, Docetaxel	1	2%
	Bevacizumab, Gemcitabine	1	2%

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	Bevacizumab, Pemetrexed	2	3%
	Bevacizumab-Awwb, Carboplatin, Paclitaxel Protein-	1	2%
	Paclitaxel, Ramucirumab	5	8%
	Subtotal	59	
Other (19%)	Cabozatinib	1	2%
	Capmatinib	1	2%
	Carboplatin/Gemcitabin	7	11%
	Carboplatin/Pemetrexed	11	17%
	Carboplatin/Vinorelbin	3	5%
	Carboplatin/Nab-Paclitaxel	2	3%
	Cisplatin/Pemetrexed	1	2%
	Mobocertinib	2	3%
	Nintedanib	1	2%
	Poziotinib	1	2%
	Afatinib, Cetuximab	1	2%
	Alectinib	1	2%
	Atezolizumab, Bevacizumab, Carboplatin, Paclitaxel	3	5%
	Carboplatin, Gemcitabine, Paclitaxel	1	2%
	Carboplatin, Paclitaxel	2	3%
	Cetuximab	1	2%
	Cisplatin, Etoposide	1	2%
	Clinical Study Drug	3	5%
	Investigational	12	18%
	Necitumumab, Osimertinib	1	2%
	Pazopanib	1	2%
	Ramucirumab	1	2%
	Sunitinib	1	2%
	Trastuzumab	1	2%
	Unknown	6	9%
	Subtotal	66	
Total		351	

Abbreviations: IO = Immuno-oncology drug, TKI = Tyrosine kinase inhibitor, VEGFi = VEGF inhibitors

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