Medicinrådet

Bilag til Medicinrådets anbefaling vedrørende nivolumab i kombination med ipilimumab til behandling af ikke-resektabel lungehindekræft

Vers. 1.1

Bilagsoversigt

1. Ansøgers endelige ansøgning
2. Forhandlingsnotat fra Amgros vedr. nivolumab (Opdivo) i kombination med ipilimumab (Yervoy)
3. Ansøgers notat til Rådet

Application for the assessment of Clinical evidence of nivolumab (Opdivo®) in combination with ipilimumab (Yervoy®) for the treatment of unresectable malignant pleural mesothelioma

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1. Basic information

Contact information	
Name	**Lars Oddershede**
Title	Market Access Manager | Market Access
Phone number	+45 4256-6030
E-mail	Lars.Oddershede@bms.com

Overview of the pharmaceutical	
Proprietary name	OPDIVO + YERVOY
Generic name	Nivolumab + ipilimumab
Marketing authorization holder in Denmark	Bristol-Myers Squibb
ATC code	L01XC17 L01XC10
Pharmacotherapeutic group	Nivolumab: programmed death receptor 1 (PD-1) blocking antibody Ipilimumab: human cytotoxic T-lymphocyte antigen 4 (CTLA-4)-blocking Antibody
Active substance(s)	Nivolumab + ipilimumab
Pharmaceutical form(s)	Concentrate for solution for infusion
Mechanism of action	Nivolumab: human immunoglobulin G4 (IgG4) monoclonal antibody (HuMAb), which binds to the programmed death-1 (PD-1) receptor and blocks its interaction with PD-L1 and PD-L2 Ipilimumab: human immunoglobulin G1κ (IgG1κ) monoclonal antibody (HuMAb), which binds to the cytotoxic T-lymphocyte antigen 4 (CTLA-4) an immune checkpoint inhibitor that blocks T-cell inhibitory signals induced by the CTLA-4 pathway
Dosage regimen	Nivolumab 360 mg every 3 weeks (30-minute IV infusion) with ipilimumab 1 mg/kg every 6 weeks (30-minute IV infusion)
Therapeutic indication relevant for assessment (as defined by the European Medicines Agency, EMA)	OPDIVO in combination with ipilimumab is indicated for the first line treatment of adult patients with unresectable malignant pleural mesothelioma

Other approved therapeutic indications	**Non-small cell lung cancer** OPDIVO as monotherapy is indicated for the treatment of locally advanced or metastatic non-small cell lung cancer after prior chemotherapy in adults (second line) OPDIVO in combination with ipilimumab and two treatment cycles of platinum-based chemotherapy is indicated as first-line treatment of metastatic non-small cell lung cancer whose tumors have no sensitizing EGFR mutations or ALK translocations **Melanoma** OPDIVO as monotherapy or in combination with ipilimumab is indicated for the treatment of advanced (unresectable or metastatic) melanoma in adults Relative to nivolumab monotherapy, an increase in progression-free survival and overall survival for the combination of nivolumab with ipilimumab is established only in patients with low tumor PD-L1 expression **Adjuvant treatment of melanoma** OPDIVO as monotherapy is indicated for the adjuvant treatment of adults with melanoma with involvement of lymph nodes or metastatic disease who have undergone complete resection **Renal cell carcinoma** OPDIVO as monotherapy is indicated for the treatment of advanced renal cell carcinoma after prior therapy in adults OPDIVO in combination with ipilimumab is indicated for the first-line treatment of adult patients with intermediate/poor-risk advanced renal cell carcinoma OPDIVO in combination with cabozantinib is indicated for the first-line treatment of adult patients with advanced renal cell carcinoma **Classical Hodgkin lymphoma** OPDIVO as monotherapy is indicated for the treatment of adult patients with relapsed or refractory classical Hodgkin lymphoma after autologous stem cell transplant and treatment with brentuximab vedotin **Squamous cell cancer of the head and neck** OPDIVO as monotherapy is indicated for the treatment of squamous cell cancer of the head and neck in adults progressing on or after platinum-based therapy **Urothelial carcinoma** OPDIVO as monotherapy is indicated for the treatment of locally advanced unresectable or metastatic urothelial carcinoma in adults after failure of prior platinum-containing therapy **Esophageal squamous cell carcinoma** OPDIVO as monotherapy is indicated for the treatment of adult patients with unresectable advanced, recurrent or metastatic esophageal squamous cell carcinoma after prior fluoropyrimidine- and platinum-based combination chemotherapy

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Overview of the pharmaceutical	
	Mesothelioma OPDIVO in combination with ipilimumab for first-line treatment of adult patients with unresectable malignant pleural mesothelioma. **Colorectal Cancer** OPDIVO in combination with ipilimumab for adult patients with dMMR/MSI-H metastatic CRC after prior fluoropyrimidine-based combination chemotherapy
Will dispensing be restricted to hospitals?	Yes
Combination therapy and/or co-medication	Yes, nivolumab in combination with ipilimumab
Packaging – types, sizes/number of units, and concentrations	Nivolumab (10.0 mg/mL): Single-use vials 40 mg/4 mL 240 mg/24 mL 100 mg/10 mL Ipilimumab (5.0 mg/mL): Single-use vials 50 mg/mL 200 mg/mL
Orphan drug designation	No

Abbreviations: ALK, anaplastic lymphoma kinase; CTLA-4, human cytotoxic T-lymphocyte antigen 4; EGFR, epidermal growth factor receptor; HuMAb, monoclonal antibody; IgG4, human immunoglobulin G4; IV, intravenous; NSCLC, non-small cell lung cancer; PD-, programmed death receptor; Q#W, every # week.

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2. Abbreviations

Abbreviation	Description
1L	First line
2L	Second line
AE	Adverse event
ASBI	Average Symptom Burden Index
AUC	Under the curve
AUP	Pharmacy sales price
BICR	Blinded independent central review
BMS	Bristol Myers Squibb
BOR	Best overall response
BSC	Best supportive care
Carb	Carboplatin
CI	Confidence Interval
CM	CheckMate
CT	Computerized tomography
CTCAE	Common Terminology Criteria for Adverse Events
CTLA-4	Cytotoxic T-lymphocyte antigen-4
DCR	Disease control rate
DKK	Danish kronor
DOR	Duration of response
ECOG PS	Eastern Cooperative Oncology Group performance status
EGFR	Epidermal growth factor receptor
EMA	European Medicines Agency
EQ-5D	EuroQol-5D
ERG	Evidence Review Group
ESMO	European Society for Medical Oncology
EU	Europe
FDA	Food and Drug Administration
FISH	Fluorescent in situ hybridization
GBD	Great Britain Pound
HR	Hazard Ratio
3-IGI	Three Item Global Index
IHC	Immunohistochemistry
IgG4	Immunoglobulin G4
IO	Immuno-oncology
IPI	Ipilimumab
IQR	Interquartile range
ITC	Indirect treatment comparison
IV	Intravenous

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LCSS	Lung Cancer Symptom Scale
LS	Least squares
MHC	Major histocompatibility complex
MID	Minimal important difference
MM	Malignant mesothelioma
MMRM	Mixed model repeated measures
MPM	Malignant pleural mesothelioma
NCCN	National Comprehensive Cancer Network
NCI	National Cancer Institute
NIVO	Nivolumab
NOCCA	Nordic Occupational Cancer Study
NSCLC	Non-small cell lung cancer
ORR	Overall response rate
OS	Overall survival
PD	Progressed disease
PD-L1	Programmed death ligand 1
PET	Positron emission tomography
PFS	Progression-free survival
PK	Pharmacokinetics
PPP	Pharmacy purchase price
PR	Partial response
PRO	Patient reported outcome
PS	Performance status
RCC	Renal cell carcinoma
RCT	Randomized control trial
RECIST	Response Evaluation Criteria in Solid Tumors
ROW	Rest of the world
SD	Standard deviation
SE	Standard Error
SLR	Systematic literature review
STA	Single technology assessment
TBA	To be announced
TCR	T-cell receptor
TRAE	Treatment related adverse event
TTD	Time to deterioration
TTF	Tumour treating fields
TTR	Time to response
UI	Utility index
UK	United Kingdom
UNS	Unspecified

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US	United States of America
VAS	Visual analogue scale
VAT	Value added tax
WHO	World Health Organization

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3. Tables and Figures

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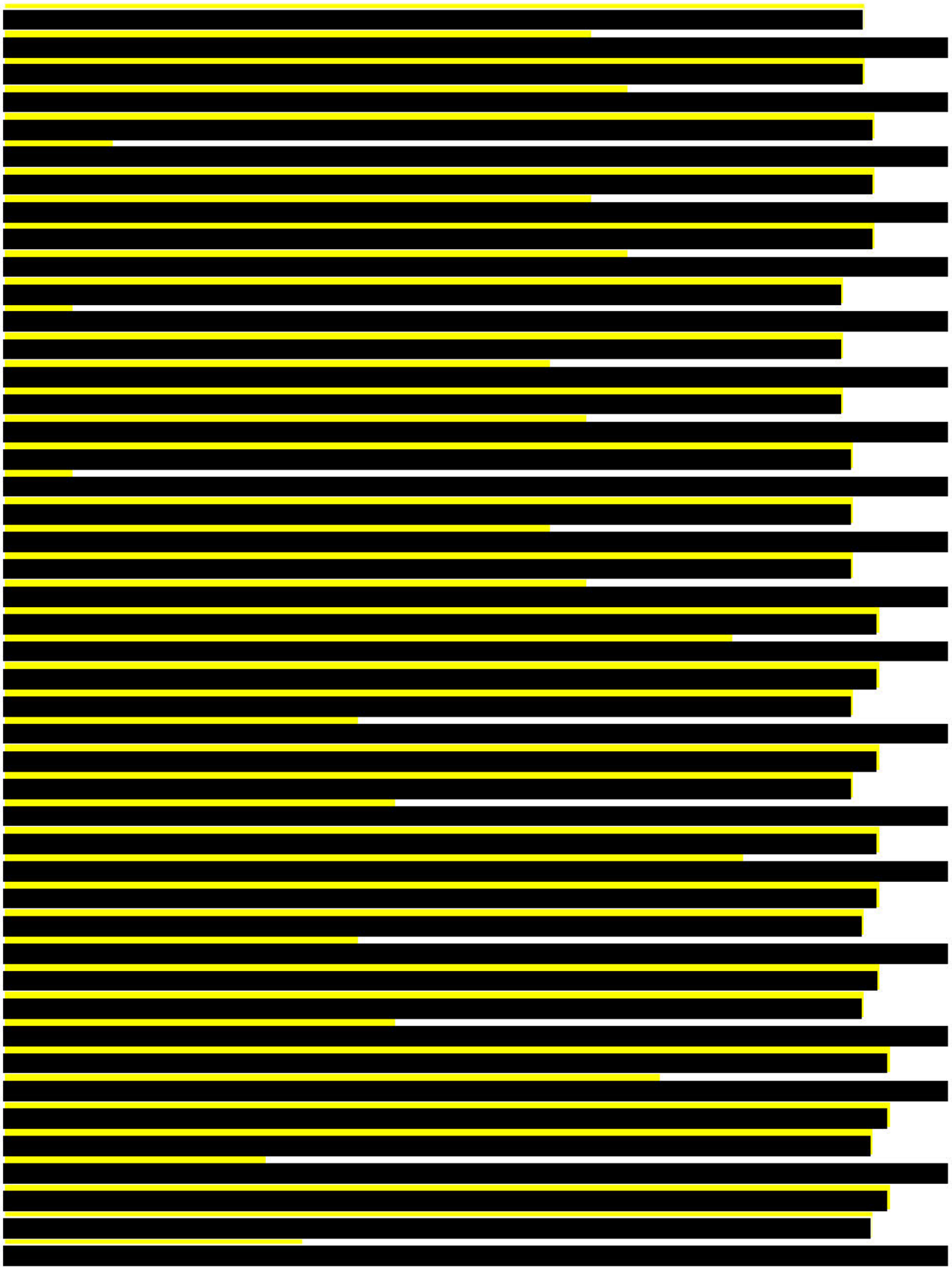

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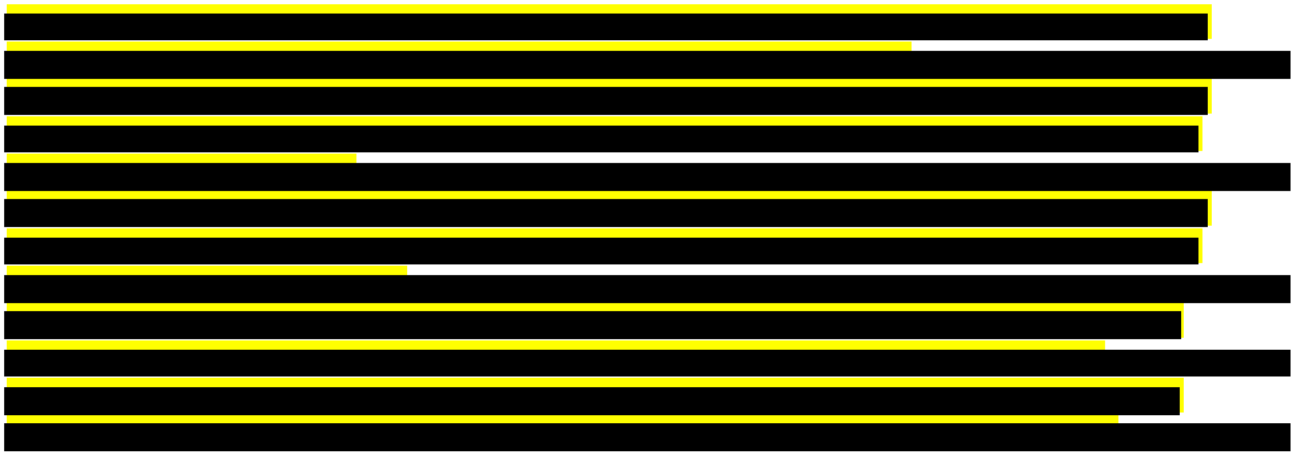

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4. Summary

Mesothelioma is a cancer that emerge in the mesothelioma derived cells in the serosa lined cavities, where the pleural cavity accounting for 90% and the peritoneal cavity for 10% of cases (German-Mesothelioma-Registry 2018). Malignant pleural mesothelioma (MPM) is a highly aggressive cancer and typically unresectable at diagnosis, with less than 10% of patients surviving beyond 5 years (Milano 2010, Van Gerwen 2019). MPM includes three histologies; epithelioid (60%), sarcomatoid (10%), and a combination of the two, called biphasic (30%) (Kirstein Jensen 2020). The three histologies correlate with sensitivity to chemotherapy, rate of residual disease, and survival. The sarcomatoid histology is associated with a worse prognosis (van Zandwijk 2013, Bibby 2016).

The incidences of MPM are tightly connected to the import and use of asbestos. The disease is more frequently seen in the male population due to occupational asbestos exposure (Bibby 2016, GBD 2016 Collaborators 2017, Kirstein Jensen 2020, National Comprehensive Cancer Network 2021). As a result of general early prohibition of asbestos use, the incidence rates were expected to be decreasing. However, in Denmark a decrease was still not seen in 2018, where, in fact, a slight increase has been observed with 147 newly diagnosed malignant mesothelioma patients (Kirstein Jensen 2020).

In selected cases of MPM, surgery is chosen as curative intended treatment. Patients qualifying for surgery are characterized by epithelioid histology, or biphasic with no or maximum 50% sarcomatoid histology. The prognosis of epithelioid MPM is significantly better than sarcomatoid MPM, with a median survival of 14-15 versus 7 months (Kirstein Jensen 2020).

Platinum based chemotherapy; cis/carboplatin and pemetrexed, has been first line treatments offered to MPM patients (PS=0-2). Vinorelbine is often used as second line treatment, though with limited response rate and survival gain (Sørensen JB 2019, Fennell 2021).

Nivolumab and ipilimumab are immune checkpoint inhibitors with distinct but complementary mechanisms of action. Combining the two checkpoint inhibitors nivolumab and ipilimumab have proven to be effective, with long-term survival benefit observed in melanoma (CheckMate 067), renal cell cancer (CheckMate 214), and non-small cell lung cancer (CheckMate 227 and CheckMate 9LA).

The pivotal trial, CheckMate 743 (NCT02899299), is a phase 3, randomised, global, multicentre, open label trial of nivolumab and ipilimumab versus pemetrexed and cisplatin or carboplatin as a first line therapy for unresectable MPM. The purpose of the trial was to test the effectiveness and tolerability of the combination of nivolumab and ipilimumab compared to pemetrexed and cisplatin or carboplatin in patients with unresectable MPM. The prespecified interim analysis shows that the study met its primary endpoint. At a minimum follow-up of 22.1 months, the median overall survival (OS) was 18.1 months (95% CI 16.8-21.4) in the nivolumab and ipilimumab group vs 14.1 months (95% CI 12.4-16.2) in the chemotherapy group (stratified HR 0.74, 96.6% CI 0.60-0.91; p=0.0002) in all randomized patients. The 2-year OS rate is 41% (95% CI 35.1–46.5) and 27% (95% CI 21.9–32.4) for nivolumab and ipilimumab vs chemotherapy, respectively. Progression free survival (PFS) was followed up for a minimum of 19.8 months and the median PFS was seen to be similar between the two treatment groups: nivolumab and ipilimumab group was 6.8 months (95% CI 5.6–7.4) and the chemotherapy group was 7.2 months (95% CI 6.9–8.0). The PFS rates at 2 years however were numerically greater in the nivolumab and ipilimumab group at 16% (95% CI 11.7–21.5), compared to only 7% (CI 4.0–11.7) in the chemotherapy group.

The dose and schedule of nivolumab plus ipilimumab in CheckMate 743 demonstrated a manageable safety profile, consistent with NSCLC clinical trials (Baas 2020a, Bristol-Myers Squibb 2020f). No new safety signals were observed with nivolumab plus ipilimumab treatment in MPM patients consistent with previously reported outcomes using the same dose and schedule (i.e. in CheckMate -227 [NSCLC]) (Disselhorst 2019, Hellmann 2019, Scherpereel 2019)

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The yearly number of Danish patients with unresectable MPM eligible for nivolumab and ipilimumab is estimated to be 60 patients, based on NORDCAN May 2020 and input from Danish clinical experts (Danish Clinical Expert 2021a, Danish Clinical Expert 2021b).

A three health-state cohort model was developed to evaluate the incremental cost-effectiveness of nivolumab and ipilimumab versus pemetrexed and cisplatin/carboplatin in patients with previously untreated unresectable MPM. The results from the cost-effectiveness analysis show that treatment with nivolumab and ipilimumab is associated with better health outcomes than pemetrexed and cisplatin/carboplatin with an expected gain of 0.788 QALYs. The treatment is also associated with an expected overall cost increase of DKK 618 188 per patient. The ICER per QALY gained is estimated to be DKK 784 237 (drug prices not discounted).

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

5.1 The medical condition and patient population

5.1.1 Malignant pleural mesothelioma

Malignant mesothelioma (MM) is a rare and aggressive form of cancer occurring in the mesothelial cells (mesothelium) that line the chest, lungs abdomen, and other internal organs (National Cancer Institute 2021). The most common of MM cases are those that develop in the pleural cavity, known as malignant pleural mesothelioma (MPM), which comprise of 70 – 90% of all forms of MM (Hiriart 2019).

Other than MPM, MM can be classified into two other types, according to the other tumor locations, namely peritoneal mesothelioma (occurring in the lining of the abdomen) and pericardial mesothelioma (affecting the lining of the heart (pericardium), the rarest form of the disease (Hiriart 2019).

Further subtypes of MPM are categorized according to one of three histological subtypes, depending on the predominant histomorphological growth pattern (Neumann 2013):

- Epithelioid mesothelioma: made up by uniform and sharply defined cells which feature a prominent nuclei. This is the most common subtype, known for its heterogenous morphology, and is associated with the most favourable prognosis out of all the subtypes with an average survival of 13.1 months (Bibby 2016, Krasinskas 2016, Brcic 2020)
- Sarcomatoid mesothelioma: defined by diffuse and infiltrative growth of spindle cells, or mesenchymal appearing cells. This subtype is the rarest form of mesothelioma, accounting for less than 10% of all cases (Wadowski 2019)
- Biphasic (mixed) mesothelioma: this subtype consists of epithelial and sarcomatoid cells (at least 10% of each type) and accounts for 20 – 30% of mesothelioma cases (Brcic 2020).

5.1.2 Epidemiology

According to Globocan statistics from 2020, there were 30 870 global incidences of MPM, with the highest incidence being recorded in Europe (13 648); Out of the recorded total cases, the mortality was significantly high, amount to 26 278 patients (Globocan 2020). Of the new cases in Northern Europe in 2020, 3244 were in males versus only 702 cases in females (Globocan 2020).

The incidence of MPM in the Nordic countries have remained relatively stable over the past years, after a steady decrease seen in the 2000s (Regionala Cancercentrum i samverkan 2020).

MPM is classed as an occupational disease due to its primary implication of asbestos exposure, typically being labor-dependent and acquired in high risk workplaces (Geltner 2016). There is an especially strong association of asbestos exposure with malignancy in the pleural site, with 80% of patients with MPM reporting a history of asbestos exposure (Bridda 2007). In the UK, more than 9 out of 10 men and more than 8 out of 10 women with this type of cancer have been in contact with asbestos (Cancer Research UK. 2021). The European Union has banned asbestos use from January 2005, where bans had already prior been adopted in the Nordic countries (Kameda 2014). However, the latent period can be lengthy with disease presentation being on average 40 years after exposure or, in some cases, as long as 60 – 70 years. Additionally, more than 90% of the patients are >55 years old with an average age at time of diagnosis >70 years (Bibby 2016, GBD 2016 Collaborators 2017, Kirstein Jensen 2020, National Comprehensive Cancer Network 2021). This is why even after bans in many developed countries, Europe is still under burden from asbestos-related cancer due to the heavy use in the past decades (Alpert 2020).

The incidence has historically been higher in males who are more likely to undergo prolonged occupational or environmental exposure first-hand, as opposed to para-occupational exposure (through contact with asbestos-exposed

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workers) (Najmi 2014, Baumann 2015, Zhang 2015, Geltner 2016), a trend which continues. However, a study conducted in Denmark has shown that close to half of women diagnosed with mesothelioma have been exposed to asbestos domestically, through their husbands, fathers, or sons, who worked with asbestos (Langhoff 2014). Further, females exhibit an up to threefold better prognosis than men (Taioli 2014).

5.1.3 Disease presentation and diagnosis

Patients who are diagnosed with MPM are often presented with chest pains, dry cough (sometimes with blood), shortness of breath, and fluid in the lungs (pleural effusion) (Bibby 2016, Geltner 2016, Bianco 2018). Due to the onset of such symptoms being insidious in nature, the disease retains a high misdiagnosis rate (Zhang 2015). Breathlessness is often caused by a pleural effusion and later due to extensive restriction of breathing capacity, resulting from pleural and pulmonary tumor masses in the thoracic cavity. The invasion of the tumor into the chest wall, and towards the neural structures of the brachial plexus or paravertebral structures can also lead to neuropathic pain (Geltner 2016). Other reported symptoms include unexplained weight loss or cachexia, which is often indicative of advanced stage disease (Bianco 2018).

In majority of cases, the diagnosis of MPM is set at the advanced stage of the disease due to the considerable time it takes to arrive at the correct diagnosis. It is rare for asymptomatic patients to be diagnosed (often undertaking imaging for different reasons) but the prognosis is better as patients appear to have longer survival due to the early detection (Bibby 2016). The anatomical features obtained by imaging are important to support a clinicopathological diagnosis, especially when biopsy tissue is insufficient to obtain a clear and definitive diagnosis (van Zandwijk 2013).

A definitive diagnosis of MPM requires biopsy for histological confirmation of the mesothelial phenotype; imaging studies are also used to demonstrate neoplastic invasion (van Zandwijk 2013, Bianco 2018, Kindler 2018). Depending on the clinical circumstances, computed tomography (CT)-guided core biopsy or video-assisted thoracoscopic-guided pleural biopsy are recommended biopsy procedures, offering high sensitivity and specificity for the diagnosis of MPM (van Zandwijk 2013, Scherpereel 2019).

Tissue biopsy is considered inadvisable for patients with poor physical condition and unable to tolerate a surgical procedure. In such cases, cytological examination of pleural effusion fluid offers an alternative for diagnosing MPM (‘cytodiagnosis’) (Mineo 2016, Scherpereel 2019). However, due to a low yield of diagnostic cells in MPM, cytodiagnosis has a lower sensitivity for reaching a diagnosis than biopsy and on its own, is not definitive (Mineo 2016, Husain 2018, Scherpereel 2019). Cytodiagnosis should therefore be supported by clinical and radiological investigations for a more definitive diagnosis (van Zandwijk 2013, Kindler 2018). Further, for screening MPM for the most common histological subtype (epithelioid MPM) or diagnosis of the cases where a biopsy is not possible (e.g., very ill patient at present or technically impossible), certain biomarkers—called ancillary diagnostic techniques for MPM—can be used, such as IHC for BAP1 and FISH for CDKN2A tumor suppressor gene, on cytological material. These biomarkers support the diagnosis if there is an obvious clinical and radiological suspicion of MPM, but, unfortunately, they have low sensitivity. Therefore, the detection of deep invasion on a histological biopsy remains the gold standard for the final diagnosis of MPM (Kirstein Jensen 2020). As such, the final diagnosis of mesothelioma is histological and thus cannot be definitively determined exclusively on cytology. Detection of the tumor cells' deep in growth in the pleura and in any adherent adipose tissue is the safest histological criterion for malignant mesothelioma. It is, therefore, important that a biopsy is taken with sufficient material and depth (Kirstein Jensen 2020).

The finding that PD-L1 is expressed in over 40% of MPM cases has spurred efforts to investigate its potential as a biomarker of response to checkpoint inhibitors in MPM (Mansfield 2014). However, currently there is insufficient evidence supporting the predictive role in MPM (Reck 2016, Ahmadzada 2018).

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5.1.4 Burden of disease

Europe, in particular Northern Europe, has the highest age standardized mortality rates in the past year (Globocan 2020) (Figure 1).

Approved systemic treatments for MPM have been limited to chemotherapy regimens that have moderate survival benefit with poor outcomes and the 5-year survival of MPM is only 5% (Brcic 2020). It is estimated that, on average, each MPM patient has lost 17.3 potential years of life to this cancer (Diandini 2013). A study assessing treatment with induction chemotherapy (with cisplatin/gemcitabine or cisplatin/pemetrexed) followed by extra pleural pneumonectomy showed a median overall not beyond 22 months; treatment with induced chemotherapy alone showed median survival of 11 months (Opitz 2015). The histological subtypes of MPM have validated prognostic significance: epithelioid variant has the most favorable prognosis with a median survival of approximately 13 months (Bibby 2016, Billé 2016, Baas 2020b) whereas, sarcomatoid variant is associated with the worst outcomes, with a median survival of only four months (van Zandwijk 2013, Bibby 2016, Baas 2020b).

The incurable nature of MPM, along with its poor prognosis and the limited treatment options result in severe emotional, physical, and psychosocial distress for the patient. Depression and anxiety negatively impact the quality of life and are commonplace in MPM patients compared to other tumors (Arber 2013). Symptoms such as chest pain, breathlessness, fatigue, and insomnia further contribute to diminished quality of life and reduced physical activity. Despite the progress in biomolecular research, the prognosis for MPM remains poor, with a median survival rate ranging from 7 to 12 months with palliative care or chemotherapy, respectively (Bianco 2018). Poor prognosis can be attributed to the lengthy latency period from the time of first exposure, resulting in late stage diagnosis, followed by factors such as rapid progression, high invasiveness, and the lack of effective treatment (Zhang 2015). Key factors in a poor prognosis include being male, older age, unfavorable histology (non-epithelial tumor type), along with the amount and type of asbestos exposure (Edwards 2000). A Danish study has shown that patients with epithelioid histology have better prognosis with both chemotherapy treatment or BSC alone (Panou 2021).

The true burden of MPM-related mortality is unknown due to the late-stage and misdiagnosis of the disease, although the peak of incidence will be reached this decade (Brcic 2020). The heavy use of asbestos in the past decade and the

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decade long latency period from asbestos exposure means that MPM continues to be a burden globally and particularly in European countries (Kameda 2014). MPM is therefore a largely preventable burden of illness that can be diminished through strict legislation and safety procedures to remove asbestos related contamination (Marsili 2016). However, since not all individuals exposed to asbestos develop MPM, there are likely genetics and other cofactors involved (Raffn 1989, Roushdy-Hammady 2001).

The financial aspect of MPM is also a substantial burden; the total cost in 2013 surmount to over € 18.6 million for 71 mesothelioma cases in Denmark, € 14.1 million for 54 cases in Norway, and € 32.2 million for 123 cases in Sweden (WHO Regional Office for Europe 2013).

5.1.5 Incidence of MPM based on histology

The pivotal trial CheckMate 743 examining nivolumab and ipilimumab versus platinum-based chemotherapy included first line unresectable malignant pleural mesothelioma patients with epithelioid or non-epithelioid (sarcomatoid (47%) or mixed/other (53%)) histology.

According NORDCAN, 147 patients are diagnosed annually with malignant mesothelioma in Denmark. Approximately 90% of these patients have malignant pleural mesothelioma. An estimated 30-35% of the malignant pleural mesothelioma patients are eligible for surgery and 1/3 of patients are expected to have a performance status ≥2. The yearly number of Danish patients with unresectable malignant pleural mesothelioma, eligible for nivolumab and ipilimumab is estimated below based on NORDCAN May 2020 and input from Dr. Jens Benn Sørensen, Rigshospitalet (Table 1).

Table 1: Estimated annual number of patients with unresectable malignant pleural mesothelioma in Denmark

	Epithelioid histology	Non-epithelioid histology
Malignant mesothelioma	147	
Non-pleural origin	-15	
Malignant pleural mesothelioma	79 (60%*)	53 (40%*)
Eligible for surgery **	-42	
Unresectable malignant pleural mesothelioma	54 (60%**)	36 (40%**)
Performance status ≥2	-30**	
Eligible for nivolumab and ipilimumab	36 (60%**)	24 (40%**)

* (Kirstein Jensen 2020); dialog with treating Danish clinician (Danish Clinical Expert 2021b)

Supporting data is derived from the Norwegian Cancer Registry from 2015 – 2019, where 391 new cases of MPM were identified (Cancer in Norway 2020). Based on this data, about 43% of all patients are diagnosed with epithelioid disease (and the rest, 57%, are biphasic, sarcomatoid or UNS) at first diagnosis of MPM. When removing patients with "unspecified histology" (UNS), 2/3 of the remaining patients are diagnosed with epithelioid histology and 1/3 with non-epithelioid histology (Table 2).

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Table 2: Proportion of histology according to the Cancer registry of Norway (2020)

Patients diagnosed 2015-2019 Source: Norwegian Cancer registry			Sorting sarcomatoid and mixed to non-epithelioid vs epithelioid only			Removing UNS; non-epithelioid vs epithelioid only		
Histology	**n**	**Proportion**	**Histology**	**n**	**Proportion**	**Histology**	**n**	**Proportion**
UNS	126	35%	**UNS**	126	35%	**Non-epithelioid**	80	34%
Sarcomatoid	51	14%	**Non-epithelioid**	80	22%			
Mixed (biphasic)	29	8%						
Epithelioid	155	43%	**Epithelioid**	155	43%	**Epithelioid**	155	66%
Total	361	100%	**Total**	361	100%	**Total**	235	100%

Source: Norwegian Cancer Registry 2020

Furthermore, in a study based on data from the Finnish Cancer registry, the National Worker's registry and the Compensation Centre Registry and the National Registry of Causes of Death, 1010 cases of MPM were analyzed based on their histology (Laaksonen 2019). In this study 31% of patients are diagnosed with epithelioid disease (and the rest, 69% were biphasic, sarcomatoid or NOS). When removing patients with "no other specified" (NOS), 2/3 of the remaining patients are diagnosed with epithelioid histology and 1/3 with non-epithelioid histology. See further details in Table 3.

Table 3: Proportion of histology according to the Finnish Cancer registry (Laaksonen 2019)

Patients diagnosed with MPM in Finland during 2000-2012			Sorting sarcomatoid and mixed to non-epithelioid vs epithelioid only			Removing UNS; non-epithelioid vs epithelioid only		
Histology	**n**	**Proportion**	**Histology**	**n**	**Proportion**	**Histology**	**n**	**Proportion**
NOS	540	53%	**NOS**	540	53%	**Non-epithelioid**	159	34%
Sarcomatoid	107	11%	**Non-epithelioid**	159	16%			
Mixed (biphasic)	52	5%						
Epithelioid	311	31%	**Epithelioid**	311	31%	**Epithelioid**	311	66%
Total	1 010	100%	**Total**	1 010	100%	**Total**	470	100%

Source: Laaksonen 2019

5.1.5.1 Estimated number of MPM patients eligible for treatment with nivolumab and ipilimumab in Denmark

Standard of care has not changed since approval of pemetrexed for malignant pleural mesothelioma in 2004 and is the same across histological subtypes. The number of eligible patients in Denmark is described in Figure 2 and the incidence and prevalence presented in Table 4 and Table 5 below.

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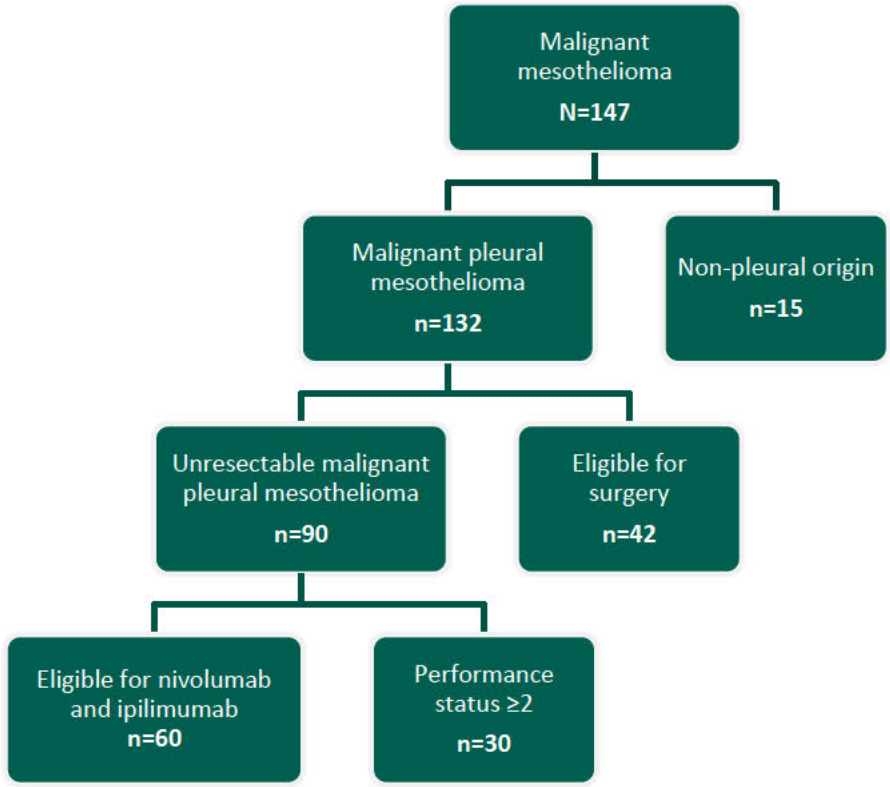
Figure 2: Overview of number of eligible patients in Denmark



Source: (Kirstein Jensen 2020); dialog with treating Danish clinician (Danish Clinical Expert 2021b)

Table 4: Incidence and prevalence of MPM in 2016

Year	2016
Incidence in Denmark	123
Prevalence in Denmark	224

Table 5: Estimated number of patients eligible for treatment

Year	2021	2022	2023	2024	2025
Number of patients in Denmark who are expected to use the pharmaceutical in the coming years	57	57	57	57	57

Note: expected estimates provided as 95% of the 60 patients eligible for nivolumab and ipilimumab.

5.1.6 Patient populations relevant for this application

5.1.6.1 Prevalence and incidence in Denmark

In Denmark, close to half of women diagnosed with malignant mesothelioma have been exposed to asbestos domestically (Langhoff 2014). According to the Cancer registry in Denmark, incidence rates in men have continuously risen from 1943-2009 with a rate of 1.76 per 100,000 whereas the rate in women remained relatively stable at a maximum of 0.5 per 100,000 (Bianco 2018).

The age adjusted incidence rates in Denmark (2012-16) is 1.7/100 000/year for men and 0.4/100 000/year for women. There are regional differences. The incidence rates for Northern Jutland is 2.6 for men and 0.6 for women as a

consequence of the presence of the asbestos cement manufacturing unit and two major shipyards. In addition, all asbestos import to Denmark was also shipped to Aalborg (NORDCAN, 2019). The latency from exposure of asbestos to occurrence of disease is 30-50 years (Baas 2015).

As a result, of general early prohibition of asbestos use the incidence rates were expected to be decreasing. However, in Denmark a decrease was still not seen in 2018 in fact a slight increase has been observed with 147 newly diagnosed malignant mesothelioma patients (Kirstein Jensen 2020). While 80% of malignant pleural mesothelioma patients are exposed to asbestos, not all of the asbestos exposed are diagnosed with malignant pleural mesothelioma (Raffn 1989). This indicates other causes or cofactors in the pathogenesis. Inherent genetic describes how certain genes influence the risk for developing malignant pleural mesothelioma (Panou 2018; Carbone 2019).

5.2 Current treatment options and choice of comparator(s)

5.2.1 Overview of treatments

Currently, there is no cure for MPM (Linton 2014). A study in Denmark has shown a 5-year survival of 32% with a median survival of 40.3 months for R0–1 patients, after pleurectomy; for R2 patients, the median survival was 32.7% (Sorensen 2021). Although the current treatment options for unresectable patients or for those who are not eligible for surgery due to comorbidities or old age may improve symptoms and prolong the life of patients with advanced MPM, their efficacy is very limited with only up to half of patients benefiting from the treatment and the median survival is approximately one year from diagnosis (Vogelzang 2003). As such, the goals of disease treatment with current options are limited to:

- Controlling symptoms
- Improving/maintaining quality of life
- Prolonging survival time (Vogelzang 2003, Zhang 2015, Schwartz 2017)

The limited efficacy of current treatments highlights the pressing need for a more effective therapy that prolongs survival and improves quality of life of MPM patients.

International evidence-based recommendations for the management of previously untreated unresectable MPM are similar across guidelines and include cisplatin in combination with antifolate (pemetrexed or raltitrexed) for patients with good PS ≤ 2) (Kindler 2018, Levitan 2018). The NCCN Panel recommends a combination regimen of nivolumab and ipilimumab for 1L systemic therapy in patients with unresectable MPM, the 2021 guideline states that the combination regimen is preferred for patients with biphasic or sarcomatoid histology and is also an option for patients with epithelioid histology (National Comprehensive Cancer Network 2020, Baas 2020a). The NCCN Panel also endorse the addition of bevacizumab to pemetrexed-platinum doublet based on evidence that it may improve survival in selected patients despite it not being approved in this indication by either the EMA or the FDA (Ceresoli 2013, Zalcman 2016). Alterative 1L options useful in certain circumstances include pemetrexed-carboplatin for those not eligible for cisplatin, gemcitabine-cisplatin or single agents vinorelbine and raltitrexed (in lieu of pemetrexed), none of which have been approved in MPM. For patients with a poor PS who cannot tolerate chemotherapy (PS ≥ 3), symptomatic treatment with best supportive care (BSC) encompassing steroids, analgesic drugs, bronchodilators and palliative radiotherapy is recommended (Baas 2015, Kindler 2018, Woolhouse 2018, National Comprehensive Cancer Network 2020).

For 2L treatment, NCCN guideline suggests administration of pemetrexed in patients who have not received it previously or those with good sustained response to 1L pemetrexed-platinum doublet (Figure 3 and Figure 4). For those who do not meet this criterion, entry into clinical trials or immunotherapy with nivolumab and ipilimumab based on results from the Mesothelioma Avastin Cisplatin (MAPS)-2 and INITIATE phase 2 trials or pembrolizumab monotherapy based on results from the KEYNOTE-028 phase 1b trial and a phase 2 trial is endorsed (Alley 2017, Metaxas 2018, Disselhorst 2019, Scherpereel 2019).

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5.2.2 Danish treatment guidelines

Platinum based chemotherapy; cis/carboplatin and pemetrexed, is current first line treatments offered to malignant pleural mesothelioma patients (PS=0-2). Vinorelbine is often used as second line treatment, though with limited response rate and survival gain (Sørensen JB 2019, Fennell 2021).

Only in selected cases of malignant pleural mesothelioma is surgery chosen as curative intended treatment, and it is only performed at Rigshospitalet in Denmark. According to Jens Benn Sørensen, Rigshospitalet, patients qualifying for surgery are characterized by epithelioid histology, or biphasic with no or maximum 50% sarcomatoid histology. The prognosis of epithelioid malignant pleural mesothelioma is significantly better than sarcomatoid malignant pleural mesothelioma with a median survival of 14-15 versus 7 months. Epithelioid histology and disease stage I and II are the most positive prognostic factors (Kirstein Jensen 2020).

Palliative radiation is used as pain relief for some patients dependent on the development of the disease. Prophylactic radiation has not been shown to have significant effect and is not recommended.

5.2.3 Choice of comparator(s)

As confirmed by the clinical experts, the relevant comparators for nivolumab plus ipilimumab for the treatment of 1L MPM in adults is pemetrexed in combination with either cisplatin or carboplatin—the comparators as also seen the clinical trial CheckMate 743.

5.2.4 Description of the comparator

Table 6 below provides a summary of the product and the relevant comparators.

Table 6: Product description of comparators

Product description	
Active ingredient	Pemetrexed
	Cisplatin
	Carboplatin

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Pharmaceutical form	Concentrate for solution for infusion
Posology	Carboplatin 10 mg/ml Cisplatin 1 mg/ml Pemetrexed 500 mg/vial
Dosing	**Pemetrexed/Cisplatin** Pemetrexed 500 mg/m2 with cisplatin at a dose of 75 mg/m² every 3 weeks for a maximum of 6 cycles. **Pemetrexed/Carboplatin** Pemetrexed at 500 mg/m2 with carboplatin at a dose of AUC 5every 3 weeks for a maximum of 6 cycles.
Method of administration	Infusion
Should the intervention be used with other drugs?	No
Treatment duration/Criteria for end of treatment	Until disease progression, unacceptable toxicity or completion a maximum of 6 cycles, or for 2 years for immunotherapy, whichever came first.
Required monitoring, under administration or during treatment period	Please see SmPC for each product*
Requirements of diagnostics or other tests	No

Source: *SmPC available at EMA (European Medicines Agency 2020b)

5.3 The intervention

Nivolumab, in combination with ipilimumab, is indicated for the 1L treatment of patients with unresectable MPM. Recommended dosing is 360 mg every 3 weeks (30-minute IV infusion) with ipilimumab 1 mg/kg every 6 weeks (30-minute IV infusion). The flat dosing for nivolumab is supported by pharmacometrics and clinical subgroup analyses by body weight (Tsao 2020); flat dosing reduces the complexity of dosing and results in less frequent hospital visits for patients and Health Care Professionals. In the analyses by Tsao et al. mean nivolumab exposures were predicted for patients in the CheckMate-743 trial for the combination of ipilimumab 1 mg/kg Q6W with, nivolumab 3 mg/kg every 2 weeks, nivolumab 240 mg every 2 weeks, and nivolumab 360 mg every 3 weeks.

While CheckMate-743 evaluated nivolumab 3 mg/kg every 2 weeks plus ipilimumab 1 mg/kg every 6 weeks, the European Commission (EC) granted approval for the nivolumab 360 mg every 3 weeks (nivolumab flat dose) in combination with ipilimumab on June 1st 2021 (Bristol-Myers Squibb 2021).

An overview of nivolumab and ipilimumab is presented in Table 7 below.

Table 7: Product description of nivolumab and ipilimumab

Product description	
Name of preparation/pharmaceutical	OPDIVO® Yervoy®
Active ingredient	Nivolumab Ipilimumab
Pharmaceutical form	Concentrate for solution for infusion
Posology	Nivolumab (10 mg/mL): Single-use vials 40 mg/4 mL 100 mg/10 mL 240 mg/24 mL Ipilimumab (5.0 mg/mL): Single-use vials 50 mg/mL or 200 mg/mL
Method of administration	Nivolumab 360 mg every 3 weeks (30-minute IV infusion) with ipilimumab 1 mg/kg every 6 weeks (30-minute IV infusion)
Should the intervention be used with other drugs?	No
Treatment duration/Criteria for end of treatment	Treatment is recommended until disease progression, unacceptable toxicity, or up to 24 months in patients. N+I treatment beyond initial investigator-assessed RECIST 1.1 defined progression was permitted if the subject had investigator assessed clinical benefit and was tolerating nivolumab and ipilimumab
Required monitoring, under administration or during treatment period	Patients should be monitored continuously (at least up to 5 months after the last dose), as an adverse reaction with nivolumab may occur at any time during or after discontinuation of therapy
Requirements of diagnostics or other tests	No testing required

Abbreviations: IV=intravenous; RECIST=The Response Evaluation Criteria in Solid Tumors
Source: (Bristol-Myers Squibb Company 2018)

5.3.1 Mechanism of action and proof of concept: nivolumab and ipilimumab

Nivolumab and ipilimumab are immune checkpoint inhibitors with distinct but complementary mechanisms of action, targeting PD-1 and CTLA-4 (Figure 5) (Weber 2009, Pardoll 2012). Ipilimumab (anti-CTLA-4) induces de novo anti-tumor T-cell responses by enabling adaptation to the evolving tumor, promotes the emergence of memory T cells and induces a compensatory increase in tumor PD-L1 (Pardoll 2012, Das 2015, Wei 2018, Wei 2019). Whilst nivolumab (anti-PD-1) restores anti-tumor T-cell function by enhancing pre-existing T-cell response and increasing cytokine production (Hamanishi 2007, Brahmer 2010, Wang 2014).

Combined nivolumab (anti-PD-1) and ipilimumab (anti-CTLA-4) mediated inhibition results in enhanced T-cell function that is greater than the effects of either antibody alone. In murine syngeneic tumor models, dual blockade of PD-1 and CTLA-4 resulted in increased anti-tumor activity (Food and Drug Administration 2020a).

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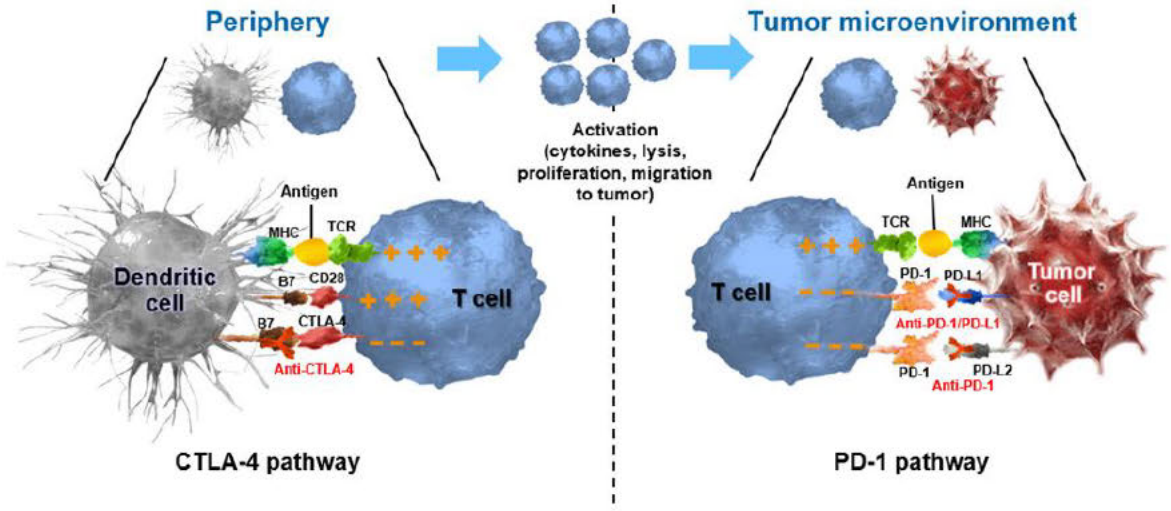
Figure 5: Nivolumab and ipilimumab: mechanism of action for dual immune checkpoint blockade

Ipilimumab (anti-CTLA-4)	Nivolumab (anti-PD-1)
Induces de novo anti-tumor T-cell responses (Pardoll 2012, Wei 2018)	Restores anti-tumor T-cell function(Brahmer 2010, Wang 2014)
Enables adaptation to evolve tumor (Wei 2018, Wei 2019) Promotes emergence of memory T cells (Das 2015) Causes compensatory increase in tumor PD-L1 (Wei 2018)	Enhances pre-existing T-cell response (Wang 2014) Increase cytokine production (Hamanishi 2007)



Abbreviations: CD28: cluster of differentiation 28; CTLA-4: cytotoxic T-lymphocyte-associated protein 4; MHC: major histocompatibility complex; PD-1: programmed cell death-1; PD-L1: programmed cell death-ligand 1; PD-L2: programmed cell death-ligand 2; TCR: T-cell receptor
Source: (Hamanishi 2007, Weber 2009, Brahmer 2010, Pardoll 2012, Wang 2014, Das 2015, Wei 2018, Wei 2019)

Nivolumab and ipilimumab have a history of demonstrating clinically durable survival benefit in several solid tumors. Dual checkpoint blockade with nivolumab and ipilimumab met its primary endpoints in Phase 3 clinical trials in previously untreated metastatic melanoma (CheckMate067), advanced renal cell carcinoma (CheckMate214) and non-small cell lung cancer (CheckMate227[1] and CheckMate9LA), resulting in approvals for these indications by the US FDA (excluding CheckMate9LA) and the EMA (Larkin 2015, Motzer 2018, Hellmann 2019, Bristol-Myers Squibb 2020a, European Medicines Agency 2020b, Paz-Ares 2021).

In metastatic melanoma (CheckMate 067), nivolumab and ipilimumab demonstrated durable responses and long-term survival benefits over IO monotherapy (Wolchok 2021) The median duration of response (mDOR) had not been reached in the nivolumab and ipilimumab and nivolumab groups and was 19.2 months in the ipilimumab group at 6.5 year study update shown at ASCO 2021. Median overall survival (mOS) and median progression free survival (mPFS) at 6.5 year follow-up in both nivolumab groups demonstrated improvements compared to the ipilimumab group: a mOS of over 72.1 (95% CI, 38.2-NR) and a mPFS of 11.5 (95% CI, 8.7-19.3) months in the nivolumab and ipilimumab group, 36.9 (95% CI, 28.2-58.7) and 6.9 (95% CI, 5.1-10.2) months in the nivolumab only group, and 19.9 (95% CI, 16.8-24.6) and 2.9 (95% CI, 2.8-3.2) months in the ipilimumab only group (Wolchok 2021) Although the trial was not designed for a formal statistical comparison between both nivolumab groups, a pre-specified descriptive analyses showed clear numerical trends favoring OS (HR: 0.84, 95% CI, 0.67-1.04) and PFS (HR: 0.81, 95% CI, 0.64-1,03) in the combination group as compared to nivolumab alone, which demonstrates the contribution of components (Figure 6) (Wolchok 2021).

[1] The CheckMate277 study based non-small cell lung cancer indication has not recieved approval by the US FDA and the EMA.

In addition, nivolumab and ipilimumab treatment lead to a median treatment-free interval (time from end of first-line to start of second-line therapy) 12-14 times longer than nivolumab and ipilimumab monotherapies, respectively (27.6 months vs. 2.3 months and 1.9 months, respectively), and was well-tolerated, as patients maintained the same level of health-related quality of life (HRQoL) at 5-year follow-up relative to that at baseline (Larkin 2019). The superior efficacy observed with nivolumab and ipilimumab as compared with nivolumab alone in CheckMate 067 was accompanied with a higher incidence of Grade 3/4 treatment-related adverse events (TRAEs) in the combination arm; however, these typically resolved in under 4 weeks and patients' HR-QoL was maintained over the 5-year follow-up period, even after treatment discontinuation (Larkin 2019).

The randomized phase 3 CheckMate 227 Part 1 study for first line (1L); NIVO + IPI (same dose as in Checkmate 743) demonstrated durable long-term OS vs. chemotherapy (chemo) in patients with advanced non-small cell lung cancer (NSCLC) regardless of programmed death ligand 1 (PD-L1) expression or histology. A recent 4-year study update demonstrated a 24% reduction in the risk of death, compared to PDC (platinum doublet chemotherapy) alone, in NSCLC patients with PD-L1 expression ≥1% (HR: 0.76, 95% CI: 0.65–0.90) (Figure 7) (Ramalingam 2020, Paz-Ares 2021). The median OS was 17.1 months in the nivolumab and ipilimumab group and 15.7 months in the NIVO monotherapy group compared to 14.9 months in the PDC group; 4-year OS rates were 29%, 21%, and 18%, respectively (Figure 7) (Paz-Ares 2021) (Ramalingam 2020). Although the trial was not designed for a formal statistical comparison between both nivolumab groups, exploratory analyses indicated that the nivolumab and ipilimumab combination was associated with numerical benefit across key efficacy metrics (OS, PFS, ORR, and DOR) compared with nivolumab monotherapy in PD-L1 ≥1% patients (Hellmann 2019, Paz-Ares 2021).

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As shown for melanoma (Checkmate 067) (Hodi 2018) as well as in RCC (Checkmate 214) (Motzer 2019), post-hoc analysis of Checkmate 227, showed that NSCLC patients who had a TRAE leading to discontinuation of NIVO + IPI still had long-term benefits, Figure 8 (Paz-Ares 2021). The NIVO+IPI responders who had a TRAE leading to discontinuation had a 53% chance of maintaining their responses for ≥ 3 years after treatment discontinuation(Paz-Ares 2021).

In the randomized, open-label, phase 3 CheckMate 9LA study, 1L NIVO + IPI + chemo significantly improved OS (primary endpoint), PFS, and ORR compared to chemo alone in patients with advanced NSCLC regardless of PD-L1 or histology, with a safety profile that was manageable with standard protocols (Reck 2021). A recent updated data-cut demonstrated continued efficacy and safety results (minimum OS follow-up, 24.4 months) from CheckMate 9LA, and a post hoc analysis in patients who discontinued NIVO + IPI + chemo due to treatment-related adverse events. Similar to the CheckMate 227 study, Checkmate 9LA, showed that NSCLC patients who had a TRAE leading to discontinuation of NIVO + IPI + chemo still had an OS benefits (Reck 2021).

Taken together, these clinical results reinforce the positive benefit risk profile of dual immunotherapy also after treatment discontinuation and support the use of NIVO + IPI, in several tumors including melanoma, RCC and patients with advanced NSCLC.

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[redacted]

5.3.2 Pack size and price

The strength, pack size, and pharmacy selling price per pack for nivolumab and ipilimumab are included in Table 8 below.

Table 8: The strength, pack size, and pharmacy selling price per pack

Treatment	Strength	Pack size	Price per pack (PPP, DKK)
Nivolumab	10 mg/ml	4 mL	3 785.32
	10 mg/ml	10 mL	9 403.31
	10 mg/ml	24 mL	22 657.94
Ipilimumab	5 mg/ml	10 mL	26 311.31
	5 mg/ml	40 mL	105 010.82

Abbreviations: DKK, Danish krone; PPP, pharmacy purchase price; VAT, value added tax.
Source: (Medicinpriser.dk 2021)

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6. Literature search and identification of efficacy and safety studies

The clinical trial CheckMate 743, provide a head-to-head comparison of nivolumab plus ipilimumab to the comparators most prevalent in Denmark—pemetrexed in combination with either cisplatin or carboplatin. However, a supportive systematic literature was conducted to identify randomized-controlled trials (RCT) involving nivolumab plus ipilimumab and relevant comparators for the treatment of first line treatment of MPM. The SLR was conducted in October 2020, where 4690 papers were identified, or which 81 publications corresponding to 28 unique clinical trials. As the outcomes of the literature review is supportive, it has not been used in the clinical and economic sections of our dossier and is merely presented below for completeness.

Additional insight into the SLR is presented in 13 . For a comprehensive overview of the SLR, please the separate Appendix 25.

6.1 Identification and selection of relevant studies

The search terms comprised disease terms, a study design filter and intervention terms. All identified studies were evaluated against predefined eligibility criteria. For RCTs deemed eligible, data relating to the study design, enrolled patients, and study outcomes were extracted. Each RCT was rated according to published criteria examining its internal and external validity. The literature review did not limit the inclusion of studies based on the treatments being evaluated, i.e., all pharmacological interventions (approved + investigational) were included. The last searches were carried out on 5 OCT 2020. Searches were restricted to the English language.

6.2 Population

The patient population of interest in the review comprises adult patients with malignant pleural mesothelioma (MPM) of any race, ethnicity, or gender. Studies which assess a population comprising both adults and children will be included only if sub-group data for an adult population is reported. Studies were not excluded based on gender, race, or ethnicity.

6.3 Eligibility criteria

There was no restriction on the basis of study design. Studies that are likely to report information in line with the objectives of the reviews are considered for inclusion.

All studies reporting clinical data, costs, resource use, utilities, treatment pattern data, PROs, and economic evaluations were included in the systematic review irrespective of the line of therapy, i.e., first-line treatment, second-and-subsequent lines of treatment.

The review focused on all the approved and investigational systemic therapies utilized in the treatment of unresectable pleural mesothelioma. Studies evaluating the best supportive care/ active symptom control were also be included. Studies evaluating radiotherapy or surgery alone were not be of interest to the review and were be excluded. Studies assessing surgery followed by chemotherapy were be included. Studies not evaluating any intervention but providing cost, resource use, patient-reported outcomes, health utilities, and economic evaluation data for MPM (the disease in general, not specific to treatment) were also included in the review.

Eligibility criteria were specified in terms of population, intervention and comparators, outcomes and study design (PICOS).

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6.4 Data sources

Searches were carried out on the following key biomedical databases: Excerpta Medica Database (Embase®), Medical Literature Analysis and Retrieval System Online (MEDLINE®), MEDLINE in-process, Cochrane Central Register of Controlled Trials (CENTRAL), and Cochrane Database of Systematic Reviews (CDSR).

MEDLINE® and Embase® were searched using the embase.com interface, while the MEDLINE in-process was searched via PubMed. CENTRAL and CDSR were searched using the Cochrane Library.

Supplementary searches of the following conference proceedings were reported for the previous three years (2018-20): American society of clinical oncology (ASCO), European society for medical oncology (ESMO), American Association for cancer research (AACR), International Society for Pharmacoeconomics and Outcomes Research (ISPOR), World Conference on Lung Cancer (WCLC), European Lung Cancer Congress (ELCC), and International Mesothelioma Interest Group (IMIG).

Bibliographic searching of included studies and relevant literature reviews were also conducted, to supplement the evidence retrieved from the biomedical databases.

6.5 Study selection

All the citations were screened by two independent reviewers, followed by a quality check by a third independent reviewer. The first screening stage included a review of citations based on their titles and abstracts. Citations that do not match the eligibility criteria were excluded at the first-pass stage. Duplicates of citations (due to the overlap in the coverage of databases) were excluded at the first-pass stage. Full-text copies of all the references that potentially met the eligibility criteria were obtained.

After the completion of first stage screening, the full texts of relevant studies were examined in more detail to determine a final list of included studies. All the citations were screened by two independent reviewers, followed by a quality check by a third independent reviewer.

Data were extracted by two independent reviewers, followed by a quality check by a third independent reviewer.

The study PRSIMA flow diagram is provided in Figure 9 below.

Figure 9: PRISMA flow diagram for studies assessing treatments for malignant pleural mesothelioma

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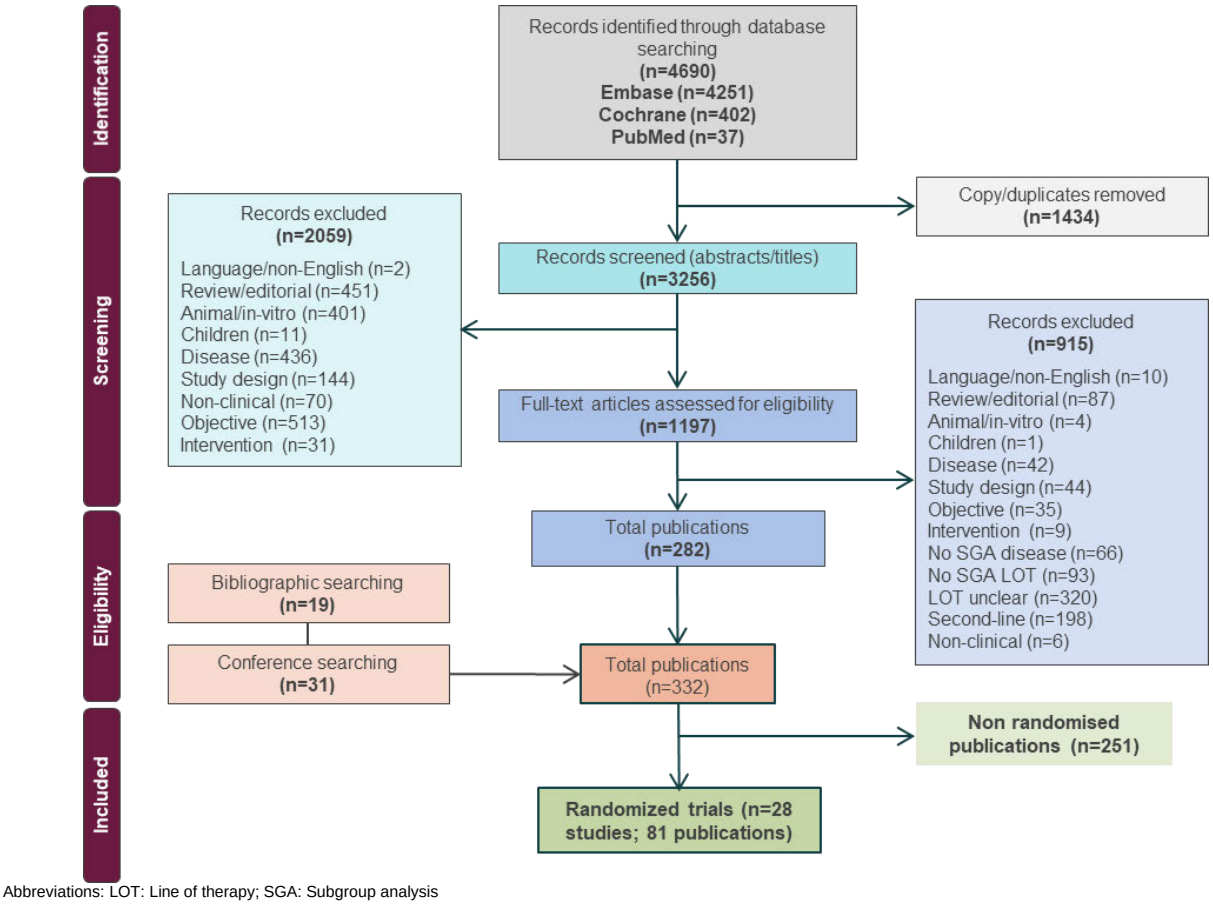

Abbreviations: LOT: Line of therapy; SGA: Subgroup analysis

6.6 Strengths and limitations of SLR

Systematic reviews involve explicit, transparent methods which are clearly stated and reproducible (minimize bias by using objective, pre-defined inclusion criteria). The robustness of the review is primarily determined by (i) the quality and (ii) the data reported in the eligible studies. Limitations concerning the systematic review and evidence synthesis include the limitations of using published data. The robustness of the evaluation may be compromised by the internal validity of the identified studies. However, to assess this, studies are critically appraised for potential bias using appropriate methodology.

6.7 List of relevant studies

The clinical trial CheckMate 743 provides a head-to-head comparison of nivolumab plus ipilimumab to the comparators most prevalent in Denmark—pemetrexed in combination with either cisplatin or carboplatin. Thus, the CheckMate 743 trial is the main relevant study for the presentation and comparison of efficacy and safety data of nivolumab plus ipilimumab compared to pemetrexed and cisplatin or carboplatin for first line therapy for unresectable MPM. For detailed information about included studies, refer to 14.

Additional insight into the SLR is presented in Appendix 25.

7. Efficacy and safety

7.1 Efficacy and safety of nivolumab plus ipilimumab compared to pemetrexed and cisplatin or carboplatin for first line therapy for unresectable malignant pleural mesothelioma (MPM)

7.1.1 Relevant study: CheckMate 743

CheckMate 743 (NCT02899299) is a phase 3, randomized, global, multicenter, open label trial of nivolumab and ipilimumab versus pemetrexed and cisplatin or carboplatin as a first line therapy for unresectable malignant pleural mesothelioma (MPM). An overview of the trial is presented in Table 9 below.

Table 9: CheckMate 743 study Overview

Trial name	CheckMate 743
NCT number	NCT02899299
Objectives	The purpose of this study is to determine whether nivolumab and ipilimumab combined is more effective than platinum-doublet chemotherapy by itself when treating unresectable malignant pleural mesothelioma as first-line treatment
Publications	Published online January 21, 2021 in *Lancet* https://doi.org/10.1016/ S0140-6736(20)32714-8
Study design	Open-label, multicenter, randomized phase 3 trial conducted to evaluate nivolumab and ipilimumab versus platinum-doublet chemotherapy alone as a first-line treatment in patients with unresectable malignant pleural mesothelioma In CM-743, patients were randomized (1:1) to one of the following arms: • Nivolumab 3 mg/Kg Q2W plus ipilimumab 1 mg/kg Q6W • Cisplatin (75 mg/m^2) or carboplatin (5 AUC) plus pemetrexed (500mg/m^2 Q3W for 6 cycles In both arms of the trial, patients were stratified according to tumor histology (epithelioid vs non-epithelioid) as well as gender (male vs female). All treatments continued until disease progression, unacceptable toxicity, or completion of study as per protocol (defined as treatment for up to 2 years for immunotherapy). Crossover between treatment arms within the study was not permitted. Tumour assessments were done 6 weeks after the date of the first dose of study drug and then every 6 weeks for the first 12 months. After 12 months, tumours were assessed every 12 weeks until blinded independent central review (BICR) confirmed disease progression per mRECIST or RECIST version 1.1 criteria, or both.
Follow-up	Minimum follow-up: 22.1 months Median follow-up: 29.7 months
Study population	Malignant pleural mesothelioma that was not amenable to curative therapy (surgery with or without chemotherapy) and an Eastern Cooperative Oncology Group performance status of 0 or 1, of epithelioid or non-epithelioid histology. **Key inclusion criteria:** • Male and female subjects (≥18 years of age) • Histologically proven diagnosis of MPM, with determination of epithelioid vs. non-epithelioid histology

	• Advanced unresectable disease that is not amenable to therapy with curative intent (surgery with or without chemotherapy). Subjects who refused potentially curative surgery were ineligible • Available (archival and/or fresh) pathological samples for centralized PD-L1 IHC testing during the screening period • Prior palliative radiotherapy was acceptable, but at least 14 days must have passed since the administration of the radiotherapy and all signs of toxicity must have remitted • ECOG PS of 0-1 • Measurable disease, defined as at least one lesion measured in up to two positions at three separate levels on transverse cuts of CT scan that is suitable for repeated assessment using adapted mRECIST for pleural mesothelioma • Adequate hematological, renal and hepatic functions **Key exclusion criteria:** • Primitive peritoneal, pericardial and tunica vaginalis testis mesotheliomas • Brain metastasis, except if surgically resected or treated with stereotaxic radiotherapy with no evolution within the 3 months before inclusion, and asymptomatic. In addition, subjects must be either off corticosteroids, or on a stable or decreasing dose of ≤10 mg daily prednisone (or equivalent) for at least 2 weeks prior to randomization • Prior treatment with adjuvant or neoadjuvant chemotherapy; radical pleuropneumonectomy with or without intensity modulated radiotherapy, or non-palliative radiotherapy • Prior intraoperative or intracavitary chemotherapy for pleural mesothelioma • Prior treatment with an anti-PD-1, anti-PD-L1, anti-PD-L2, anti-CTLA-4 antibody, or any other antibody or drug specifically targeting T-cell co-stimulation or checkpoint pathways • History of chronic inflammatory or autoimmune disease • Concurrent or prior malignancy requiring or anticipated to require concurrent intervention • Subjects with interstitial lung disease that is symptomatic or may interfere with the detection or management of suspected drug-related pulmonary toxicity
Intervention (n=303)	• Nivolumab administered at 3 mg/kg Q2W and Ipilimumab at 1 mg/kg Q6W
Comparator (n=302)	• Cisplatin (75 mg/m2) or carboplatin (AUC 5) plus pemetrexed (500 mg/m2) Q3W for 6 cycles
Primary, secondary, and exploratory endpoints	The primary endpoint included: • Overall survival (OS) The secondary endpoints included: • ORR, DCR, and PFS by BICR • PD-L1 expression as a predictive biomarker
Pre-defined subgroups	The study is stratified by histology (epithelioid vs non-epithelioid) and sex

Abbreviations: ECOG, Eastern Cooperative Oncology Group; IV, Intravenous; MPM, malignant pleural mesothelioma; TTR, time to response ; OS, Overall survival; ORR, objective response rate; DCR, disease control rate; PFS, progression free survival; PD-L1, programmed death-ligand 1.
Source: (Baas 2021); ClinicalTrials.gov: NCT02899299.

7.1.1.1 Study design

CheckMate 743 (NCT02899299) is a phase 3, randomized, multicentre, open label trial investigating the effectiveness and tolerability of nivolumab and ipilimumab versus chemotherapy (pemetrexed and cisplatin or carboplatin) as a first line therapy for unresectable MPM (Figure 10). The global study recruited patients with previously untreated, histologically confirmed unresectable MPM from 103 hospitals located in Australia, Belgium, Brazil, Chile, China, Colombia, France, Germany, Greece, Italy, Japan, Mexico, Netherlands, Poland, Romania, Russia, South Africa, Switzerland, Turkey, U.K. and U.S.A.

Eligible patients were 18 or over (all sexes) with histologically confirmed unresectable MPM with ECOG performance status of 0 or 1. Any previous palliative radiotherapy was completed 2 weeks or longer before study initiation, with no residual signs of toxicity. Along with acceptable blood work, tumor samples were taken from patients for programmed cell death ligand 1 (PD-L1) testing. The exclusion criteria included brain metastases (unless treated and asymptomatic for at least 3 months before study inclusion), autoimmune disease and if previous treatments with drugs that target T-cell costimulation or checkpoint pathways were used.

When CheckMate 743 trial was designed, there was emerging evidence that anti-PD-1 and -CTLA-4 combinations (nivolumab and ipilimumab) could provide higher benefit to single-agent immunotherapy in multiple tumors. Data from non-small cell lung cancer (NSCLC) (CheckMate 012) showed that nivolumab and ipilimumab had better efficacy compared to nivolumab monotherapy in 1L NSCLC (Hellmann 2017). In mesothelioma, data from DETERMINE study did not show an improvement of progression-free survival (PFS) or OS with tremelimumab (CTLA-4 inhibitor) vs placebo in previously treated patients; these data were available by the time CheckMate 743 was designed (Maio 2017).

In addition, the randomized, phase 3 PROMISE-meso trial also failed to show an improved median OS and PFS among relapsed MPM patients for pembrolizumab over single-agent chemotherapy (Popat 2020). Further, the MAPS-2 study, a non-comparative randomized phase 2 study in pre-treated MPM of nivolumab and ipilimumab vs nivolumab was ongoing during the study design of CheckMate 743 and was expected to provide data to support the contribution of components (Scherpereel 2019).

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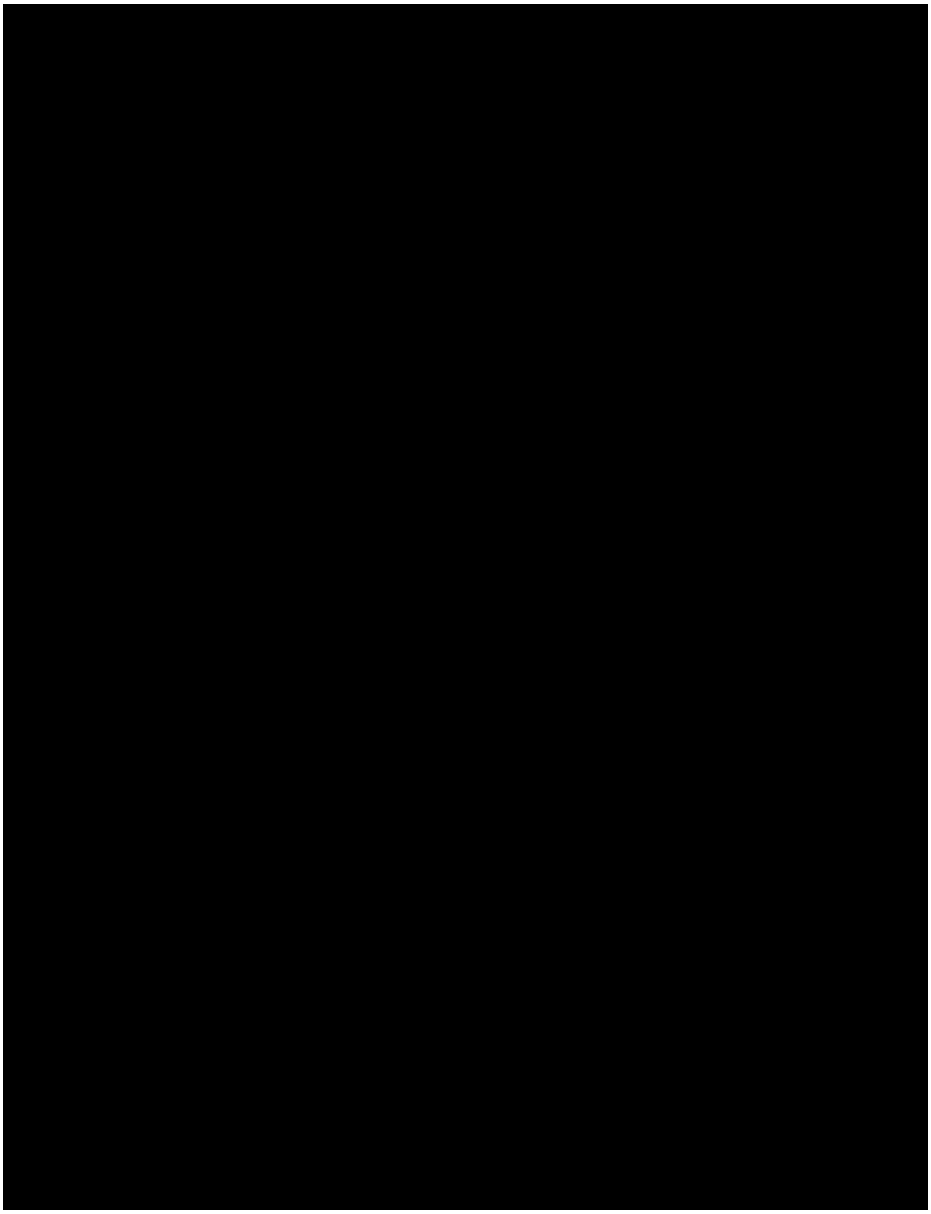

In total, 713 patients were enrolled between November 2016 and April 2018 of which 605 were randomized (1:1 ratio) to either the experimental arm and given nivolumab (3 mg/kg IV once every 2 weeks) plus ipilimumab (1 mg/kg) intravenously once every 6 weeks) for up to 2 years, or to the comparator arm, where chemotherapy was administered (pemetrexed [500 mg/m² intravenously] plus cisplatin [75 mg/m² IV] or carboplatin [area under the concentration-time curve 5 mg/mL per min intravenously]). Data from the phase 2, randomized, non-comparative MAPS-2 trial, showed that this dose and schedule was active and tolerable in second-line (2L) MPM. The dose and schedule were also shown to be tolerable in NSCLC (Checkmate 012 & CheckMate 227), with a well-established safety profile. In addition, nivolumab (3mg/kg Q2W) and ipilimumab (1mg/Kg Q6W) demonstrated superior OS in 1L NSCLC patients expressing PD-L1 ≥1% in CheckMate 227 (primary endpoint) and PD-L1<1% (pre-specified descriptive analysis) (Hellmann 2017, Hellmann 2019). (Hellmann 2017, Hellmann 2019)

Patients were stratified by sex and histology (epithelial versus non-epithelioid, including sarcomatoid and mixed subtypes). The tumor assessments were conducted six weeks after the first dose of the study drug and then every six weeks for the first year, following which assessments were done every twelve weeks until blinded independent central

review (BICR) confirmed disease progression according to the modified Response Evaluation Criteria in Solid Tumors (mRECIST) and/or Response evaluation criteria in solid tumors (RECIST) version 1.1 criteria (Baas 2021).

From the time of Checkmate 743 database lock (April 3, 2020), 5 (2%) of 300 patients who received nivolumab and ipilimumab remained on treatment while none remained on treatment in the chemotherapy group, as was shown in Figure 10. The main cause of discontinuation of treatment in the nivolumab and ipilimumab group was progression of disease (182 of 300 patients, 61%) and drug toxicity. Within the chemotherapy group, 176 of 284 patients (62%) completed all six cycles and 44 patients (16%) discontinued because of disease progression or due to study drug toxicity (24 patients, 8%). The median duration of treatment was higher in the nivolumab and ipilimumab group, at 5.6 months (IQR 2.0–11.4) compared to 3.5 months (IQR 2.7–3.7) in the chemotherapy group (Baas 2021).

7.1.1.2 Study endpoints

The trial's primary endpoint measured overall survival of all patients who were randomly assigned to treatment. The OS was defined as the date of randomization to the date of death (due to any cause).

Secondary endpoints included:

- Objective response rate (ORR) defined as the proportion of all randomized subjects whose best overall response (BOR) was either a complete response (CR) or partial response (PR) per adapted mRECIST and/or response evaluation criteria in solid tumors (RECIST) 1.1 criteria assessed by blinded independent central review (BICR)
- Disease control rate (DCR) defined as the proportion of all randomized subjects whose BOR was CR, PR, or stable disease (SD) per adapted mRECIST and/or RECIST 1.1 criteria assessed by BICR
- Progression free survival (PFS) defined as the time from randomization to the date of the first documented tumor progression (per adapted m-RECIST and/or RECIST 1.1 criteria) as assessed by BICR or death due to any cause
- Composite correlation of PD-L1 expression level and efficacy determined by ORR, PFS, and OS (PD-L1 expression level is defined as the percent of tumor cells demonstrating plasma membrane PD-L1 staining of any intensity using the validated DAKO PD-L1 IHC assay)

On April 25, 2019, the study protocol was revised to change PFS from a co-primary to a secondary endpoint, based on guidance from the US FDA. Briefly, the US FDA guidance document explains that radiographic tumour assessments in MPM can be imprecise because of the absence of distinguishable tumour margins over time and successive computed tomography (CT) evaluations (Baas 2021). Additionally, based on previous trials with immuno-oncology regimens, it has been observed that objective response rate (ORR) and PFS may not adequately characterize the long-term benefit of immuno-oncology treatment. Further, PFS has not been statistically validated as a surrogate endpoint for survival in many settings (Wilson 2015, FDA 2018) and, therefore, may not be a reliable endpoint to assess clinical benefit with immuno-oncology regimens.

Exploratory endpoints:

- Incidence rates of AEs, SAEs, deaths, and laboratory abnormalities
- Serum concentrations of nivolumab and ipilimumab to explore exposure-safety and exposure-efficacy relationships
- Overall health status and health utility using the 3-level version of the EQ-5D-3L (Rabin 2003), VAS and UI, respectively
- Disease-related symptom deterioration/improvement rate evaluated by mesothelioma adaption of Lung Cancer Symptom Scale-Mesothelioma (LCSS-Meso)
- Healthcare resource utilization
- The relationship of candidate biomarkers to clinical response.

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7.1.1.3 Patients baseline characteristics

All patients who were recruited into the study had unresectable MPM and the baseline characteristics between the two groups were well balanced. Out of the 605 participants, 303 were assigned on to nivolumab and ipilimumab and 302 were on chemotherapy. 467 patients (77%) were male and the median age was 69 years (IQR 64-75). Overall, 456 patients (75%) had epithelioid and 149 patients (25%) had non-epithelioid (included 47% sarcomatoid and 53% mixed/other in the nivolumab and ipilimumab arm and 48% and 52%, respectively) tumor histology (Baas 2021) (Table 10).

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Table 10: Baseline characteristics CheckMate 743

	Nivolumab + ipilimumab group (n=303)	Chemotherapy group (n=302)
Age, years	69 (65-75)	69 (62-75)
<65	71 (23%)	96 (32%)
≥65 to <75	154 (51%)	127 (42%)
≥75	78 (26%)	79 (26%)
Sex		
Male	234 (77%)	233 (77%)
Female	69 (23%)	69 (23%)
Region		
North America	32 (11%)	27 (95)
Europe	177 (58%)	175 (58%)
Asia	26 (9%)	39 (13%)
ROW*	68 (22%)	61 (20%)
ECOG performance status†		
0	114 (38%)	128 (42%)
1	189 (62%)	173 (57%)
Smoking Status		
Current or former	173 (57%)	171 (57%)
Never	127 (42%)	122 (40%)
Unknown	3 (1%)	9 (3%)
Histology		
Epithelioid	229 (76%)	227 (75%)
Non-epithelioid	74 (24%)	75 (25%)
Sarcomatoid	35 (12%)	36 (12%)
Mixed or other	39 (13%)	39 (13%)
Stage		
1	12 (4%)	20 (7%)
2	23 (8%)	22 (7%)
3	103 (34%)	106 (35%)
4	160 (53%)	149 (49%)
Not reported	5 (2%)	5(2%)
Previous cancer therapy		
Radiotherapy‡	29 (10%)	28 (9%)
Systemic therapy§	1 (‹1%)	0
PD-L1 status		
Quantifiable	289 (95%)	297 (98%)
<1%¶	57/289 (20%)	78/297 (26%)
≥1%¶	232/289 (80%)	219/297 (74%)

Data are median (IQR) or n (%). PD-L1=programmed cell death ligand 1. *Includes Australia, Brazil, Chile, and South Africa. †On a score of 0 to 5, with higher scores indicating greater disability. One patient in the chemotherapy group had a baseline Eastern Cooperative Oncology Group performance status of 2 (protocol deviation). ‡Previous radiotherapy was provided for palliative support, pain management, or prophylactic track irradiation for tumour biopsy. §Due to incorrect data entry, one patient was reported as having previous systemic cancer therapy in the nivolumab and ipilimumab group. ¶Calculated as a proportion of quantifiable patients.
Abbreviations: ECOG, Eastern cooperative oncology group; PD-L1, Programmed death-ligand 1; ROW, Rest of the world.
Source: (Baas 2021)

7.1.2 Efficacy and safety – results per study

7.1.2.1 Study 1: CheckMate 743

The purpose of the CheckMate743 trial was to test the effectiveness and tolerability of the combination of nivolumab and ipilimumab compared to pemetrexed and cisplatin or carboplatin in patients with unresectable pleural mesothelioma. A sample of approximately 600 patients randomly assigned to treatment with a death toll of 473 was calculated to provide 90% power to detect a target hazard ratio (HR) of 0.72 with a two-sided type 1 error of 0.05, through the use of a log-rank test (Baas 2021).

7.1.2.1.1 Overall survival

The prespecified interim analysis was performed at the database lock in April 3, 2020, and it showed that the study met its primary endpoint. At a minimum follow-up of 22.1 months, the median overall survival (OS) was 18.1 months (95% CI 16.8-21.4) in the nivolumab and ipilimumab group versus 14.1 months (95% CI 12.4-16.2) in the chemotherapy group (stratified HR 0.74, 96.6% CI 0.60-0.91; p=0.0002) in all randomized patients (Figure 11A) (Baas 2021). The p-value for the time-dependent covariate was 0.9646, indicating that there was no evidence of a non-constant treatment effect over time. In the nivolumab and ipilimumab group, the OS rates at 12 months were 68% (95% CI 62.3–72.8) versus 58% (95% CI 51.7–63.2) in the chemotherapy group, thus, the study drugs nivolumab in combination with ipilimumab showed notable improvements in prolonging survival in patients compared to chemotherapy alone, regardless of the tumor histology (Figure 11B- Figure 11C) (Baas 2021). The observed delayed separation of the curve in the first 3 – 4 months is consistent with previous studies evaluating immunotherapy vs chemotherapy in other tumors, which could be due to the mechanism of action of immunotherapy compared to chemotherapy, targeting the patient's immune system rather than directly attacking the tumor (Quinn 2020). In addition, the plateau known with nivolumab and ipilimumab treatment in other indications—Melanoma (trial CheckMate 067), RCC (CheckMate 214) and NSCLC (CheckMate 227)—has not yet established in CheckMate 743, likely requiring a longer follow-up to see such an effect.

This combination showed an improved OS for both histologies included which is remarkable for non-epithelioid MPM, traditionally associated to poor responses to chemotherapy. Some evidence was seen of higher relative treatment effect in patients with non-epithelioid histology (HR 0.46, [95% CI 0.31–0.68]) than in those with the epithelioid subtype (0.86 [0.69–1.08]). However, the results are positive for the combination overall with consistent nivolumab and ipilimumab performance between histologies, showing clinically meaningful survival improvements across both groups. . In the primary disclosure, nivolumab and ipilimumab median OS [mOS] was 18.7 months for epithelioid subgroup and 18.1 months in non-epithelioid subgroup; 1-year OS rates for epithelioid vs. non-epithelioid were 69% vs 63%, respectively; 2-year OS rates were 42% vs 38%. Chemotherapy did not perform as well in the non-epithelioid patients with a mOS of 16.5 months and 8.8 months, respectively; 1-year OS rates for the chemo arm, epithelioid vs. non-epithelioid were 66% vs 32%, respectively; and the 2-year OS rates were 33% vs 8%.

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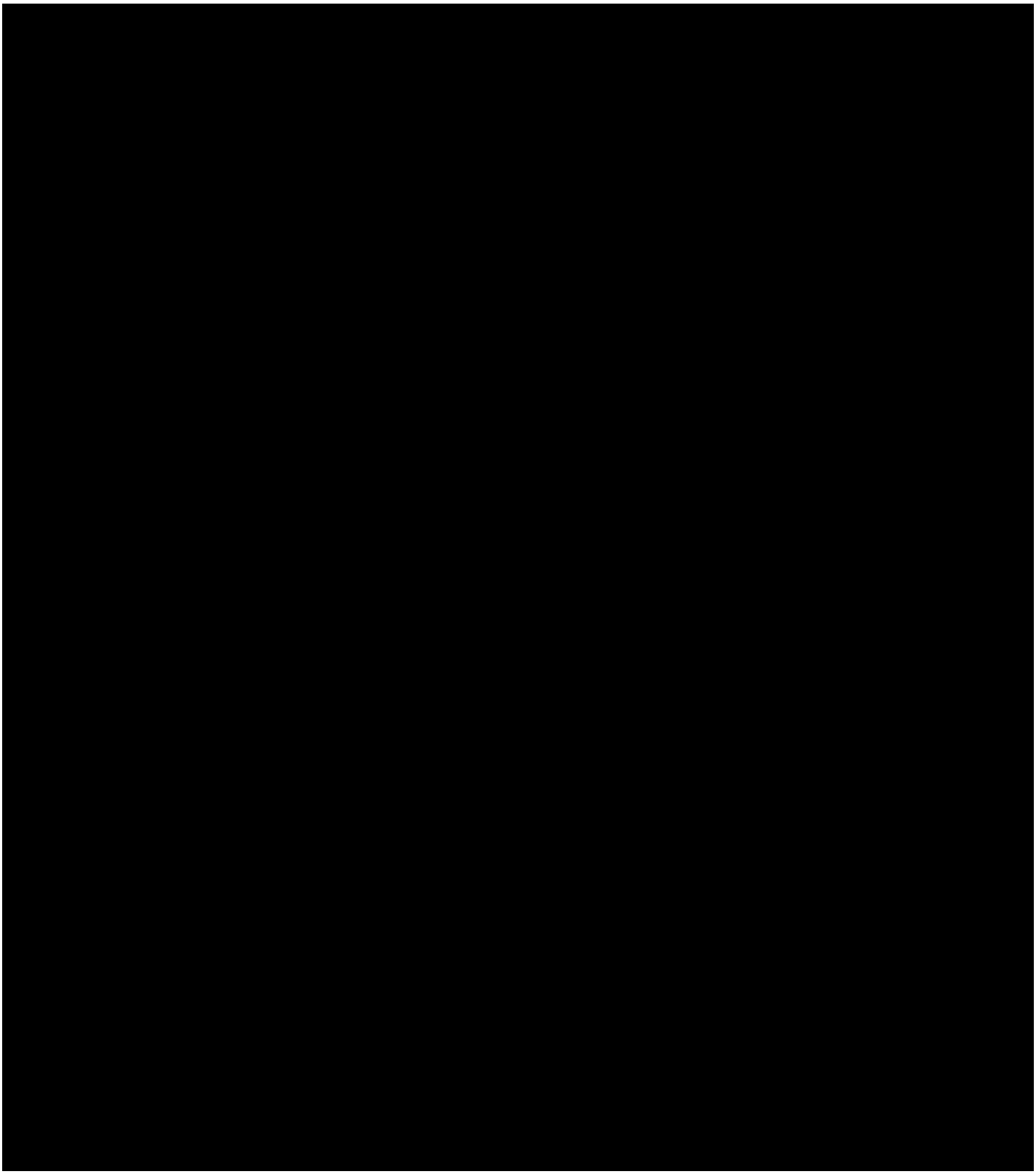

7.1.2.1.1.1 Overall survival in predefined subgroups

OS favored the combination experimental arm (nivolumab and ipilimumab) across most of the subgroups as well, though the OS in patients aged 75 and above (n=157) was similar between both treatment arms (Figure 12). In the

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nivolumab and ipilimumab group, investigators found evidence of higher treatment effect in patients in the non-epithelioid subtype (HR 0.46 [95% CI 0.31–0.68]) than those with epithelioid histology. For nivolumab and ipilimumab, the median OS was similar between both subtypes. By contrast, the median OS differed significantly between the epithelioid and non-epithelioid subtypes for those in the chemotherapy group: 8.8 months (95% CI 7.4–10.2) in non-epithelioid tumor types, whereas 16.5 months (14.9–20.5) in patients with epithelioid tumor histology) (Baas 2021).

In a descriptive analysis from the CheckMate 743 trial, the overall survival benefit with nivolumab and ipilimumab relative to chemotherapy was more pronounced in subjects whose tumor expressed PD-L1 ≥1% versus <1% (HR for PD-L1 ≥1% [95% CI]: 0.69 [0.55, 0.87]; HR for PD-L1<1% [95% CI]: 0.94 [0.62, 1.40]).

For nivolumab and ipilimumab, median overall survival outcomes were comparable regardless of PD-L1 expression. Median overall survival with nivolumab and ipilimumab was 18.0 months for the PD-L1 ≥1% group and 17.3 months for the PD-L1 <1% group, with similar one- and two-year overall survival rates observed between the two populations. However, median overall survival in the chemotherapy arm was different: 13.3 months and 16.5 months, respectively. In CheckMate 743, PD-L1 status was not a stratification factor, and as a result, the data are limited by potential imbalances in known or unknown prognostic factors. Moreover, sample sizes were small, particularly in the PD-L1 negative group (20% in nivolumab and ipilimumab arm and 26% in chemo arm). For all of these reasons, no definitive conclusions can be drawn (Baas 2021).

7.1.2.1.2 Progression free survival

PFS was followed up for a minimum of 19.8 months and the median PFS was seen to be similar between the two treatment groups: nivolumab and ipilimumab group was 6.8 months (95% CI 5.6–7.4) and the chemotherapy group was

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7.2 months (95% CI 6.9–8.0). The PFS rates at 2 years however were numerically greater in the nivolumab and ipilimumab group at 16% (95% CI 11.7–21.5), compared to only 7% (CI 4.0–11.7) in the chemotherapy group, as shown in Figure 13A (Baas 2021). The progression-free survival Kaplan-Meier curves crossed at approximately 8 months, reflecting more rapid, although not durable, disease control with chemotherapy.

The median duration of response was 11.0 months (95% CI 8.1–16.5) in the nivolumab and ipilimumab arm versus 6.7 months (95% CI 5.3-7.1) in the chemotherapy arm (Figure 13B). Dudek et al. do not recommend maintenance pemetrexed as their study showed that maintenance pemetrexed following initial pemetrexed and platinum chemotherapy does not improve PFS in patients with MPM (Dudek 2020).

As mentioned previously in the study design and overview, PFS was originally defined as a co-primary outcome in the CheckMate 743 but was updated to a secondary outcome during a revision of the study protocol in April 2019. Since MPM is a heterogeneous tumor that grows as a pleural thickening or a circumferential sheet around the lungs, it may or may not be well-delineated and lack clearly demarcated margins (Sureka 2013). As such, radiographic assessment of

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tumor margins—used in PFS as well as ORR assessment—in MPM, is faced with inherent challenges due to the natural history of this disease and location of lesions (FDA 2018).

7.1.2.1.3 Objective response rate, time to response, duration of response and disease control rate

Other than PFS, the other secondary endpoints measured in this study included, ORR. TTR, DoR and DCR. The outcomes are summarized in Table 11. In the nivolumab and ipilimumab group, 120 out of 303 patients reported objective response (40%; 95% CI 34.1–45.4) whereas in the chemotherapy group, 129 out of 302 patients (43%; 95% CI 37.1–48.5). Only the nivolumab and ipilimumab group showed complete responses (CR) in 5 out of 303 patients (2%). 232 out of 303 of patients (77%; 95% CI 71.4-81.2) in the nivolumab and ipilimumab group showed disease control and an average time TTR of 2.7 months (IQR 1.45-3.27), compared to 257 out of 302 patients (85%; 95% CI 80.6-88.9) in the chemotherapy group, where the average TTR was 2.5 months (IQR 1.41–3.02) (Baas 2021).

The DOR seen with chemotherapy in CheckMate 743 is consistent with other trials in multiple tumor types across the indications. Administration of nivolumab and ipilimumab for a much longer duration than chemotherapy is consistent with numerous previous trials, which have also shown the beneficial effects of nivolumab and ipilimumab treatment to be reproducible and persistent (Nakano 2018, Larkin 2019, Motzer 2019, Yau 2019). In accordance with the standard of care, duration of the chemotherapy regimens was 6 cycles, as there is no reported additional survival benefit for longer pemetrexed maintenance.

As alluded to during the description of reporting PFS in MPM, ORR faces the same challenges when it comes to the radiographic assessment of tumor margins in MPM (FDA 2018).

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Table 11: Summary of secondary endpoint results

	Nivolumab + ipilimumab group (n=303)	Chemotherapy group (n=302)
Objective response		
N (%)	120 (40%)	129 (43%)
95% CI	34.1-45.4	37.1-48.5
Best overall response		
Complete response	5 (2%)	0
Partial response	115 (38%)	129 (43%)
Stable disease	112 (37%)	125 (41%)
Non-complete response and non-progressive disease	0	3 (1%)
Progressive disease	55 (18%)	14 (5%)
Unable to determine	4 (1%)	5 (2%)
Not reported	12 (4%)	26 (9%)
Disease control rate		
N (%)	232 (77%)	257 (85%)
95% CI	71.4-81.2	80.6-88.9
Time to response, months		
Median	2.7	2.5
IQR	1.45-3.27	1.41-3.02
Duration of response, months		
Median	11.0	6.7
95% CI	8.1-16.5	5.3-7.1
Proportion of patients with at least 1 year or 2 years *		
At 1 year	47%	26%
95% CI	37-56	18-34
At 2 years	32%	8%
95% CI	23-41	3-15

*Estimates are based on Kaplan-Meier estimates of duration of response
Source: (Baas 2021)

7.1.2.1.4 Patient-reported outcomes

In CheckMate 743, prespecified patient reported outcomes (PRO) endpoints were measured to assess subjects' self-reported symptom burden and health-related quality of life by treatment group. Cancer-related symptoms and quality of life were evaluated using the mesothelioma adaptation of the Lung Cancer Symptom Scale (LCSS-Meso) instrument (Hollen 2005). Subjects' overall health status and health utility were measured with the three-level version of the EuroQol Group's self-reported EQ-5D-3L instrument (EuroQol Group 2015). In the CheckMate 743 statistical analysis plan, PROs were defined as exploratory endpoints hence no formal sample size calculations for these endpoints were performed *a priori*. Statistical analyses of PRO outcomes are described in more detail below.

Schedule of patient-reported outcome assessments

Symptoms and HRQoL were assessed prior to each nivolumab and ipilimumab or chemotherapy dose starting with the initial dose up to Week 12, then every 6 weeks until Week 48, and every 12 weeks thereafter until study discontinuation (Figure 14). The exact timing of the PRO assessments in the two treatment arms differed due to differences in the dosing schedule. In the nivolumab and ipilimumab arm, the dosing took place on Day 1, Day 15 and Day 29 of each six-week cycle, while dosing in the chemotherapy arm occurred on Day 1 of each three-week treatment cycle.

Post-treatment assessments occurred at two follow-up visits (follow-up 1: 30 [±7] days from the last dose or coincided with the date of discontinuation [±7 days] if date of discontinuation is over 35 days after the last dose; follow-up 2: 90 [±7] days from follow-up visit 1). Only EQ-5D-3L was measured during the survival follow-up phase, with assessments taking place approximately every 3 months (±7 days) from follow-up visit 2 for the first year, and every six months thereafter.

The LCSS-Meso questionnaire evaluates five domains associated with lung malignancies and their effect on overall symptomatic distress, functional activities, and global HRQoL (Hollen 2005). Although it includes both a patient and an observer scale, only the patient portion of the LCSS-Meso was administered in CheckMate-743. It consists of five symptom-specific questions that address cough, dyspnea, fatigue, pain, and appetite, with three additional items that measure overall symptom burden, disease-related activity limitations, and global HRQoL. Each question is scored on a VAS scale, with 0 being the best and 100 the worst score on the symptom scale, while the reverse is true for the HRQoL scale (Symanowski 2014, Bristol-Myers Squibb 2020b).

Evaluation of the patient portion of LCSS-Meso produced three measures of interest:

- the Average Symptom Burden Index (ASBI) score at each assessment, derived as the mean of the five symptom-specific questions
- the 3-Item Global Index (3IGI) score at each assessment, computed as the sum of the three summary HRQoL items, and
- responses to the individual items.

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The 3-IGI score ranges from 0 to 300, with 0 being the worst and 300 being the best possible score (Symanowski 2014). The individual responder definition threshold and minimally important difference (MID) were set at 10 for ASBI scores, and at 30 for 3IGI scores, based on established thresholds and MIDs for the LCSS (Hollen 1994, Sarna 2008).

7.1.2.1.4.2 Three level EQ-5D

The EQ-5D-3L is a standardized instrument for measuring subject's self-reported general health status and functioning (EuroQol Group 2015). It is comprised of the EQ-5D-VAS and the EQ-5D UI descriptive system. The EQ-5D-VAS allows respondents to rate their own current health on a 101-point scale ranging from 0="Worst imaginable health state" to 100="Best imaginable health state". The higher scores indicate better health status.

The instrument's descriptive system consists of five dimensions: mobility, self-care, usual activities, pain/discomfort, and anxiety/depression. Each dimension has three levels reflecting "no health problems", "moderate health problems," and "extreme health problems." A unique health state is defined by combining one level from each of the five dimensions. A total of 243 possible health states, represented with a five-digit code, are defined in this way. For example, state 11111 indicates no problems on any of the five dimensions, while state 11223 indicates no problems with mobility and self-care, some problems with performing usual activities, moderate pain or discomfort, and extreme anxiety or depression. Empirically derived weights can be applied to an individual's responses to the EQ-5D descriptive system to generate an index measuring the value to society of his or her current health. Such preference-weighting systems have been developed for many countries. The UK weights were used for general analysis, yielding the utility index score ranging from -0.59 to 1, with 0, 1, and negative values corresponding to death, full health, and health states worse than death, respectively (Bristol-Myers Squibb 2020b).

Evaluation of EQ-5D-3L questionnaire produced three measures of interest:

- mean EQ-5D VAS scores at each assessment
- mean EQ-5D utility index scores at each assessment
- mean utility value for each of the health states in the economic model of MPM

[redacted]

7.1.2.1.4.3 Statistical analyses of patient-reported outcomes

The PRO analysis population included all randomized subjects who had either at least one item completed on the LCSS-Meso or a valid EQ-5D VAS or EQ-5D-3L UI score at baseline and at least one matched on-treatment post-baseline

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assessment. The number of subjects in the PRO population and the reasons for exclusion (e.g., no baseline, no post-baseline) for all randomized subjects were recorded for each treatment group. For each instrument, the questionnaire completion rate was provided by visit and no unscheduled data was included in the analysis. The LCSS-Meso was considered completed at a visit if there was a valid LCSS-Meso ASBI score. The EQ-5D-3L was considered completed at a visit if either the VAS was completed or there was a valid utility index. The LCSS-Meso items and subscale scores, and EQ-5D-3L scores, were treated as continuous variables: the scores and their change from baseline for each instrument, by treatment and timepoint, were described by the number of subjects, mean, standard deviation, standard error, median, 25th and 75th percentiles, minimum, and maximum. Primary PRO statistical analysis was longitudinal mixed model regression of PRO data from baseline and on-treatment visits common to both treatment arms (week 6, week 12, week 18, week 24, and subsequent visits). The model was fitted to data up until a cut-off point with at least ten subjects in each arm (i.e., week 30). Scores from the LCSS-Meso ASBI, LCSS-Meso 3IGI, LCSS-Meso items, EQ-5D VAS, and EQ-5D-3L UI were all analyzed using separate mixed models, based on the PRO analysis population. The mixed model analysis yielded the overall and by-visit estimate of:

- least square mean and standard error for each treatment arm
- difference in least square mean between arms with the 95% CI for the difference
- estimate of change from baseline least square mean and standard error for each treatment arm

Time to deterioration (TTD) was defined as the time (in months) between the date of randomization and the first date of a worsening change from baseline meeting or exceeding the responder definition threshold, provided sufficient number of events (≥20% of the all-randomized population) had been observed. TTD was analyzed using data from on-treatment and follow-up timepoints common to both arms in the all-randomized population. The HR, 95% CI of HR, and p-value were calculated from a Cox proportional hazards model stratified for the randomization stratification factors (Bristol-Myers Squibb 2020b).

7.1.2.1.4.4 PRO results

PRO completion rates were generally similar between treatment arms and mostly above 80% for each assessment timepoints. Completion rates out of expected patients for the LCSS-Meso were comparable with those for the EQ-5D-3L (Scherpereel 2020a).

7.1.2.1.4.5 Disease-related symptom burden: change in symptom burden as measured by LCSS-Meso ASBI (on treatment)

For the LCSS-Meso analyses, of the 303 nivolumab and ipilimumab treated patients, data were collected from 258 patients, and of the 302 chemotherapy-treated patients, data were collected from 233 patients (Bristol-Myers Squibb 2020c). The disease-related symptom burden change from baseline measured by LCSS-Meso ASBI is presented in Figure 16. Symptom burden (LCSS ASBI) demonstrated numerical improvement with nivolumab and ipilimumab and numerical deterioration with chemotherapy, compared with baseline, though respective MIDs were not reached (Scherpereel 2020a).

Table 14 shows the LCSS-Meso ASBI mean change from baseline as stratified by histology subtype—epithelioid and non-epithelioid. The figures reflect similar patterns as observed in the overall study population and that improvements in disease-related symptoms are seen irrelevant of histology (Popat 2021).

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7.1.2.1.4.6 [redacted]-related symptom burden and quality of life: LCSS-Meso 3-IGI (on treatment)

The disease-related symptom burden change from baseline measured by LCSS-Meso 3-IGI is presented in Figure 18. LCSS-Meso 3-IGI demonstrated an improvement with nivolumab and ipilimumab vs. chemotherapy compared to baseline (Scherpereel 2020a).

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The MMRM analyses are a longitudinal assessment which considers all measurements across time for each subject and are adjusted in order to control for baseline score and multiplicity (Bristol-Myers Squibb 2020c).

In CM-743, the MMRM analyses show numerical improvement favoring nivolumab and ipilimumab; however, no clinically meaningful changes over time (based on MID) were observed overall within either treatment arm (Figure 19) (Scherpereel 2020a).

7.1.2.1.4.7 Overall health status: change from baseline in EQ-5D-3L VAS (on treatment)

For the EQ-5D-3L analyses, data from 272 patients in the nivolumab and ipilimumab arm and 247 patients in the chemotherapy arm were analyzed (Bristol-Myers Squibb 2020c).

Overall, the mean EQ-5D VAS scores increased (improved) gradually over time in the nivolumab and ipilimumab arm whilst on treatment, reaching a peak score at week 72 of 82.8. HRQoL (EQ-5D-3L VAS scores) improved over time with nivolumab and ipilimumab compared with chemotherapy and approximated UK population norms (82.8) over time (Figure 20) (Scherpereel 2020a).

For the chemotherapy arm, although the mean scores over time and mean change over time visually appear to decline after week 30, no firm conclusions can be made. The results for the health status of patients treated with chemotherapy should be interpreted with caution due to the low sample size after week 30 (n<10) (Bristol-Myers Squibb 2020c).

[redacted] the change in mean EQ-5D VAS from baseline by the histology subtypes, epithelioid and non-epithelioid. The figures reflect similar patterns as observed in the overall study population with improvements in mean EQ-5D VAS for both histology subtypes (Popat 2021).

[redacted]

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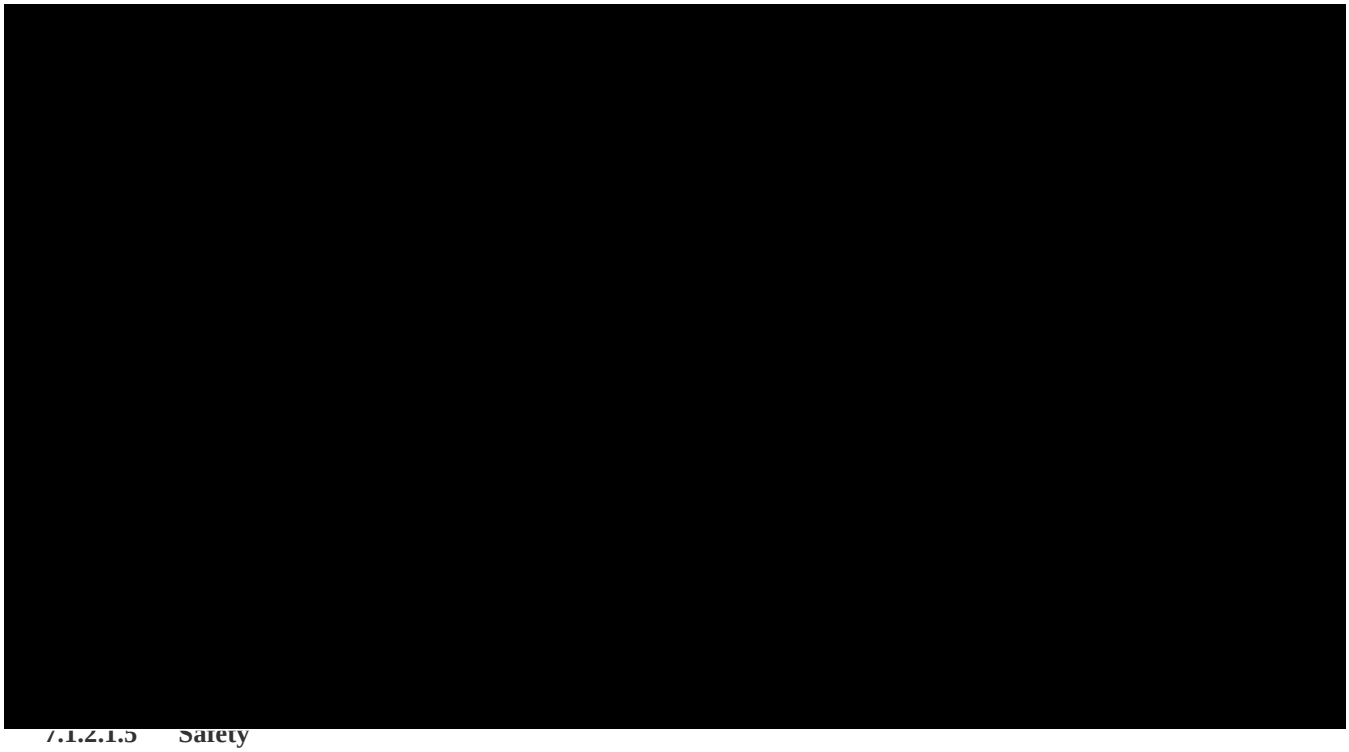
7.1.2.1.4.8 Time to deterioration (on treatment and follow-up)

The time to definitive deterioration is defined as the time (in months) between the date of randomization and the date of the first deterioration. Patients with no further assessments after the date of first deterioration were classed as definitively deteriorated (Bristol-Myers Squibb 2020b). TTD was analyzed for the LCSS-Meso ASBI, LCSS-Meso 3-IGI, EQ-5D VAS, and EQ-5D-3L UI scores. Time to definitive deterioration showed a numerical improvement in favor of nivolumab and ipilimumab (Figure 22).



7.1.2.1.5 Safety

7.1.2.1.5.1 Treatment-related adverse events

The dose and schedule of nivolumab plus ipilimumab in CheckMate 743 demonstrated a manageable safety profile, consistent with NSCLC clinical trials (Baas 2020a, Bristol-Myers Squibb 2020f). No new safety signals were observed with nivolumab plus ipilimumab treatment in MPM patients consistent with previously reported outcomes using the same dose and schedule (i.e. in CheckMate -227 [NSCLC]) (Disselhorst 2019, Hellmann 2019, Scherpereel 2019)

Of 300 patients treated with nivolumab and ipilimumab, 28 (9%) discontinued ipilimumab early. In the chemotherapy group, dose reductions occurred in 89 (31%) of 284 participants who were given pemetrexed, 18 (17%) of 104 patients who were given cisplatin, and 85 (41%) of 209 participants who were given carboplatin, whereas dose reductions were not permitted for the nivolumab plus ipilimumab group. Grade 3–4 treatment-related adverse events (TRAEs) were reported in 91 (30%) of 300 participants treated with nivolumab and ipilimumab and 91 (32%) of 284 participants treated with chemotherapy. Any-grade serious TRAEs were reported in 64 (21%) patients treated with nivolumab and ipilimumab versus 22 (8%) patients treated with chemotherapy; grade 3–4 treatment-related serious events were reported in 46 (15%) patients treated with nivolumab and ipilimumab versus 17 (6%) treated with chemotherapy (Table 12). Any-grade TRAEs that led to discontinuation (of either component of the regimen) were reported in 69 (23%) of 300 patients treated with nivolumab and ipilimumab and 45 (16%) of 284 patients treated with chemotherapy, and 45 (15%) patients treated with nivolumab and ipilimumab and 21 (7%) patients treated with chemotherapy had grade 3–4 events that led to discontinuation. The most frequent any-grade TRAE were diarrhea in the nivolumab and ipilimumab group (62 [21%] of 300 patients) and nausea in the chemotherapy group (104 [37%] of 284 patients). The most

frequently reported any-grade serious TRAE were colitis in the nivolumab and ipilimumab group (nine [3%]) and anemia in the chemotherapy group (six [2%]). The median exposure time was 6.5 months (IQR 2.99–12.22) for nivolumab and ipilimumab and 4.5 months (3.65–4.68) for chemotherapy. Treatment exposure was 220.3 person-years with nivolumab and ipilimumab and 94.5 person-years with chemotherapy. The overall exposure-adjusted incidence of treatment-related adverse events was 502.1 per 100 person-years with nivolumab and ipilimumab versus 1355.3 per 100 person-years with chemotherapy (Baas 2021).

Table 12: Summary of treatment-related adverse events in all treated patients

	Nivolumab and ipilimumab group (n=300)			Chemotherapy group (n=284)		
	Grade 1-2	Grade 3	Grade 4	Grade 1-2	Grade 3	Grade 4
Any	148 (49%)	79 (26%)	12 (4%)	141 (50%)	73 (26%)	18 (6%)
Diarrhoea	52 (17%)	10 (3%)	0	19 (7%)	2 (1%)	0
Pruritus	46 (15%)	3 (1%)	0	1 (<1%)	0	0
Rash	40 (13%)	3 (1%)	0	15 (5%)	0	0
Fatigue	38 (13%)	3 (1%)	0	50 (18%)	5 (2%)	0
Hypothyroidism	32 (11%)	0	0	0	0	0
Nausea	29 (10%)	1 (<1%)	0	97 (34%)	7 (2%)	0
Anaemia	5 (2%)	1 (<1%)	0	70 (25%)	32 (11%)	0
Decreased appetite	27 (9%)	2 (1%)	0	48 (17%)	2 (1%)	0
Constipation	12 (4%)	0	0	41 (14%)	1 (<1%)	0
Vomiting	8 (3%)	0	0	35 (12%)	6 (2%)	0
Asthenia	25 (8%)	0	0	32 (11%)	12 (4%)	0
Increased lipase	7 (2%)	11 (4%)	2 (1%)	0	1 (<1%)	0
Colitis	3 (1%)	7 (2%)	0	1 (<1%)	1 (<1%)	0
Increased amylase	10 (3%)	6 (2%)	1 (<1%)	1 (<1%)	0	0
Thrombocytopenia	0	2 (1%)	0	16 (6%)	4 (1%)	6 (2%)
Neutropenia	0	1 (<1%)	1 (<1%)	28 (10%)	31 (11%)	12 (4%)

Source (Baas 2021)

7.1.2.1.5.2 Supporting evidence of safety for nivolumab and ipilimumab

CheckMate 568 is a two-part, phase 2, single-arm study of immunotherapy combinations for first-line treatment of patients with advanced NSCLC where Part 1 evaluated nivolumab and ipilimumab and Part 2 evaluated nivolumab and ipilimumab combined with 2 cycles of PDC. Results from minimum follow-up of 6 months showed that any grade and grade 3 to 4 TRAEs led to discontinuation in 16% and 9% of patients, respectively, with most treatment-related select AEs—those with a potential immunologic cause—were grade 1 to 2. Most common treatment-related select AEs of any grade were skin reactions (30%), and the most common grade 3 to 4 treatment-related select AEs were GI toxicities (5%). (Barlesi 2019, Ready 2019, Gainor 2020).

Furthermore, the latest results of CheckMate 817, a single arm study of nivolumab and ipilimumab in first-line NSCLC, the OS observed in a general population (ECOG PS 0–1, cohort A (n=391)) was consistent with CheckMate 227 Part 1 and despite poor performance status or comorbidities, special populations (ECOG PS 2 or ECOG PS 0–1 and one of the following: asymptomatic untreated brain metastases, hepatic or renal impairment, HIV, cohort A1 (n=198)) had promising efficacy outcomes with 1-year OS rate of 47% (clinicaltrials.gov 2021). Importantly, the treatment-related

select AE profile of flat-dose nivolumab plus weight-based ipilimumab was consistent across Cohorts A and A1, select AEs occurred early after treatment initiation and resolved quickly with guidelines-based management (Barlesi 2019, Ready 2019, Gainor 2020).

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7.1.3 Comparative analyses of efficacy and safety

As the data presented in this submission is derived from CheckMate 743, the comparative analysis is captured in section 7.1.

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8. Health economic analysis

8.1 Model

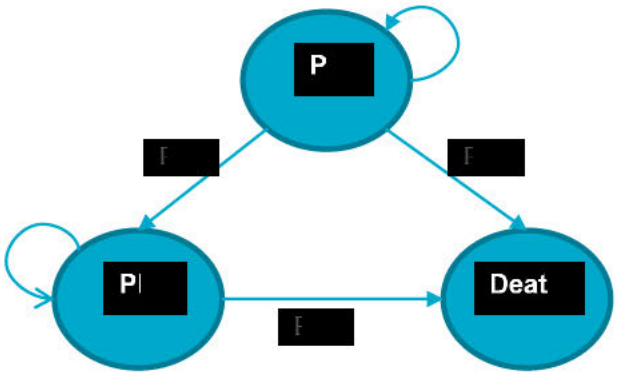
8.1.1 Model structure

A three health-state cohort model was developed to evaluate the incremental cost-effectiveness of nivolumab and ipilimumab versus pemetrexed and cisplatin/carboplatin in patients with previously untreated unresectable MPM. The model was developed in Microsoft Excel® and programmed using standard Excel functions wherever possible. Visual basic was used sparingly and was limited to running Monte-Carlo simulations in the probabilistic sensitivity analysis (PSA), for generating survival estimates. All model references and assumptions are clearly described within the Excel file.

The model structure comprised three key health states; progression-free (PF), progressed disease (PD), and death. These health states correspond to the primary and secondary endpoints of the CheckMate 743 trial. The model structure was consistent with the approaches adopted in previous published economic evaluations and technology appraisals with nivolumab.

Figure 23 provides a visual depiction of the standard three health-state model structure. The three health states represent the primary stages of disease in MPM: PF with 1L treatment, the occurrence of disease progression, and death. Each state represents the point at which health-related quality of life is expected to worsen, from patients receiving 1L therapy for MPM to experiencing PD, and death.

Figure 23: Overview of the standard three health-state model *

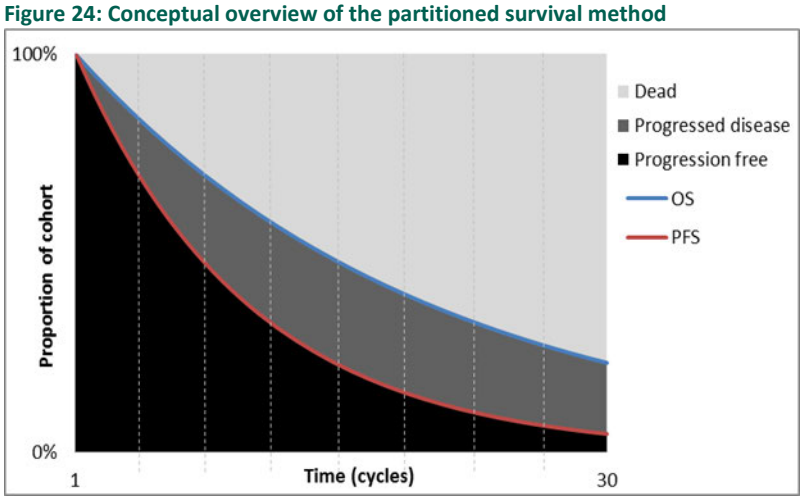


Note: *Health state transitions are not explicitly modelled in the partitioned survival analysis; the direction of transition in the model is provided as an illustration
Abbreviations: OS: Overall survival; P1: Transition probability 1; P2: Transition probability 2; P3: Transition probability 3; PD: Progressed disease; PF: Progression-free
Arrows represent possible transition probabilities in the semi-Markov model., the partitioned survival model uses an area under the curve approach to estimate state occupancy

8.1.2 Health state overview

The base case model used a partitioned survival model approach. This method requires the calculation of state occupancy from parametric survival curves for PFS and OS estimated directly from the CheckMate 743 trial. The number of patients occupying each state in the model is derived directly from the cumulative survival probabilities of PFS and OS (area under the curve approach). Figure 24 presents a visual description of the partitioned survival method.

Figure 24: Conceptual overview of the partitioned survival method



Abbreviations: OS: Overall survival; PFS: Progression-free survival

8.1.3 Model outcomes

The costs and outcomes (LYs, QALYs) of treatments were calculated by combining the estimated time spent in the PF and PD states with the costs and health utilities assigned to those states.

The healthcare costs considered in the evaluation included the cost of drug acquisition, drug administration, monitoring, disease management, end-of-life care, management of AEs and subsequent treatment. In the base case analysis, a two-year maximum treatment duration was applied to the nivolumab and ipilimumab regimen, consistent with the CheckMate 743 clinical trial design, and comparators were treated according to administration in the CheckMate 743 clinical trial or until disease progression.

The quality of life aspect of treatment was modelled using data derived from the CheckMate 743 clinical trial. The comparative efficacy and tolerability of treatment in the evaluation were assumed to impact on three aspects of disease prognosis:

- To increase or decrease the time spent in the PF state
- To increase or decrease the time spent alive, in either the PF or PD states
- To increase or decrease the incidence of Grade 3 or 4 AEs

The primary outcomes of the analysis are total costs and QALYs for the respective treatments, as well as the incremental cost per QALY for treatment with nivolumab and ipilimumab compared to pemetrexed and cisplatin/carboplatin, known as the incremental cost-effectiveness ratio (ICER).

8.1.4 Analysis overview

8.1.4.1 Perspective

General guidelines published by the Danish Medicines Council (DMC), recommend that a limited societal perspective is used when undertaking an economic evaluation of a medicinal product. For this reason, all treatment-related costs are included in the analysis, regardless of who pays them. These include patient transportation costs, and the cost of patients' time in relation to treatment. Productivity losses due to the disease and any impact that treatment may have are however omitted from the analysis, in line with DMC guidelines.

8.1.4.2 Time horizon

Early clinical evidence of nivolumab indicates durable long-term survival benefits for patients on treatment. In order to fully capture the benefits of nivolumab in comparison with alternative systemic therapies, this analysis uses a time

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horizon of 20 years, corresponding to a life-time horizon, based on patient age at diagnosis and the severity of the disease.

8.1.4.3 Discount rate

A discount rate of 3.5% is applied for both costs and health outcomes within the base case analysis (Medicinrådet 2020b, Medicinrådet 2021a). The user can specify which discount rates should apply independently for costs and QALYs. A scenario analysis is included where no discounting is applied.

8.1.4.4 Cycle length

A one-week cycle length was used in the analysis. This enables high granularity of results, and makes it easier to capture events with short duration only.

8.1.4.5 Model summary

A summary of the core elements of the economic model is shown in Table 13.

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Table 13: Summary of economic model

Aspect	Details	Comment
Analytical method	3-health state partitioned survival economic model	Analytical technique that has been applied in previous technology appraisals for anti-cancer treatments and corresponds to the primary and secondary endpoints of the CheckMate 743 trial
Software used	Microsoft Excel 365	Transparent, widely available software
Time horizon	Up to 20 years	Captures long-term benefits of the cohort
Cycle length	Weekly	Weekly cycles to accommodate differing administration cycles for therapies in the model
Discounting options	Costs and health outcomes	Both costs and outcomes were subject to annual discounting in the evaluation (4.0% in line with SLV guidelines)
Treatment arms	• Nivolumab and ipilimumab • Pemetrexed and cisplatin or carboplatin	The comparator (pemetrexed + cisplatin/carboplatin) is based on the comparator in the CheckMate 743 clinical trial, and aligns with Danish clinical practice
Half-cycle correction	Yes	The model calculates mid-cycle estimates in each health state by taking the average of patients present at the beginning and at the end of each cycle
Input		
Clinical efficacy and safety	CheckMate 743 trial – based on the April 2020 database lock	The CheckMate 743 trial is the key registrational trial for nivolumab regimens in 1L unresectable MPM. Dataset used for external validation were SEER and trials focusing on mesothelioma
Costs	A review of published studies and previous HTA submissions reporting the economic burden in patients with MPM	Endpoint for treatment costs estimates is PFS for all treatments Endpoint for health state costs is PFS for all treatments
Nivolumab and ipilimumab dosage	Nivolumab: 360 mg every 3 weeks Ipilimumab: 1mg/kg every 6 weeks	Flat dosing is used in line with recommendation by EMA (European Medicines Agency 2021a, European Medicines Agency 2021b). Weight-based nivolumab dosing of 3 mg every 2 weeks is tested in scenario analysis
Utilities	CheckMate 743 EQ-5D data (utilities for PF and PD) A review of previous HTA submissions within unresectable MPM and other cancers of the lung (disutility of AEs)	Based on AIC, BIC and p-values (significant difference in treatment effect), treatment-specific progression-based health state utilities were used for the base case. Treatment-specific time-to-death (TTD) utilities are explored in scenario analysis.

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Consideration of subsequent therapies	Yes, from CheckMate 743	Subsequent treatment options and proportions were validated by Danish KOLs (Danish Clinical Expert 2021a, Danish Clinical Expert 2021b).
Maximum time on treatment	2 year stopping rule for nivolumab and ipilimumab	In line with CheckMate 743 trial design
Output		
Costs	Aggregate and breakdown	-
Outcomes	Aggregate and breakdown	-
ICER	Ratio presented alongside the incremental costs and outcomes	-
Incremental cost-effectiveness plane	Yes	-
Cost-effectiveness acceptability curve and frontiers	Yes	-
Automated PSA and DSA	Yes	-

Abbreviation: 1L: First-line; AE: Adverse events; DSA: Deterministic sensitivity analysis; EQ-5D: EuroQol-5 dimensions; HTA: Health technology assessment; MPM: Malignant pleural mesothelioma; PD: Progressed disease; PF: Progression-free; PSA: Probabilistic sensitivity analysis; SEER: Surveillance, Epidemiology, and End Results program.

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

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

8.2.1.1 Patient population

This analysis considers first line treatment of patients with unresectable MPM. The characteristics of the patient population considered in the evaluation are based on patients enrolled in the CheckMate 743 clinical trial. To ensure that the analysis accurately evaluates current Danish clinical practice, patient characteristics were validated through interviews with Danish clinical experts (Danish Clinical Expert 2021a, Danish Clinical Expert 2021b). Where the experts perceived patient characteristics to differ between Danish clinical practice and the CheckMate 743 trial, the clinical experts themselves provided estimations for this analysis. Where estimations differed between experts the arithmetic mean was used.

Table 14 presents the patient characteristics both for CheckMate 743 and the Danish input values used in the economic model.

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Table 14: Patient characteristics in the economic analysis

Patient characteristic	CheckMate 743	Danish values used in model	Source for Danish values
Starting age (years)	68.2	70	Danish KOL interviews
Proportion female	22.8	17.5%	
Average body weight	72.75	72.75 kg	
Average height	172	172 cm	
Body surface area	1.82	1.86 m^2	Calculated based upon estimated height and weight
Proportion epithelioid	75.4%	60%	Danish KOL expert guidance and interviews (Panou 2021, Danish Clinical Expert 2021a, Danish Clinical Expert 2021b)

8.2.1.2 Intervention

Nivolumab, in combination with ipilimumab, is indicated for the 1L treatment of patients with unresectable MPM. Recommended dosing is 360 mg every 3 weeks (30-minute IV infusion) with ipilimumab 1 mg/kg every 6 weeks (30-minute IV infusion). The base case health economic analysis reflects the **approved** label (fixed dosing). Weight-based nivolumab dosing of 3 mg every 2 weeks is tested in scenario analysis.

Treatment with nivolumab and ipilimumab was capped at 2 years in the CheckMate 743 trial. The same treatment cap was applied within this economic analysis.

The intervention is summarized in Table 15. For more details, see section 5.3. For more details about the duration of treatment applied within this analysis, see section 8.3.1.3.

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Table 15: Summary of the intervention in the economic analysis

Intervention	Clinical documentation (including source)	Used in the model	Expected Danish clinical practice (including source if known)
Posology			
Nivolumab	CheckMate 743 trial, Tsao et al. (Tsao 2020)	Flat dose: 360 mg given every 3 weeks	Flat dose: 360 mg given every 3 weeks Weight-based nivolumab dosing of 3 mg every 2 weeks is tested in scenario analysis
Ipilimumab	CheckMate 743 trial, Tsao et al. (Tsao 2020)	Weight-based dose: 1 mg/kg every 6 weeks	Weight-based dose: 1 mg/kg every 6 weeks
Length of treatment			
Nivolumab	CheckMate 743	Up to 2 years	Up to 2 years or until disease progression or unacceptable toxicity
Ipilimumab	CheckMate 743	Up to 2 years	Up to 2 years or until disease progression or unacceptable toxicity

8.2.1.3 Comparators

The comparator arm in the CheckMate 743 trial was pemetrexed and cisplatin/carboplatin, where one third of patients received pemetrexed and cisplatin, and two thirds of patients received pemetrexed and carboplatin. Danish clinical experts (Danish Clinical Expert 2021a, Danish Clinical Expert 2021b) validated this as the most relevant comparator for first-line treatment in Denmark, but estimated that the proportion of patients receiving cisplatin and carboplatin respectively would be different from the clinical trial. In this analysis, the proportion of patients receiving pemetrexed and cisplatin versus the proportion receiving pemetrexed and carboplatin was 21.5% and 78.5%, respectively.

The comparators used in the analysis are presented in Table 16. For more details about the choice of comparator, see section 5.2.3.

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Table 16: Summary of the comparator in the economic analysis

Comparator	Clinical documentation (including source)	Used in the model	Expected Danish clinical practice (including source)
Posology			
Pemetrexed	CheckMate 743 trial	500 mg/m^2 every 3 weeks	500 mg/m^2 every 3 weeks
Cisplatin	CheckMate 743 trial	75 mg/m^2 every 3 weeks	75 mg/m^2 every 3 weeks
Carboplatin	CheckMate 743 trial	550 mg every 3 weeks	550 mg every 3 weeks
Length of treatment			
Pemetrexed	CheckMate 743 trial	Until disease progression	Until disease progression or unacceptable toxicity
Cisplatin	CheckMate 743 trial	Until disease progression	Until disease progression or unacceptable toxicity
Carboplatin	CheckMate 743 trial	Until disease progression	Until disease progression or unacceptable toxicity

8.2.1.4 Relative efficacy outcomes

The relative efficacy outcomes in the submitted clinical documentation: As CheckMate 743 is a head-to-head study including a comparison with pemetrexed and cisplatin/Carboplatin, which is the relevant comparator in Danish clinical practice according to Danish clinical experts (Danish Clinical Expert 2021a, Danish Clinical Expert 2021b), the efficacy results from CheckMate 743 are utilized for this analysis.

Relevance of the documentation for Danish clinical practice: As CheckMate 743 is a head-to-head study including a comparison with pemetrexed and cisplatin/carboplatin, which is the relevant comparator in the Danish clinical practice, the clinical documentation from CheckMate 743 is highly relevant for the Danish clinical practice.

The relative efficacy outcomes in the submitted health economic analysis: the submitted health economics model utilizes the parametrizations of the KM curves presented in the CheckMate 743 for both the intervention and comparators. More details about the survival extrapolations are presented in section 8.3, as well as in Appendix G (section 19).

8.2.1.5 Adverse reaction outcomes

The analysis included grade 3 or higher treatment-emergent AEs with at least 2% incidence. Treatment related AEs with nivolumab and ipilimumab and pemetrexed and cisplatin/carboplatin were obtained from the CheckMate 743 clinical trial. Table 29 presents the AE rates used in the economic model.

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8.3 Extrapolation of relative efficacy

8.3.1 Time to event data – summarized:

This section provides a brief description of the methods used for extrapolating overall and progression-free survival. A more detailed description is provided in Appendix G (section 19)

8.3.1.1 Survival extrapolations

OS and PFS were extrapolated based upon Kaplan-Meier (KM) data from CheckMate 743. The curve selection was based upon a combination of statistical fit, clinical plausibility and external validation with data from the MAPS and SEER trials (Zalcman 2016, SEER 2021); for more details, see Appendix G (section 19). The KM-curves were generally more favorable for nivolumab and ipilimumab, but the proportional hazards assumption did not hold for neither treatment arm or survival type. For nivolumab and ipilimumab, OS and PFS were extrapolated using log-normal and Generalized Gamma distributions, respectively. For pemetrexed and cisplatin/carboplatin, OS were extrapolated using a 1-knot Spline Odds curve, and PFS was modelled using Log-logistic distribution.

8.3.1.2 Adjustment by histological subtype

In the CheckMate 743 trial, patients treated with nivolumab and ipilimumab experienced similar overall and progression-free survival irrespective of epithelioid status. However, among patients treated with pemetrexed and cisplatin/carboplatin, the relative survival of non-epithelioid patients was considerably lower than for epithelioid patients. As a consequence, the relative difference in clinical efficacy between treatment arms was greater among non-epithelioid patients. The overall survival by histology subgroup for nivolumab and ipilimumab compared to pemetrexed and cisplatin/carboplatin are shown in Figure 25 and Figure 26.

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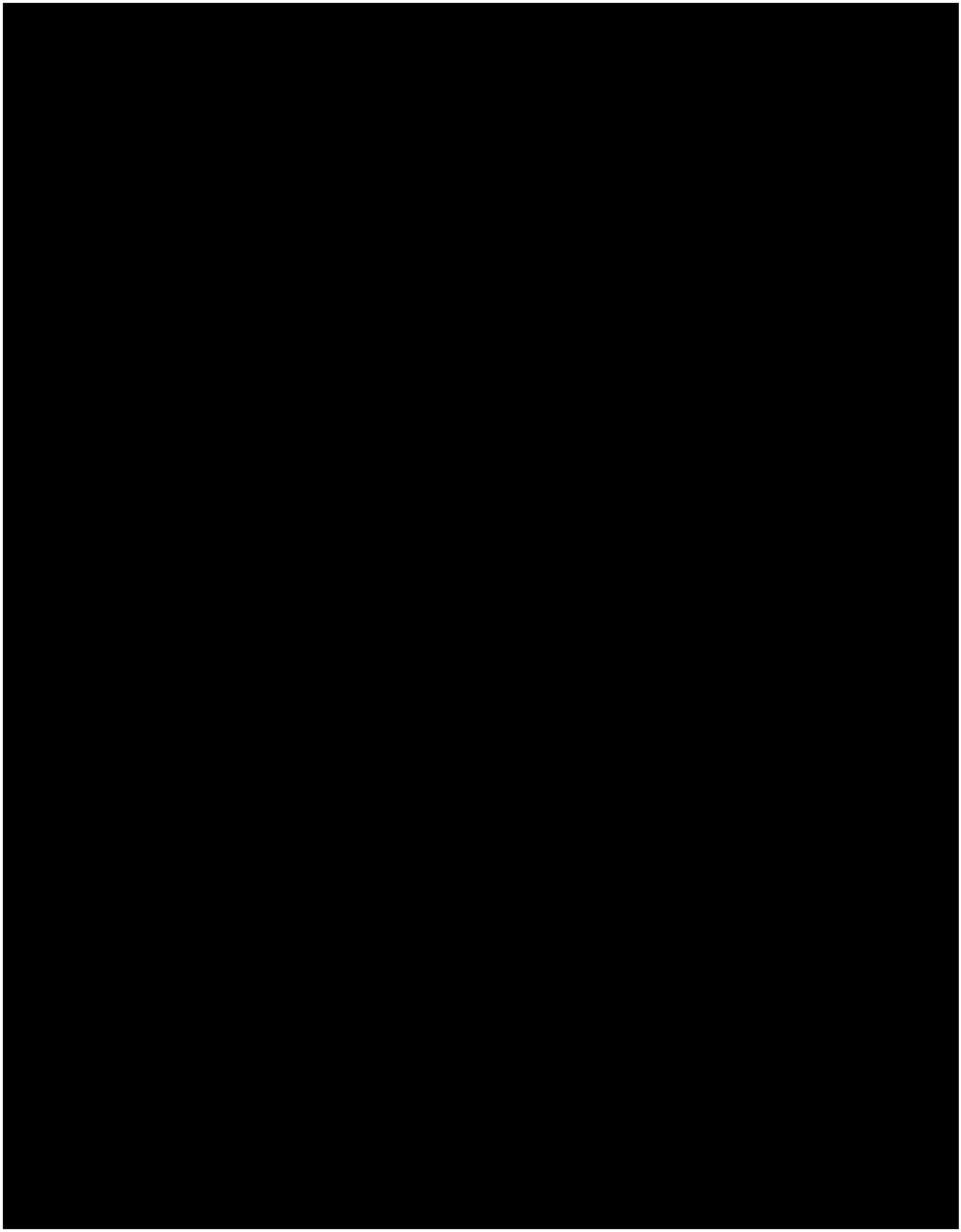

The proportion of epithelioid patients in Denmark is estimated to be around 60% (Kirstein Jensen 2020). This also aligns with data from Denmark where the share of epithelioid patients was 59.5% (Panou 2021) . By contrast, the proportion

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of epithelioid patients in CheckMate 743 was considerably higher at 75.4%. If survival extrapolations would be based upon ITT data from CheckMate 743, without factoring in the lower proportion of epithelioid patients in Danish clinical practice, the expected increased mortality among patients treated with pemetrexed and cisplatin/carboplatin would not be accurately captured. To overcome this, an approach using hazard ratios to adjust the survival curves and re-weight them was applied. The adjustment was estimated numerically so that the weighted average of survival in each point would align with the survival observed in the ITT analysis, if the share of epithelioid patients was identical to the share observed in CheckMate 743. This required solving the following simultaneous equations (for more details, see Appendix G (section 19)):

- S1(t) = S2(t)hr– i.e. the subgroup survival probabilities respect the proportional hazards assumption; and
- w1 S1(t) + w2 S2(t) = S(t) – i.e. in aggregate the subgroup survival probabilities combine to match the ITT survival probabilities when weighted according to their proportions in the ITT population.

The hazard ratio adjustment was only applied to the pemetrexed and cisplatin/carboplatin treatment arm since there was no statistical evidence for a difference in survival between non-epithelioid and epithelioid patients. This approach could be considered conservative from the perspective of nivolumab and ipilimumab, but was justified in the absence of any stronger evidence that histological subtype is a prognostic factor for patients treated with this combination. In any case, the effect of also applying a hazard ratio adjustment to the nivolumab and ipilimumab treatment arm would be considerably smaller for this group, since survival was similar for patients regardless of histological subtype. Overall, the approach of applying hazard ratio adjustments by subgroup ensures that the survival for patients treated with pemetrexed and cisplatin/carboplatin is adjusted for the higher proportion of non-epithelioid patients in Danish clinical practice than what was the case in CheckMate 743. The relationship between the survival for non-epithelioid and epithelioid patients is presented in Table 18. Table 19 compares the extrapolated OS with and without hazard-ratio adjustment, and as a function of the proportion of epithelioid patients.

† The proportion of epithelioid patients in CheckMate 743 differed between treatment arms. For the overall study it was 75.4%, whereas for the arm treated with pemetrexed and cisplatin/carboplatin it was 75.2%. The proportion sued for the economic analysis was 60.0% to reflect Danish clinical practice.

Figure 27 and Figure 28 demonstrates the impact of the adjustment on overall survival and progression free survival with the 60% epithelioid proportion used in the base case analysis. The results of the base case analysis with histology weighting and the unadjusted analyses are shown in section 8.7.3.

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8.3.1.3 Adjustment for general population mortality

The mortality risk for the general Danish population increases with age. Over time, this could result in a situation when the general population mortality hazard exceed those of MPM patients. To prevent this, the underlying mortality hazard for the general population was estimated for every model cycle, using life tables for Denmark (Statistics Denmark 2021); average mortality for years 2016-2020 was used for this analysis. OS per cycle was then calculated as the highest among 1) the mortality hazard from the OS extrapolations, or 2) the mortality hazard of the general population.

8.3.1.4 Duration of treatment

The Kaplan-Meier curves for DoT in the nivolumab and ipilimumab and pemetrexed and cisplatin/carboplatin arms are shown in Figure 29. Given the maturity of the trial data for DoT, no parametric extrapolation was needed, and the Kaplan-Meier data was used directly in the analysis for DoT.

Treatment duration for nivolumab and ipilimumab was capped at 2 years. This treatment cap was included in line with the clinical study report for CheckMate 743, where it is stated that patients receiving nivolumab and ipilimumab are treated until progression, unacceptable toxicity, or other reasons specified in the protocol, or up to 24 months, whichever comes first (Bristol-Myers Squibb 2019, Baas 2021).

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8.3.2 Summary of parametric models:

Table 20 provides a summary of the parametric survival models recommended in Appendix G (section 19). For the base case analysis, independent models were used for OS and PFS. DoT was based on KM data from CM743 trial.

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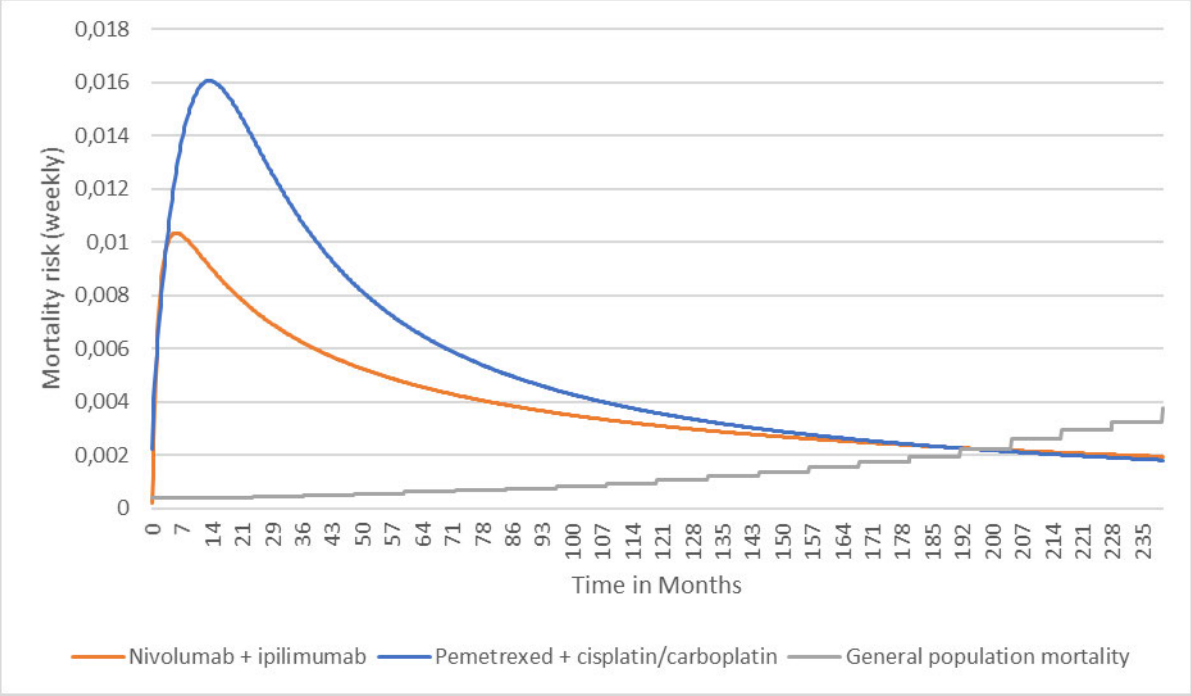
[redacted]

It should be noted that the overall survival in the model was adjusted for general population mortality. When the extrapolated mortality was below general population mortality, mortality within the analysis was assumed to be equivalent to the general population at that given age. This is demonstrated in Figure 30, where the predicted mortality for nivolumab and ipilimumab and pemetrexed and cisplatin/carboplatin was lower than the general population mortality towards the end of the time horizon.

Figure 30: Predicted mortality versus general population mortality



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

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8.4.1 Health state utility values used in the health economic model

For this analysis, the EQ-5D-5L value set (Jensen 2021) was applied to the EQ-5D-3L responses by the means of a validated mapping method (van Hout 2021). The mapping was done according to the preferred method which was an ordinal logistic regression that disregarded age and gender and accounted for unobserved heterogeneity using a latent factor. The HSUVs used in the model are presented in Table 21. Two type of utility values were used for the analysis: progression-based values, and values based upon time-to-death (TTD). The former was used for the base case, as progression-based utilities have historically been more commonly used in HTA evaluations.

Disutility values associated with adverse events were also identified though a systematic literature review (Bristol-Myers Squibb 2020e). However, the disutility from such adverse events have already implicitly been captured in the treatment-specific utility values from CheckMate 743. To avoid double counting the disutility from adverse events, such utility decrements should therefore only be applied when not using treatment-specific utility weights.

Treatment-specific utilities were used for the base case of this analysis. This was preferred for two reasons. First, a statistically significant difference in post-progression utility values between nivolumab and ipilimumab compared to pemetrexed and cisplatin/carboplatin was identified. Secondly, since the disutility values associated with adverse events were not derived in a Danish context, it was hard to establish their magnitude if applied alongside utility values that had been derived using Danish population preferences. By contrast, the treatment-specific values accounted for both the patient experience of treatment and the preferences of the Danish population, without relying on assumptions for value-mapping.

Table 21: Summary of the HSUV used in the model

	HSUV	95% C.I.	Source (literature search, study, ITC, etc.)
Health state			
Progression-free (overall)	[redacted]		EQ-5D-3L responses from CheckMate 743 mapped to 5L responses (van Hout 2021) and valued with the DK 5L value set (Jensen 2021)
Progression-free (nivo + ipi)			
Progression-free (peme + chemo)			
Progressed disease (overall)			
Progressed disease (nivo + ipi)			
Progressed disease (peme + chemo)			
Time-to-death †			
<52 weeks (nivolumab and ipilimumab)			EQ-5D-3L responses from CheckMate 743 mapped to 5L responses (van Hout 2021) and valued with the DK 5L value set (Jensen 2021)
27-52 weeks (nivolumab and ipilimumab)			
5-26 weeks (nivolumab and ipilimumab)			
≤4 weeks (nivolumab and ipilimumab)			
<52 weeks (pemetrexed and cisplatin/carboplatin)			

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	HSUV	95% C.I.	Source (literature search, study, ITC, etc.)
27-52 weeks (pemetrexed and cisplatin/carboplatin)	[redacted]		
5-26 weeks (pemetrexed and cisplatin/carboplatin)			
≤4 weeks (pemetrexed and cisplatin/carboplatin)			
Adverse reaction ‡			
Neutropenia	0.090	0.015	Nafees et al. 2008 (Nafees 2008)
Anaemia	0.125	0.013	Lloyd et al. 2008 (Lloyd 2008)
Diarrhoea	0.047	0.016	Nafees et al. 2008 (Nafees 2008)
Asthenia	0.073	0.018	Nafees et al. 2008, (Nafees 2008) assumed to be the same as fatigue
Lipase increased	0.000	0.000	Assumption
Thrombocytopenia	0.184	0.018	Attard et al. 2014 (Attard 2014)
Nausea	0.048	0.016	Nafees et al. 2008 (Nafees 2008)
Vomiting	0.048	0.016	Nafees et al. 2008 (Nafees 2008)
Amylase increased	0.000	0.000	Assumption
Leukopenia	0.090	0.016	Nafees et al. 2008 (Nafees 2008), assumed the same as neutropenia

† Applied in scenario analysis only
‡ Disutilities for adverse events are not applied when treatment-specific utility values are used in the analysis.

8.4.1.1 Age-adjusted utilities

In line with DMC guidelines, an age-adjustment of the utility values was performed to ensure that the relative level of utility values would decline in a rate consistent with the expected decline in health-related quality of life (HRQoL) observed within the general Danish population. The adjustment index recommended by the DMC was used for this analysis (Medicinrådet 2021b).

8.5 Resource use and costs

Cost input values for the analysis was obtained through interviews with Danish clinical experts (Danish Clinical Expert 2021a, Danish Clinical Expert 2021b). The experts were allowed to see the estimated resource usage for mesothelioma treatment in the UK but could freely estimate the frequencies they deemed appropriate for a Danish clinical setting.

They were also asked to list any other health care resources that they thought may be applicable in Denmark. Where frequency estimates differed in between the experts, the input values used for the model were based upon the arithmetic mean from the different estimates.

Different sources were used to obtain the unit cost for all resource types. All costs were updated to 2021 prices.

8.5.1 Health care resource utilization

8.5.1.1 Disease management costs

Table 22 presents the disease management costs for patients by disease progression status. The disease management costs are presented as resource use required every week to provide care to unresectable MPM patients regardless of treatment. Frequency estimates were provided by Danish KOLs (Danish Clinical Expert 2021a, Danish Clinical Expert 2021b). However, the overall disease management costs differ between treatment arms as a result of differences in expected overall and progression-free survival.

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Table 22: Disease management costs in the progression-free and progressed disease health states

Resource name	Weekly resource use PF	Weekly resource use PD	Unit cost (DKK)	Reference for unit costs
Outpatient visit	0.166	0.166	1368	Kommunernes og Regionernes Løndatakontor 2021, Overlæger, lægelige chefer m.v.. bruttolön MAJ 2021 (97038DKK). available from: https://krl.dk/ Calculated: salary/hours per month and multiplied by two according to Medicine council 2020.
CT scan (chest)	0.079	0.079	2007	Sundhedsdatastyrelsen (2021). Interactive DRG: 30PR06 (UXCC75) CT-skanning af lunger (DC349M) Kræft i bronkier eller lunge med metastaser. Available at: http://interaktivdrg.sundhedsdata.dk/
CT scan (other)	0	0	2007	Sundhedsdatastyrelsen (2021). Interactive DRG: 30PR06 (UXCC75) CT-skanning af lunger (DC349M) Kræft i bronkier eller lunge med metastaser. Available at: http://interaktivdrg.sundhedsdata.dk/
Chest radiology	0	0	1732	Sundhedsdatastyrelsen (2021). Interactive DRG: 04MA98 (DZ016) Contact for radiological examination; (DC349M) Kræft i bronkier eller lunge med metastaser. Available at: http://interaktivdrg.sundhedsdata.dk/
ECG	0	0	1732	Sundhedsdatastyrelsen (2021). Interactive DRG: 04MA98 (ZZ3925) EKG; (DC349M) Kræft i bronkier eller lunge med metastaser. Available at: http://interaktivdrg.sundhedsdata.dk/
MR	0.010	0.010	2738	Sundhedsdatastyrelsen (2021). Interactive DRG: 30PR02 (UXMH00)MR-skanning af hele kroppen; (DC349M) Kræft i bronkier eller lunge med metastaser. Available at: http://interaktivdrg.sundhedsdata.dk/
Therapist	0	0	1732	Sundhedsdatastyrelsen (2021). Interactive DRG: 04MA98 (BRSP1)Individuel psykoterapi; (DC349M) Kræft i bronkier eller lunge med metastaser. Available at: http://interaktivdrg.sundhedsdata.dk/
Radiotherapy (brain)	0	0	1732	Sundhedsdatastyrelsen (2021). Interactive DRG:04MA98 (BWGC)Ekstern strålebehandling; (DC349M) Kræft i bronkier eller lunge med metastaser. Available at: http://interaktivdrg.sundhedsdata.dk/
Radiotherapy (bone)	0	0	1732	Sundhedsdatastyrelsen (2021). Interactive DRG:04MA98 (BWGC)Ekstern strålebehandling; (DC349M) Kræft i bronkier eller lunge med metastaser. Available at: http://interaktivdrg.sundhedsdata.dk/
99Tc bone scintigraphy	0	0	3081	Sundhedsdatastyrelsen (2021). Interactive DRG: 36PR06 (WKBGD19XX) Knogleskintigrafi, flerfaset, Tc-99m-XPD; (DC349M) Kræft i bronkier eller lunge med metastaser. Available at: http://interaktivdrg.sundhedsdata.dk/
Blood transfusion	0	0.010	4628	Sundhedsdatastyrelsen (2021). Interactive DRG: 16PR02 (BOQA0) Blodtransfusion; (DC349M) Kræft i bronkier eller lunge med metastaser. Available at: http://interaktivdrg.sundhedsdata.dk/
Hospitalization	0	0.013	1732	Sundhedsdatastyrelsen (2021). Interactive DRG: 04MA98 (BXXB0) Tværfaglig udredning og behandling; (DC349M) Kræft i bronkier eller lunge med metastaser. Available at: http://interaktivdrg.sundhedsdata.dk/

Abbreviations: CT: Computed tomography; ECG: electrocardiogram; MR: Magnetic resonance imaging; DKK: Danish Kroner; PD: Progressive disease; PF: Progression-free

8.5.1.2 Drug acquisition costs

Drug acquisition costs were based upon pharmacy purchasing price (PPP) excluding VAT. Drug costs were obtained from Medicinpriser.dk (Medicinpriser.dk 2021), using the lowest available price per mg for the package size. The input values for drug costs in this analysis are presented in Table 23.

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Table 23: Drug acquisition costs

Subtype	Vial / package information				Cost per pack (DKK) PPP excl. VAT	Reference for unit costs
	Strength	Unit	Size	Unit		
Nivolumab	10	mg/ml	4	ml	3 785.32	Medicinpriser.dk https://www.medicinpriser.dk/Default.aspx?id=15&vnr=539385
	10	mg/ml	10	ml	9 403.31	Medicinpriser.dk https://www.medicinpriser.dk/Default.aspx?id=15&vnr=579240
	10	mg/ml	24	ml	22 657.94	Medicinpriser.dk https://www.medicinpriser.dk/Default.aspx?id=15&vnr=479954
Ipilimumab	5	mg/ml	10	ml	26 311.31	Medicinpriser.dk https://www.medicinpriser.dk/Default.aspx?id=15&vnr=597433
	5	mg/ml	40	ml	105 010.82	Medicinpriser.dk https://www.medicinpriser.dk/Default.aspx?id=15&vnr=199940
Pembrolizumab	25	mg/ml	4	ml	23 799.6	Medicinpriser.dk https://www.medicinpriser.dk/Default.aspx?id=15&vnr=585359
Bevacizumab	25	mg/ml	4	ml	2 090.82	Medicinpriser.dk https://www.medicinpriser.dk/Default.aspx?id=15&vnr=019445
	25	mg/ml	16	ml	7 707.76	Medicinpriser.dk https://www.medicinpriser.dk/Default.aspx?id=15&vnr=019781
Carboplatin	10	mg/ml	15	ml	84	Medicinpriser.dk https://www.medicinpriser.dk/Default.aspx?id=15&vnr=424629
	10	mg/ml	45	ml	203	Medicinpriser.dk https://www.medicinpriser.dk/Default.aspx?id=15&vnr=439635
	10	mg/ml	60	ml	n/a	n/a
Cisplatin	1	mg/ml	10	ml	n/a	n/a
	1.0	mg/ml	50	ml	100	Medicinpriser.dk https://www.medicinpriser.dk/Default.aspx?id=15&vnr=598049
	1	mg/ml	100	ml	200	Medicinpriser.dk https://www.medicinpriser.dk/Default.aspx?id=15&vnr=548680
Pemetrexed	100	mg	1	mg	2 114.26	Medicinpriser.dk https://www.medicinpriser.dk/Default.aspx?id=15&vnr=120062
	500	mg	1	mg	8 809.43	Medicinpriser.dk https://www.medicinpriser.dk/Default.aspx?id=15&vnr=019797
Gemcitabine	100	mg/ml	20	ml	1 200	Medicinpriser.dk https://www.medicinpriser.dk/Default.aspx?id=15&vnr=128608
	100	mg/ml	10	ml	1 000	Medicinpriser.dk https://www.medicinpriser.dk/Default.aspx?id=15&vnr=420712
	100	mg/ml	2	ml	n/a	n/a
Vinorelbine	10	mg/ml	5	ml	1 240	Medicinpriser.dk https://www.medicinpriser.dk/Default.aspx?id=15&vnr=584287
	10	mg/ml	1	ml	2 500	Medicinpriser.dk https://www.medicinpriser.dk/Default.aspx?id=15&vnr=168997

Abbreviations: DKK: Danish Kroner; VAT: value added tax; PPP: Pharmacy purchasing price

8.5.1.3 Drug administration costs

The administration costs associated with drug infusion is presented in Table 24. The same infusion costs were applied for both treatment arms. The frequency of administrations were based upon the SmPC of each drug. Nivolumab, pemetrexed, cisplatin and carboplatin were all administered every 21 days, a frequency of 0.33 times per week. Ipilimumab would only be administered every 42 days, however, it was assumed that multiple drugs could be administered at the same time, so that the number of administrations would not exceed those required for the respective drug with the highest frequency.

Table 24: Administration cost per included treatment

Resource	Frequency (per week)	Unit cost (DKK)	Reference for unit cost
Complex parenteral chemotherapy delivery - Outpatient setting	0.33	1732	Sundhedsdatastyrelsen (2021). Interactive DRG: 04MA98 (BWAA60) Medicingivning ved intravenøs injektion for (DC349M) Kræft i bronkier eller lunge med metastaser. Available at: http://interaktivdrg.sundhedsdata.dk/

Abbreviations: DKK, Danish kroner

8.5.1.4 Drug monitoring costs

In addition to the disease management costs outlined in Table 22, drug monitoring costs are included in the model. The monitoring costs reflect treatment specific resource use such as labs and scans which are required to ensure patients are tolerating the treatment well. Therefore, these costs are both treatment specific and are required in addition to the disease management costs for patients in the PF health state outlined in Table 22. Drug monitoring costs are included both for first-line treatments as well as subsequent treatments. The monitoring cost for first-line treatment are presented in Table 25. The monitoring costs for subsequent treatments are presented in Table 26.

Table 25: First-line treatment monitoring costs associated with nivolumab and ipilimumab and for pemetrexed and cisplatin/carboplatin

Resource	Weekly frequency: Nivolumab + ipilimumab	Weekly frequency: Pemetrexed + cisplatin/carboplatin	Unit cost (DKK)	Reference for unit cost
Outpatient visit	0.415	0.29	1368	Kommunernes og Regionernes Løndatakontor 2021, Overlæger, lægelige chefer m.v.. bruttolön MAJ 2021 (97038DKK). available from: https://krl.dk/ Calculated: salary/hours per month and multiplied by two according to Medicine council 2020.
CT Scan	0.076	0.069	2007	Sundhedsdatastyrelsen (2021). Interactive DRG: 30PR06 (UXCC75) CT-skanning af lunger (DC349M) Kræft i bronkier eller lunge med metastaser. Available at: http://interaktivdrg.sundhedsdata.dk/
Hepatic function test	0.415	0.29	213	Rigshospitalets Labportal (2021). Test code for hepatic tests included (codes): NPU19651, NPU19654, NPU27783, NPU19673, NPU01370, NPU03278. https://labportal.rh.dk/Labportal.asp
Renal function test	0.415	0.29	261	Rigshospitalets Labportal (2021). Test code for renal tests included (codes): NPU01459, NPU01472, NPU03429, NPU03230, NPU01536, NPU23745, NPU02192, NPU04998, NPU19673 https://labportal.rh.dk/Labportal.asp
CBC	0.415	0.328	460	Rigshospitalets Labportal (2021). Test code for CBC tests included (codes): NPU02902 (cost for test assumed as

				proxy for codes: NPU01960, NPU01961, NPU02593), NPU01473 (cost for test assumed as proxy for codes: B-Hb (Hemoglobin), Erc(B)-MCV, Erc(B)-MCH, Erc(B)-MCHC), and RGH00982. https://labportal.rh.dk/Labportal.asp
Thyroid test	0.415	0.165	79	Rigshospitalets Labportal (2021). Test code for thyriod included (code): (NPU03577) Thyrotropin. https://labportal.rh.dk/Labportal.asp

Abbreviations: CT: Computerized tomography; DKK: Danish kroner

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Table 26: Subsequent treatment monitoring frequencies (weekly) and costs per subsequent treatment type

Subsequent treatment	Outpatient visit	CT Scan	Hepatic function test	Renal function test	Complete blood count	Thyroid test
Nivolumab	0.50	0.00	0.50	0.50	0.50	0.50
Ipilimumab	0.25	0.00	0.25	0.25	0.25	0.25
Pembrolizumab	0.00	0.00	0.00	0.00	0.00	0.00
Bevacizumab	0.00	0.00	0.00	0.00	0.00	0.00
Carboplatin	0.25	0.00	0.25	0.25	0.33	0.00
Cisplatin	0.25	0.00	0.25	0.25	0.33	0.00
Pemetrexed	0.25	0.00	0.25	0.25	0.33	0.00
Gemcitabine	0.00	0.00	0.00	0.00	0.00	0.00
Vinorelbine	0.29	0.06	0.29	0.29	0.33	0.00
Unit cost (DKK)	1 368	2 007	213	261	460	79
Reference	Kommunernes og Regionernes Løndatakontor 2021, Overlæger, lægelige chefer m.v.. bruttolön MAJ 2021 (97038DKK). available from: https://krl.dk/ Calculated: salary/hours per month and multiplied by two according to Medicine council 2020..	Sundhedsdatastyrelsen (2021). Interactive DRG: 30PR06 (UXCC75) CT-skanning af lunger (DC349M) Kræft i bronkier eller lunge med metastaser. Available at: http://interaktivdrg.sundhedsdata.dk/	Rigshospitalets Labportal (2021). Test code for hepatic tests included (codes): NPU19651, NPU19654, NPU27783, NPU19673, NPU01370, NPU03278. https://labportal.rh.dk/Labportal.asp	Rigshospitalets Labportal (2021). Test code for renal tests included (codes): NPU01459, NPU01472, NPU03429, NPU03230, NPU01536, NPU23745, NPU02192, NPU04998, NPU19673 https://labportal.rh.dk/Labportal.asp	Rigshospitalets Labportal (2021). Test code for CBC tests included (codes): NPU02902 (cost for test assumed as proxy for codes: NPU01960, NPU01961, NPU02593), NPU01473 (cost for test assumed as proxy for codes: B-Hb (Hemoglobin), Erc(B)-MCV, Erc(B)-MCH, Erc(B)-MCHC), and RGH00982. https://labportal.rh.dk/Labportal.asp	Rigshospitalets Labportal (2021). Test code for thyriod included (code): (NPU03577) Thyrotropin. https://labportal.rh.dk/Labportal.asp

Abbreviations: CT: Computerized tomography; DKK: Danish kroner

8.5.1.5 Cost of treatment-related adverse events

The costs associated with adverse events (AE) were applied as a one-off cost during the first model cycle. An overview of the costs used in the analysis is presented in Table 27 .

Table 27: Cost and resource use for adverse events

Adverse events	Unit cost per event (DKK)	Share of patients with AE considered for the treatment †	Reference for unit costs
Neutropenia	9 526	15%	Sundhedsdatastyrelsen (2021). Interactive DRG: 04MA98 (BXXB0) Tværfaglig udredning og behandling; (DC349M) Kræft i bronkier eller lunge med metastaser. Available at: http://interaktivdrg.sundhedsdata.dk/ Hospitalization for 5.5 days as per KOL input (2 – 6 days).
Anaemia	0	100%	Managed with monitoring visit
Diarrhoea	1 732	30%	Sundhedsdatastyrelsen (2021). Interactive DRG: 04MA98 (BXXB0) Tværfaglig udredning og behandling; (DC349M) Kræft i bronkier eller lunge med metastaser. Available at: http://interaktivdrg.sundhedsdata.dk/ Hospitalization for 1 day as per KOL input.
Asthenia	0	100%	Managed with monitoring visit
Lipase increased	0	100%	Managed with monitoring visit
Thrombocytopenia	0	100%	Managed with monitoring visit
Nausea	0	100%	Managed with monitoring visit
Vomiting	4330	5%	Sundhedsdatastyrelsen (2021). Interactive DRG: 04MA98 (BXXB0) Tværfaglig udredning og behandling; (DC349M) Kræft i bronkier eller lunge med metastaser. Available at: http://interaktivdrg.sundhedsdata.dk/ Hospitalization for 2.5 days as per KOL input (2 – 3 days).
Amylase increased	0	100%	Managed with monitoring visit
Leukopenia	0	100%	Managed with monitoring visit

Abbreviation: DKK, Danish krone, KOL, key opinion leader.
† The share of patients receiving the resource refers to the share among patients with a grade ≥3 event who would require the specific resource. For example, the likelihood of a patient treated with pemetrexed and cisplatin/carboplatin experiencing a grade ≥3 event relating to neutropenia is 15.14%. Among these, it is further estimated by clinical experts that 15% would require a hospitalization for 5.5 days.

The application of AE costs in week one is potentially a conservative assumption for two reasons:

- AEs which are incurred after one year on treatment require discounting of the costs incurred; therefore, applying these costs in week one will overestimate the impact of AEs.
- Week one has the maximum number of patients on treatment (patients in PFS at risk of experiencing AEs); therefore, applying the cost of AEs in week one will overestimate the impact of AEs.

8.5.1.6 Subsequent treatment costs

Upon disease progression, patients were assumed to receive a subsequent systemic anti-cancer therapy as second line (2L) treatment. To ensure consistency with Danish clinical practices and treatment guidelines, interviews were held with Danish KOLs (Danish Clinical Expert 2021a, Danish Clinical Expert 2021b). The KOLs were presented with data on the share of patients who received which subsequent treatment within each treatment arm of the CheckMate 743 trial, however, they could freely estimate the subsequent treatment proportions in Denmark.

Table 28 presents the proportion of patients receiving each type of subsequent treatment in the economic model. Since nivolumab and ipilimumab are not currently used as a first line treatment for unresectable malignant pleural mesothelioma in Denmark, there is no experience regarding which second line treatments would follow. For this reason, it was assumed that second line treatments following treatment with nivolumab and ipilimumab could be based upon current first line treatment in Denmark, i.e. pemetrexed and cisplatin/carboplatin. It was further estimated that some patients would be too frail to receive any subsequent treatment at all except best supportive care (BSC).

Table 28 Subsequent treatments used for unresectable MPM patients (2L)

Treatment	Proportion on each treatment in economic model		
	% after nivolumab and ipilimumab	% after pemetrexed and cisplatin/carboplatin	Time on Treatment (months)
Nivolumab	0%	0%	1.60
Ipilimumab	0%	0%	1.60
Pembrolizumab	0%	0%	1.60
Bevacizumab	0%	0%	1.60
Carboplatin	73.35%	0%	1.60
Cisplatin	16.65%	0%	1.60
Pemetrexed	90%	0%	1.60
Gemcitabine	0%	0%	1.60
Vinorelbine	5%	90%	1.60
Best supportive care	5%	10%	n/a

These subsequent treatment costs entered the economic analysis as a one-off cost upon progression to the progressed-disease state. Data on the average time spent on subsequent treatment was obtained from a study which analysed treatment patterns of advanced MPM in a community practice setting in the US. Among 474 analysed patients, most had received either pemetrexed and cisplatin (n=194, 41%) or pemetrexed and carboplatin (n=175, 37%) as first line treatment. This study showed that the mean duration of 2L treatment was 1.6 months (Waterhouse 2021). Overall costs for subsequent treatments were a function of the proportion of patients receiving each subsequent treatment and its duration, as well as the drug acquisition costs, administration costs, and monitoring costs associated with each treatment. These are presented in Table 23, Table 24 and Table 26, respectively.

8.5.1.7 End of life costs

End of life/terminal care costs were applied as a one-off cost to all patients which were newly entering the death state over the time horizon of the model. Resource usage was estimated by Danish clinical experts and the cost for end of life/terminal care is presented in Table 29. Note that the cost for advanced medical home care is considered a municipal cost, and for this reason also presented below in section 8.5.3.

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Table 29: End of life costs

Resource	Share of patients requiring resource	Frequency (days)	Unit cost (DKK)	Reference for unit costs
Terminal care in hospital	30%	6	1 734	Sundhedsdatastyrelsen (2021). Interactive DRG: 04MA98 (BXBA)Specialiseret palliativ indsats; (DC349M) Kræft i bronkier eller lunge med metastaser. Available at: http://interaktivdrg.sundhedsdata.dk/
Terminal care in hospice	25%	30	1 734	Assumed same as hospital care
Advanced medical home care	45%	60	414	Kommunernes og Regionernes Løndatakontor 2021, Husassistenter, KL. bruttolön May 2021 (29373 DKK). available from: https://krl.dk/ Calculated: salary/hours per month and multiplied by two according to Medicine council 2020.

Abbreviation: DKK, Danish krone

8.5.2 Patient costs

Patient costs for transportation and time were included in this analysis for every drug administration. These are presented in Table 30. For treatment with nivolumab and ipilimumab, the frequency of administration for nivolumab was used since this drug is given more frequently to the patient. Given this, patients were expected to visit a treatment clinic every 21 days, a frequency of 0.33 appointments per week. The transportation cost per visit was estimated to DKK 100, in line with DMC guidelines (Medicinrådet 2020a).

It was further assumed that every administration would require 2 hours of patient time, including the time of transportation. This yielded a frequency of 0.67 hours of the patient's time per week. The unit cost for patient time was estimated to DKK 179, in line with DMC guidelines (Medicinrådet 2020a).

Table 30: Patient costs used in the model

Cost type	Frequency per week		Unit cost (DKK)
	Nivolumab and ipilimumab	Pemetrexed and cisplatin/carboplatin	
Patient transport costs	0.33	0.33	100
Patient time for drug administration (hours)	0.67	0.67	179

Abbreviation: DKK, Danish krone

8.5.3 Municipality costs

Towards the end-of-life, Danish KOLs estimated that 45% of patients would require advanced medical home care (Danish Clinical Expert 2021a, Danish Clinical Expert 2021b) for an average of 60 days. The unit cost per day was estimated to DKK 414 (Kommunernes og Regionernes Løndatakontor 2021). This yielded an average municipal cost for every deceased patient of DKK 10 072. It was assumed that this cost would apply equally irrespective of whether patients had been treated with nivolumab and ipilimumab or with pemetrexed and cisplatin/carboplatin. The only difference in overall municipal costs between treatment arms hence derived from differences in estimated survival. The municipal costs used in the analysis is summarized in Table 31.

Table 31: Municipality costs used in the model

Resource	Share of patients requiring resource	Frequency (days)	Unit cost (DKK)	Source
Advanced medical home care	45%	60	414	Danish KOL interviews (Kommunernes og Regionernes Løndatakontor 2021, Danish Clinical Expert 2021a, Danish Clinical Expert 2021b)

Abbreviation: DKK, Danish krone, KOL, key opinion leader.

8.6 Results

8.6.1 Base case overview

The model settings used in the base case analysis are presented in Table 32.

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Table 32: Summary of settings used for the base case analysis

Input	Base case	Justification/Source
Time horizon	20 years	DMC guidelines
Perspective	Restricted societal perspective	DMC guidelines
Starting age of cohort	70 years	Based upon Danish KOL feedback
Weight	72.75 kg	Based upon Danish KOL feedback
Proportion female	17.5 %	Based upon Danish KOL feedback
Dosing	Flat dose (nivolumab: 360mg every 3 weeks, ipilimumab: 1 mg/kg at every 6 week)	Drug label
Estimation approach	All-comers, weighted by histology	See section 8.3.1.1 and Appendix G
Hazard ratio adjustment	HR adjustment applied only to treatment with pemetrexed and cisplatin/carboplatin (for both OS and PFS)	See sections 8.3.1.2 and Appendix G
Curve selection for survival extrapolation	Nivolumab and ipilimumab: • OS: Log-normal • PFS: Generalized Gamma Pemetrexed and cisplatin/carboplatin: • OS: 1 Spline Odds • PFS: Log-logistic	See sections 8.3.1.1 and Appendix G
Share of non-epithelioid patients	40%	Based upon Danish KOL feedback (Kirstein Jensen 2020, Panou 2021)
Extrapolation of DoT	DoT KM data from CM743	See section 8.3.1.3
Drug acquisition costs	List prices, PPP excl. VAT	DMC guidelines
Comparators	Pemetrexed and cisplatin/carboplatin (21.5% vs 78.5%)	Verified through Danish KOL interviews
Health state utilities	Progression-based utilities with Danish value set, treatment specific	DMC guidelines; CheckMate 743 utility analysis
Resource usage	Weighted mean of KOL estimates	Based upon Danish KOL feedback
Subsequent treatments: nivolumab and ipilimumab	Pemetrexed + cisplatin (16.65%), pemetrexed + carboplatin (73.35%), vinorelbine (5%), best supportive care (5%)	Based upon Danish KOL feedback
Subsequent treatments: pemetrexed and cisplatin/carboplatin	Vinorelbine (90%), best supportive care (10%)	Based upon Danish KOL feedback
Wastage	Vial sharing allowed (wastage excluded)	Based upon Danish KOL feedback
Treatment cap	Treatment cap at 2 years	CheckMate 743 trial
Discounting	3.5% for costs and effectiveness	DMC guidelines

Abbreviations: DMC, Danish Medicines Council; DoT, duration of treatment; KOL, key opinion leader; PPP, pharmacy purchase price; VAT, value added tax;

8.6.2 Base case results

A summary of the base case results is presented in Table 33. The results indicate that nivolumab and ipilimumab is associated with better health outcomes than pemetrexed and cisplatin/carboplatin, but also increases overall costs. The biggest cost increase stems from the higher drug acquisition costs for nivolumab and ipilimumab. The extended survival

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also yields additional costs as both drug monitoring costs and costs for subsequent treatment increases. The costs and health outcomes in Table 33 have been discounted by 3.5%.

Table 33: Base case results

	Nivolumab and Ipilimumab	Pemetrexed and Cisplatin/carboplatin	Incremental
Life years gained			
Total life years gained	2.585	1.612	0.974
QALYs			
Total QALYs	1.966	1.178	0.788
Costs (DKK)			
PF Disease-related costs	29 502	17 139	12 363
PD Disease-related costs	31 100	20 877	10 224
Drug acquisition costs	639 169	85 450	553 719
Drug administration costs	10 750	8 873	1 876
Drug monitoring costs	38 842	11 189	27 653
Adverse event management costs	27	224	-197
Subsequent treatment costs	23 185	12 065	11 121
End of life costs	25 111	26 163	-1 051
Patient costs	4 083	1 603	2 480
Total costs	801 770	183 582	618 188
Incremental cost per QALY (ICER, DKK)			
784 237			

Abbreviation: ICER, incremental cost effectiveness ratio; DKK, Danish krone, QALY, quality adjusted life years

The drug acquisition costs for nivolumab and ipilimumab constitute a big part of the incremental cost of the treatment. For this reason, the ICER per QALY gained is sensitive towards changes in the prices of these two drugs. The ICER per QALY as a function of discount levels for nivolumab and ipilimumab is illustrated in Figure 31 and the corresponding ICERs per discount level are outlined in Table 34, below. These analyses assume that the cost of other drugs would be unchanged.

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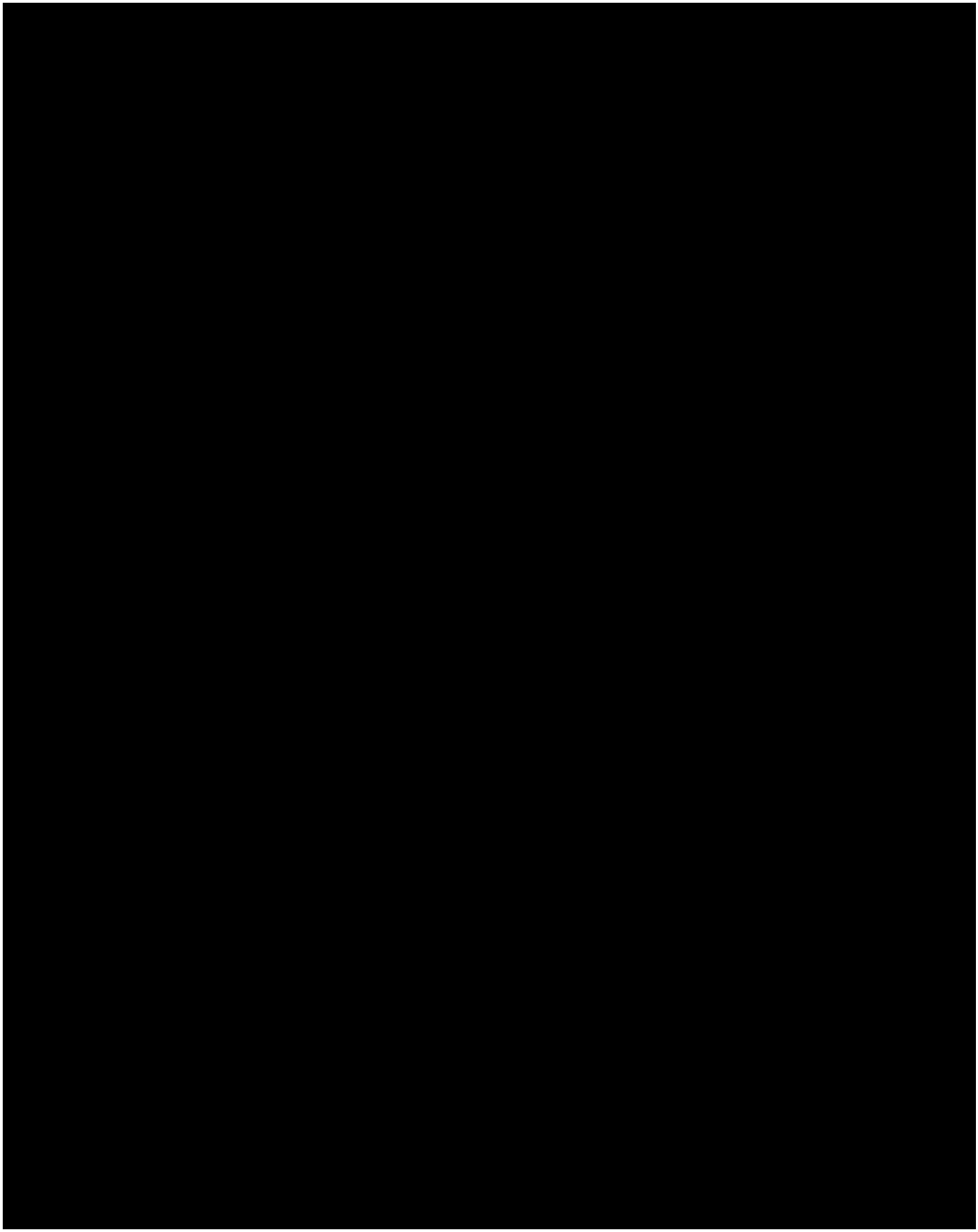

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8.7 Sensitivity analyses

8.7.1 Deterministic sensitivity analyses

8.7.1.1 Deterministic sensitivity analysis overview

Deterministic sensitivity analysis (DSA) was undertaken by varying key parameters by their standard error, 95% CI or +/- 20% of the expected values (base case) based on data availability. The parameter input values used in the analysis is presented in Table 36.

[redacted]

Parameters	Lower	Mean	Higher
Discount rate for costs	0.0%	3.5%	6.0%
Discount rate for outcomes	0.0%	3.5%	6.0%
Starting age of cohort	56	70	84
Percentage of females	14%	18%	21%
Average body weight (Kg)	71	73	74
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
PF health state costs	330	413	496
PD health state costs	392	490	588

† Change applied to treatment-specific utility weights for both treatment arms
Abbreviations: PD, Progressed disease; PF, progression-free

8.7.1.2 Deterministic sensitivity analysis results

Table 37 summarizes the deterministic sensitivity analyses for nivolumab and ipilimumab versus pemetrexed and cisplatin/carboplatin. Figure 32 illustrates the magnitude that the ICER per QALY changes when each input was varied. The ICERs from the sensitivity analyses were compared to the base case ICER to determine the absolute and proportional change. The ICER was found to be most sensitive to changes in the discount rate for outcomes and the utility values for progression-free and progressed disease..

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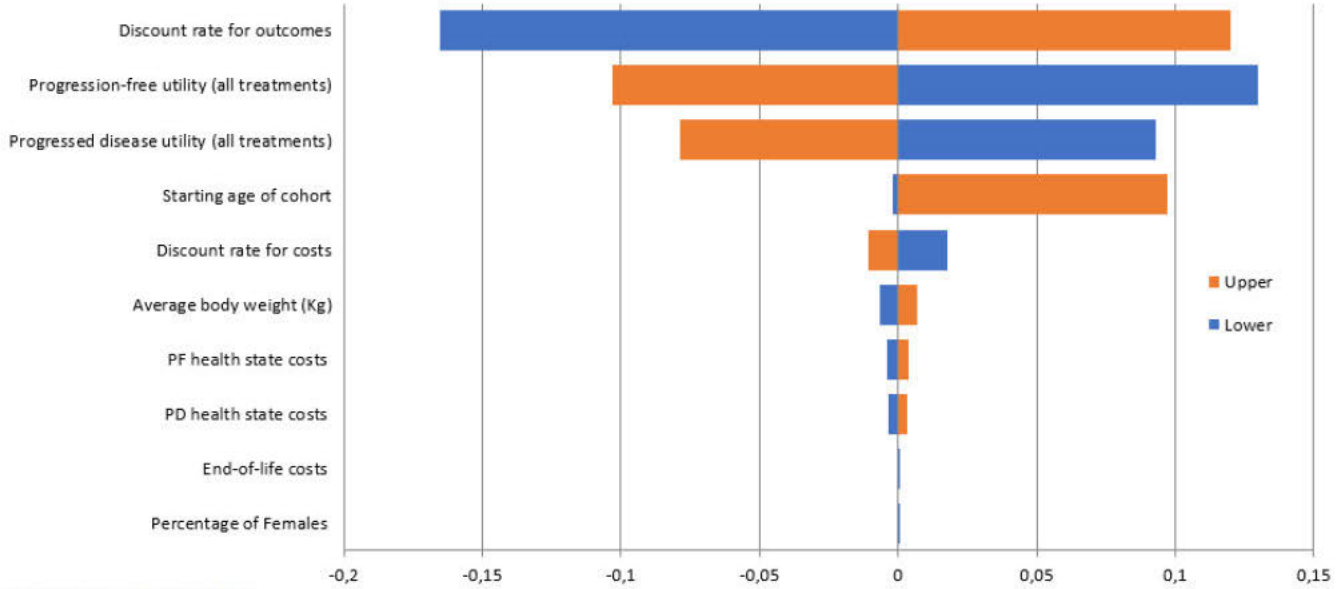
Table 37: Deterministic sensitivity analysis of nivolumab and ipilimumab versus pemetrexed and cisplatin/carboplatin

Parameters	ICER: Cost/ QALY		Absolute change (DKK)	
	Lower	Upper	Lower	Upper
Discount rate for costs	798 033	775 984	13 796	-8 253
Discount rate for outcomes	654 646	878 487	-129 591	94 250
Starting age of cohort	782 736	860 561	-1 501	76 324
Percentage of Females	784 301	784 178	64	-59
Average body weight (kg)	779 028	789 487	-5 209	5 250
Progression-free utility (all treatments)	885 960	703 467	101 723	-80 770
Progressed disease utility (all treatments)	857 262	722 677	73 025	-61 560
PF health state costs	781 100	787 374	-3 137	3 137
PD health state costs	781 643	786 831	-2 594	2 594

Abbreviations: PD: progressed disease; PF: progression free; PFS: progression free survival QALY: quality adjusted life year.

Figure 32: Tornado diagram for DSA of nivolumab and ipilimumab versus pemetrexed and cisplatin/carboplatin showing impact on the ICER



Base case ICER per QALY: DKK 764 361

Abbreviations: DSA: deterministic sensitivity analysis; ICER: incremental cost-effectiveness ratio; PD: progressed disease; PF: progression free; QALY: quality-adjusted life year.

8.7.2 Probabilistic sensitivity analyses

The results of the PSA (for 1,000 iterations) are presented in Table 38 which also presents results from the deterministic analysis for comparison. This analysis generally supports the conclusions from the deterministic analysis but suggest that the ICER per QALY gained should be slightly lower for nivolumab and ipilimumab than what was found in the deterministic analysis.

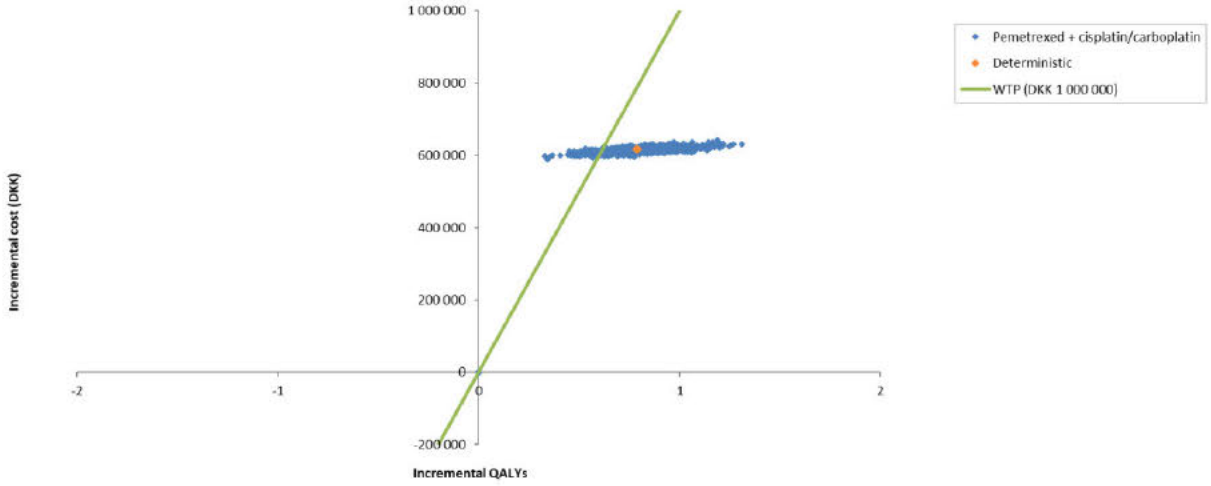
The result of the cost-effectiveness analyses is presented in a cost-effectiveness plane in Figure 33. The cost-effectiveness acceptability curve (CEAC) is shown in Figure 34. The WTP threshold per QALY gained used for these analyses was DKK 1 000 000.

Table 38: Result summary from probabilistic sensitivity analysis

Nivolumab and ipilimumab vs.	Analysis	Inc. costs, DKK	Inc. QALYs	Incremental cost per QALY, DKK
Pemetrexed and cisplatin/carboplatin	Deterministic	618 188	0.788	784 237
	Probabilistic	614 693	0.796	772 065

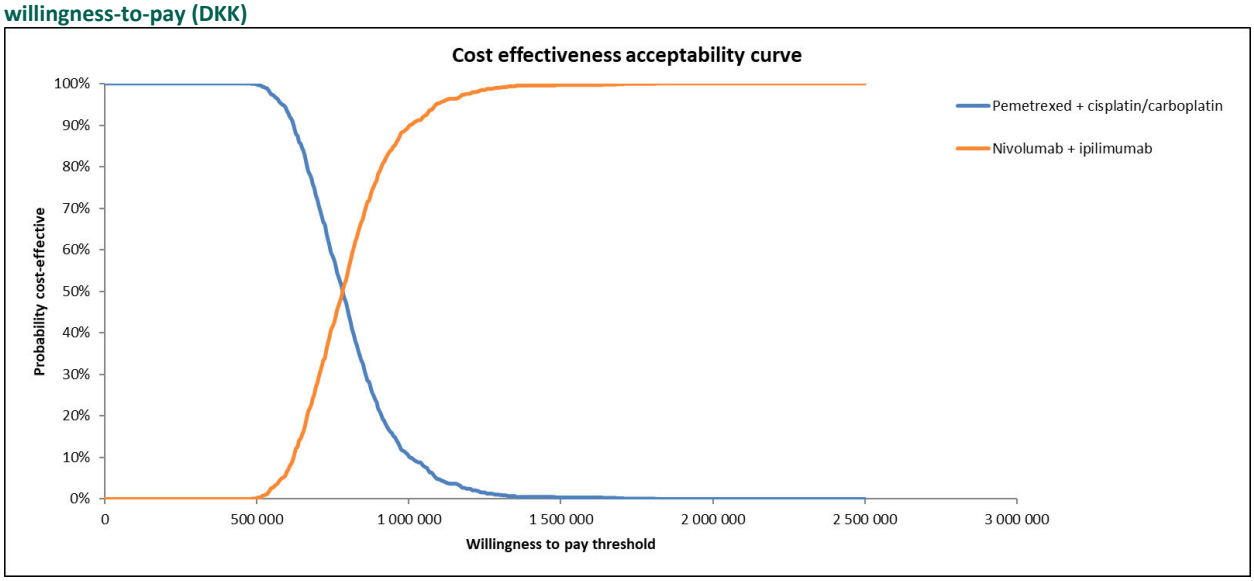
Abbreviations: DKK, Danish krone Inc: Incremental; LY: Life years, QALY: Quality adjusted life year; WTP: willingness-to-pay.

Figure 33: Cost-effectiveness plane: nivolumab and ipilimumab versus pemetrexed and cisplatin/carboplatin



Abbreviations: QALY: quality adjusted life years; WTP: Willingness to pay threshold

Figure 34: Cost-effectiveness acceptability curve showing the probability of treatments being cost-effective as a function of the willingness-to-pay (DKK)



Abbreviations: DKK, danish krone

8.7.3 Scenario analyses

Scenario analyses were undertaken to investigate the effect of structural assumptions and evaluate the model's sensitivity towards the settings chosen for the base case. Table 39 presents a list of scenario analyses and their descriptions. The outcome for the scenario analyses is presented in Table 40.

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Table 39: List of scenario analyses

Scenario	Scenario description	Detailed description
Scenario 1	No discounting	Discounting: 0% for both costs and QALYs
Scenario 2	Alternative OS extrapolation	Nivolumab and ipilimumab OS extrapolated with Log-logistic
Scenario 3	Alternative OS extrapolation	Nivolumab and ipilimumab OS extrapolated with Spline Odds 1 knot
Scenario 4	Weight-based nivolumab dosing	Nivolumab dose: 3 mg/kg every 2 weeks
Scenario 5	Include wastage	No vial sharing
Scenario 6	Alternative utility values	Treatment-specific time-to-death utilities
Scenario 7	15 year time horizon	15 year time horizon
Scenario 8	10 year time horizon	10 year time horizon
Scenario 9	Alternative estimation approach	Analysis is based upon ITT analysis of CheckMate 743 only. No weighting by histology (share of epithelioid patients: 75.4%)

Abbreviations: OS, overall survival; QALY, quality adjusted life years

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Table 40: Result from scenario analyses

Scenario	Cost nivo+ipi	Cost peme + chemo	QALYs nivo+ipi	QALYs peme + chemo	Incremental costs	Incremental QALYs	ICER
Base case	801 770	183 582	1.966	1.178	618 188	0.788	784 237
Discounting: 0% for both costs and QALYs	816 214	187 151	2.188	1.244	629 063	0.944	666 162
Nivolumab and ipilimumab OS extrapolated with Log-logistic	801 018	183 582	1.944	1.178	617 437	0.767	805 273
Nivolumab and ipilimumab OS extrapolated with Spline Odds 1 knot	795 929	183 582	1.800	1.178	612 348	0.622	983 755
Weight-based nivolumab dosing	760 636	183 582	1.966	1.178	577 054	0.788	732 054
No vial sharing	894 338	190 415	1.966	1.178	703 923	0.788	893 001
TTD utilities (treatment-specific)	801 770	183 582	2.068	1.259	618 188	0.809	764 607
15 year time horizon	800 022	183 176	1.924	1.168	616 846	0.755	816 538
10 year time horizon	796 027	182 202	1.827	1.146	613 824	0.681	900 817
Alternative approach: not weighted by histology	801 770	187 069	1.966	1.286	614 700	0.679	904 713

Abbreviations: Chemo, chemotherapy (cisplatin/carboplatin); ICER, incremental cost effectiveness ratio; LYG, Life years gained; nivo, nivolumab; peme, pemetrexed; QALY, quality-adjusted life year; TTD, time to death

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9. Budget impact analysis

A budget impact analysis was performed for expected cost of nivolumab and ipilimumab. The economic model described in section 8 was used for estimating total costs. The increased expected survival from treatment with nivolumab and ipilimumab is captured within this analysis. However, unlike the cost-effectiveness analysis, the discount rate for costs were set to 0% for this analysis.

In line with guidelines from the DMC, a time horizon of 5 years was used for this analysis (Medicinrådet 2021a). The number of patients eligible for treatment with nivolumab and ipilimumab in Denmark was estimated to 60 patient annually (for more details, see section 5.1.5.1). In the absence of firm evidence to suggest otherwise, it was assumed that the incidence of new MPM patients would not change from one year to another.

It is expected that the uptake of nivolumab and ipilimumab will be big, considering that it would be the first immunotherapy with approved indication for 1L MPM treatment in Denmark, and that evidence from CheckMate 743 suggest that it is a more effective treatment than the current standard of care. However, it is challenging to estimate the market share exactly. For this analysis, it was assumed that 95% of patients would be treated with nivolumab and ipilimumab, if this treatment would be recommended in Denmark. The remaining patients are assumed to be treated with pemetrexed and cisplatin/carboplatin. The total number of patients receiving each treatment if nivolumab and ipilimumab is recommended as standard treatment is presented in Table 41. If nivolumab and ipilimumab is not recommended, all patients are assumed to be treated with pemetrexed and cisplatin/carboplatin. The number of patients per year and treatment in this scenario is presented in Table 42.

Table 41: Number of incident patients expected to be treated over the next five-year period - if nivolumab and ipilimumab is recommended as standard treatment

	Year 1	Year 2	Year 3	Year 4	Year 5
Nivolumab and ipilimumab	57	57	57	57	57
Pemetrexed and cisplatin/carboplatin	3	3	3	3	3
Total number of patients	60	60	60	60	60

Table 42: Number of incident patients expected to be treated over the next five-year period - if nivolumab and ipilimumab is NOT recommended as standard treatment

	Year 1	Year 2	Year 3	Year 4	Year 5
Nivolumab and ipilimumab	0	0	0	0	0
Pemetrexed and cisplatin/carboplatin	60	60	60	60	60
Total number of patients	60	60	60	60	60

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The total cost per patient treated with nivolumab and ipilimumab for years 1-5 is presented in Table 43. This table also presents a breakdown of the total costs into its different components. An equivalent table outlining the per patient costs for patients treated with pemetrexed and cisplatin/carboplatin is presented in Table 44.

Table 43: Cost per patient and year for patients treated with nivolumab and ipilimumab, years 1-5

Resource type	Analysis year 1	Analysis year 2	Analysis year 3	Analysis year 4	Analysis year 5
PF disease-related costs (DKK)	12 299	4 897	3 007	2 144	1 652
PD disease-related costs (DKK)	6 541	7 190	5 178	3 756	2 792
Drug acquisition costs (DKK)	512 437	131 168	0	0	0
Drug admin costs (DKK)	8 602	2 223	0	0	0
Drug monitoring costs (DKK)	30 945	8 449	0	0	0
AE management related costs (DKK)	27	0	0	0	0
Subsequent treatment costs (DKK)	16 764	3 429	1 342	709	435
End of life costs (DKK)	10 287	6 198	3 367	2 050	1 348
Indirect treatment costs (DKK) †	0	0	0	0	0
Total cost (DKK)	**597 901**	**163 553**	**12 894**	**8 658**	**6 227**

† Indirect treatment costs include the costs of patient time and transportation. These are excluded from the budget impact analysis.
Abbreviations: AE: adverse events; DKK, danish kroner; PD: progressed disease; PF: progression-free disease

Table 44: Cost per patient and year for patients treated with pemetrexed and cisplatin/carboplatin, years 1-5

Resource type	Analysis year 1	Analysis year 2	Analysis year 3	Analysis year 4	Analysis year 5
PF disease-related costs (DKK)	13 248	2 488	778	361	204
PD disease-related costs (DKK)	4 732	6 600	3 646	2 151	1 405
Drug acquisition costs (DKK)	85 450	0	0	0	0
Drug admin costs (DKK)	8 873	0	0	0	0
Drug monitoring costs (DKK)	11 189	0	0	0	0
AE management related costs (DKK)	224	0	0	0	0
Subsequent treatment costs (DKK)	9 488	2 140	411	135	59
End of life costs (DKK)	12 542	8 381	3 216	1 398	714
Indirect treatment costs (DKK) †	0	0	0	0	0
Total cost (DKK)	**145 746**	**19 609**	**8 051**	**4 044**	**2 381**

† Indirect treatment costs include the costs of patient time and transportation. These are excluded from the budget impact analysis.
Abbreviations: AE: adverse events; DKK, Danish kroner; PD: progressed disease; PF: progression-free disease

The total expected cost for a scenario where nivolumab and ipilimumab is recommended as standard treatment is presented in Table 45. The total expected cost for a scenario where nivolumab and ipilimumab is NOT recommended is presented in Table 46. The resulting budget impact if nivolumab and ipilimumab is recommended is the difference in costs between these two scenarios. The expected budget impact from a recommendation of nivolumab and ipilimumab is presented in Table 47.

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Table 45: Cost per year if nivolumab and ipilimumab is accepted as standard treatment (DKK)

Nivolumab and ipilimumab	Analysis year 1	Analysis year 2	Analysis year 3	Analysis year 4	Analysis year 5
Number of patients	57	57	57	57	57
Costs of new patients	34 080 349	34 080 349	34 080 349	34 080 349	34 080 349
Costs of patients from previous years		9 322 508	10 057 452	10 550 964	10 905 898
Total cost for treatment	34 080 349	43 402 858	44 137 801	44 631 314	44 986 247
Pemetrexed and cisplatin/carboplatin					
Number of patients	3	3	3	3	3
Costs of new patients	437 239	437 239	437 239	437 239	437 239
Costs of patients from previous years		58 826	82 979	95 112	102 254
Total cost for treatment	437 239	496 065	520 218	532 351	539 494
Total cost if nivolumab and ipilimumab is accepted as standard treatment	34 517 589	43 898 923	44 658 019	45 163 665	45 525 741

Table 46: Cost per year if nivolumab and ipilimumab is NOT accepted as standard treatment (DKK)

Nivolumab and ipilimumab	Analysis year 1	Analysis year 2	Analysis year 3	Analysis year 4	Analysis year 5
Number of patients	0	0	0	0	0
Costs of new patients	0	0	0	0	0
Costs of patients from previous years		0	0	0	0
Total cost for treatment	0	0	0	0	0
Pemetrexed and cisplatin/carboplatin					
Number of patients	60	60	60	60	60
Costs of new patients	8 744 787	8 744 787	8 744 787	8 744 787	8 744 787
Costs of patients from previous years		1 176 514	1 659 582	1 902 240	2 045 087
Total cost for treatment	8 744 787	9 921 301	10 404 369	10 647 027	10 789 874
Total cost if nivolumab and ipilimumab is NOT accepted as standard treatment	8 744 787	9 921 301	10 404 369	10 647 027	10 789 874

Table 47: Expected annual budget impact if Nivolumab and ipilimumab is recommended as standard treatment (DKK)

	Analysis year 1	Analysis year 2	Analysis year 3	Analysis year 4	Analysis year 5
Cost if treatment is recommended	34 517 589	43 898 923	44 658 019	45 163 665	45 525 741
Cost if treatment is not recommended	8 744 787	9 921 301	10 404 369	10 647 027	10 789 874
Total budget impact	25 772 802	33 977 622	34 253 651	34 516 639	34 735 867

Including the effect from survival in this analysis is a conservative approach since nivolumab and ipilimumab is expected to increase survival, and hence also raise the overall budget impact of this treatment. However, this approach yields a more accurate estimation of how the budget is affected from an approval decision, compared to an approach where differences in survival had been ignored.

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10. Discussion on the submitted documentation

The reported results of nivolumab in combination with ipilimumab for the 1L treatment of MPM are considered relevant. Malignant pleural mesothelioma is a rare and aggressive disease with poor prognosis and usually diagnosed in advanced stages. Standard treatment, platinum + pemetrexed chemotherapy, was authorized in 2004 showing a survival benefit of 12 months, but no other treatment combination has showed better results thus far.

This analysis has found that nivolumab and ipilimumab is an effective 1L treatment for patients with unresectable MPM. Compared to treatment with pemetrexed and cisplatin/carboplatin, treatment with nivolumab and ipilimumab is expected to yield an additional 0.788 QALYs. The expected cost for this is DKK 618 188. The resulting ICER per QALY is DKK 784 237. All the analyses presented for the base case and scenarios are based upon list prices for the acquisition costs of nivolumab and ipilimumab. The analyses are based on best practice methods and according to the guidance provided by the DMC methods guidance. The standard three-health state model structure is consistent with the approaches adopted in economic evaluations and technology appraisals with nivolumab alone or in combination with ipilimumab.

The findings from the deterministic cost-effectiveness analysis are supported by the results from the deterministic and probabilistic sensitivity analyses. The main drivers of the ICER are the utility values applied to progression-free and progressed disease, as well as the drug acquisition costs for each treatment, particularly the cost of nivolumab and ipilimumab.

Scenario analyses were performed to ascertain how sensitive the results were to structural assumptions in the model. Reducing the time horizon of the analysis leads to a reduced value of treatment with nivolumab and ipilimumab, since the expected increases to survival is given a smaller impact. Similarly, a lower discount rate improves the value of the treatment relative to the comparator, since it increases the value placed upon increased survival.

The choice of survival extrapolation methods for both treatment arms is also an important factor. Several combinations and methods have been analyzed, resulting in both higher and lower ICERs for nivolumab and ipilimumab against the comparator. It is common that the choice of extrapolation method is an important driver of cost-effectiveness in survival-enhancing treatments for which only limited follow-up time is available. For this analysis, several different methods have been used to determine which base case settings should be used: statistical analysis (AIC and BIC), external validation and landmark analysis against expert expectations, and analysis of smoothed hazard curves. Great care has been taken to ensure that the base case should reflect as accurately as possible the expected value of treatment with nivolumab and ipilimumab in this population.

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11. List of experts

[redacted]

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13. Appendix A: Literature search for efficacy and safety of intervention and comparator

A systematic literature review (SLR) was conducted to identify and summarize the clinical efficacy and safety of treatments used in the first-line setting of MPM.

For more comprehensive overview of the SLR, please see the Appendix 25 document attached with this submission.

13.1 Search strategy

Summary of searches is provided in Table 48. The literature was identified via electronic search of: Excerpta Medica Database (Embase®), Medical Literature Analysis and Retrieval System Online (MEDLINE®), MEDLINE in-process, Cochrane Central Register of Controlled Trials (CENTRAL), and Cochrane Database of Systematic Reviews (CDSR). MEDLINE® and Embase® were searched using the embase.com interface, while the MEDLINE in-process was searched via PubMed. CENTRAL and CDSR were searched using the Cochrane Library.

Supplementary searches of the following conference proceedings were reported for the previous three years (2018-20): American society of clinical oncology (ASCO), European society for medical oncology (ESMO), American Association for cancer research (AACR), International Society for Pharmacoeconomics and Outcomes Research (ISPOR), World Conference on Lung Cancer (WCLC), European Lung Cancer Congress (ELCC), and International Mesothelioma Interest Group (IMIG).

Bibliographic searching of included studies and relevant literature reviews was also conducted, to supplement the evidence retrieved from the biomedical databases.

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Table 48: Summary of searches

Databases searched	
Databases (from inception to October 5, 2020)	• Embase® via Embase.com • MEDLINE® via Embase.com • MEDLINE® In-Process via PubMed • Cochrane Central Register of Controlled Trials (CENTRAL) via Cochrane Library • Cochrane Database of Systematic Reviews (CDSR) via Cochrane Library
Conference data sources searched	
Conference proceedings (Last three years; 2018-2020)	• American society of clinical oncology (ASCO) • European society for medical oncology (ESMO) • American Association for cancer research (AACR) • International Society for Pharmacoeconomics and Outcomes Research (ISPOR) • World Conference on Lung Cancer (WCLC) • European Lung Cancer Congress (ELCC) • International Mesothelioma Interest Group (IMIG)
Information extracted	
Clinical review outcomes of interest	• Overall survival • Progression-free survival • Disease control rate (Complete response + Partial response + Stable disease) • Overall response rate (Complete response + Partial response) • Safety (any grade and grade 3-4 adverse events)
Critical appraisal	• Randomized controlled trials were appraised using the NICE checklist

Eligibility criteria were specified in terms of population, intervention and comparators, outcomes and study design (PICOS) (Higgins). The population of interest in the SLR comprised adult patients with MPM of any ethnicity, race, or gender. The literature review did not limit the inclusion of studies based on the treatments being evaluated, i.e., all pharmacological interventions (approved + investigational) were included. The last searches were carried out on 5 OCT 2020. Searches were restricted to the English language. Eligibility criteria for the studies are presented in Table 49.

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Table 49: Eligibility criteria for the SLR

Patient population		
Population	• Gender: Any • Race: Any • Ethnicity: Any • Disease: Malignant pleural mesothelioma	
Interventions and comparators (No restriction) **Approved + In-development treatments were included in the SLR (Monotherapy or in combination)**	• Doxorubicin • Picoplatin • Oxaliplatin • Raltitrexed • Cyclophosphamide • Pemetrexed • Carboplatin • Gemcitabine • Vinorelbine • Fluorouracil • Vinblastine • Pemetrexed + Cisplatin/Carboplatin • Erlotinib • Bevacizumab	• Cisplatin • Navelbine • Platinum • Topotecan • Liposomal doxorubicin • Irinotecan • Mitomycin • Paclitaxel • Adriamycin • Nivolumab + ipilimumab • Pembrolizumab • Best supportive care • Active symptom control
Language	• Current review included studies for which full-text publications were available in English	
Publication timeframe*	• Database inception to October 5, 2020	
Study design of interest	• Randomized controlled trials	

All the citations were screened by two independent reviewers, followed by a quality check by a third independent reviewer. The first screening stage included a review of citations based on their titles and abstracts. Citations that do not match the eligibility criteria were excluded at the first-pass stage. Duplicates of citations (due to the overlap in the coverage of databases) were excluded at the first-pass stage. Full-text copies of all the references that potentially met the eligibility criteria were obtained.

After the completion of first stage screening, the full texts of relevant studies were examined in more detail to determine a final list of included studies. All the citations were screened by two independent reviewers, followed by a quality check by a third independent reviewer.

Data were extracted by two independent reviewers, followed by a quality check by a third independent reviewer.

13.2 Systematic selection of studies

The study flow diagram is provided in Figure 35 below.

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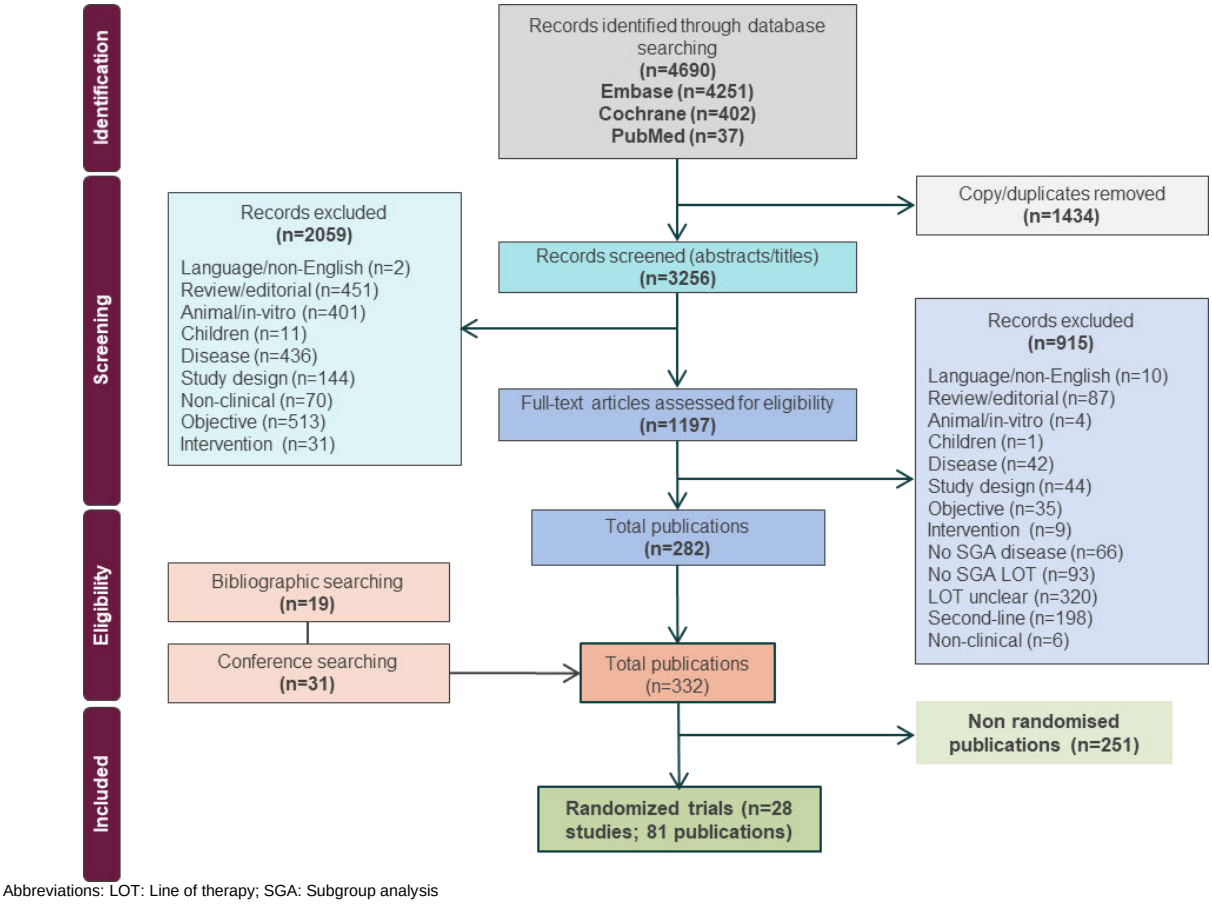
Figure 35: PRISMA flow diagram for studies assessing treatments for malignant pleural mesothelioma



Abbreviations: LOT: Line of therapy; SGA: Subgroup analysis

Systematic literature searches resulted in the retrieval of 4690 citations. Following the pre-determined inclusion/exclusion criteria, detailed screening of the abstracts and full-texts resulted in the final inclusion of 332 publications, 282 through electronic database searches, 50 through the conference and bibliographic searching. Of the 332 publications included, 81 publications (28 studies) were conducted in a randomized controlled setting, while 251 publications were conducted in a non-randomized setting inclusive of multi-arm observational, single-arm, and non-randomized controlled studies.

13.3 Quality assessment

Systematic reviews involve explicit, transparent methods which are clearly stated and reproducible (minimize bias by using objective, pre-defined inclusion criteria). The robustness of the review is primarily determined by (i) the quality and (ii) the data reported in the eligible studies. Limitations concerning the systematic review and evidence synthesis include the limitations of using published data. The robustness of the evaluation may be compromised by the internal validity of the identified studies. However, to assess this, studies are critically appraised for potential bias using appropriate methodology.

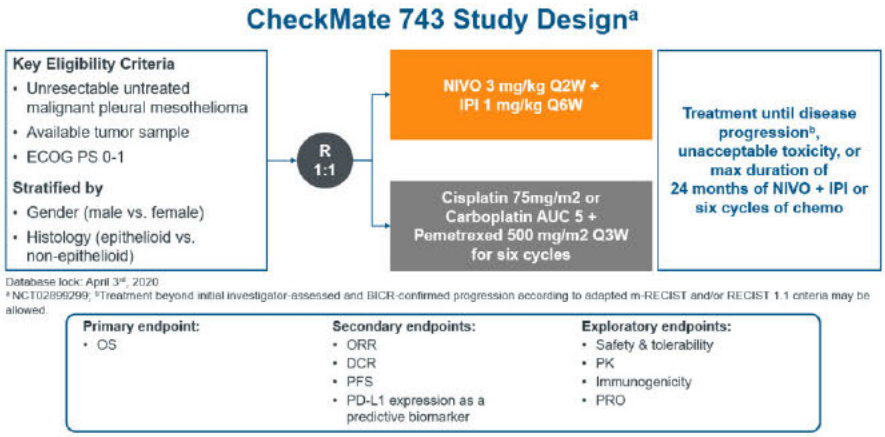
13.4 Unpublished data

The unpublished data used in this submission are all sourced from the CheckMate 743 clinical trial.

14. Appendix B: Main characteristics of included study

The main trial supporting this submission document is the CheckMate 743 (NCT02899299) clinical trial, which is described in Table 50 below.

Table 50: Key characteristics of the CheckMate 743 trial

Trial name: CheckMate 743	NCT number: NCT02899299
Objective	To test the effectiveness and tolerability of the combination of Nivolumab and Ipilimumab compared to Pemetrexed and Cisplatin or Carboplatin in patients with unresectable pleural mesothelioma
Publications – title, author, journal, year	Baas P, et al. First-line nivolumab plus ipilimumab in unresectable malignant pleural mesothelioma (CheckMate 743): a multicentre, randomised, open-label, phase 3 trial. Lancet. 2021 Jan 30;397(10272):375-386. Wright K. FDA Approves Nivolumab Plus Ipilimumab for Previously Untreated Unresectable Malignant Pleural Mesothelioma. Oncology (Williston Park). 2020 Nov 12;34(11):502-503.
Study type and design	CM-743 is an open-label, multi-center, randomized phase 3 trial evaluating nivolumab plus ipilimumab compared to chemotherapy (pemetrexed with cisplatin or carboplatin) as 1L therapy in patients with previously untreated unresectable MPM (Baas 2020a). CM-743 patients were randomized (1:1) to one of the following (Baas 2020a): • Arm A: nivolumab administered intravenously (IV) over 30 minutes at 3 mg/kg every 2 weeks (Q2W) combined with ipilimumab administered IV over 30 minutes at 1 mg/kg every 6 weeks (Q6W) for up to 2 years • Arm B: pemetrexed (500 mg/m^2) combined with either cisplatin (75 mg/m^2) or carboplatin (area under the curve [AUC] 5) all on day one every 3 weeks for six cycles or until disease progression or unacceptable toxicity. Cisplatin was the preferred choice of treatment; however, the use of carboplatin was at the discretion of the investigator, and the reason for using carboplatin was required to be documented in the case report form. Patients in each arm were stratified by histology (epithelioid versus non-epithelioid) and gender. All treatments continued until disease progression, unacceptable toxicity, or for up to 2 years for immunotherapy or up to six cycles for chemotherapy (Baas 2020a). Crossover between treatment arms within the study was not permitted (Baas 2020a). **Figure 36. CM-743: Study design**  Abbreviations: AUC: area under the curve; BICR: blinded independent central review; DCR: disease control rate; ECOG: Eastern Cooperative Oncology Group; IPI: ipilimumab; mRECIST: modified response evaluation criteria in solid tumors; NIVO: nivolumab; ORR: objective response rate; OS: overall survival; PD-L1: programmed cell death-ligand 1; PFS: progression-free survival; PK: pharmacokinetics; PRO: patient reported outcomes; PS: performance status; vs.: versus; Q2W: every 2 weeks; Q3W: every 3 weeks; Q6W: every 6 weeks; R: Randomization

Trial name: CheckMate 743	NCT number: NCT02899299
Sample size (n)	N=605
Main inclusion and exclusion criteria	**Key inclusion criteria:** • Male and female subjects (≥18 years of age) • Histologically proven diagnosis of MPM, with determination of epithelioid vs. non-epithelioid histology • Advanced unresectable disease that is not amenable to therapy with curative intent (surgery with or without chemotherapy). Subjects who refused potentially curative surgery were ineligible • Available (archival and/or fresh) pathological samples for centralized PD-L1 IHC testing during the screening period • Prior palliative radiotherapy was acceptable, but at least 14 days must have passed since the administration of the radiotherapy and all signs of toxicity must have remitted • ECOG PS of 0-1 • Measurable disease, defined as at least one lesion measured in up to two positions at three separate levels on transverse cuts of CT scan that is suitable for repeated assessment using adapted mRECIST for pleural mesothelioma • Adequate hematological, renal and hepatic functions **Key exclusion criteria:** • Primitive peritoneal, pericardial and tunica vaginalis testis mesotheliomas • Brain metastasis, except if surgically resected or treated with stereotaxic radiotherapy with no evolution within the 3 months before inclusion, and asymptomatic. In addition, subjects must be either off corticosteroids, or on a stable or decreasing dose of ≤10 mg daily prednisone (or equivalent) for at least 2 weeks prior to randomization • Prior treatment with adjuvant or neoadjuvant chemotherapy; radical pleuropneumonectomy with or without intensity modulated radiotherapy, or non-palliative radiotherapy • Prior intraoperative or intracavitary chemotherapy for pleural mesothelioma • Prior treatment with an anti-PD-1, anti-PD-L1, anti-PD-L2, anti-CTLA-4 antibody, or any other antibody or drug specifically targeting T-cell co-stimulation or checkpoint pathways • History of chronic inflammatory or autoimmune disease • Concurrent or prior malignancy requiring or anticipated to require concurrent intervention Subjects with interstitial lung disease that is symptomatic or may interfere with the detection or management of suspected drug-related pulmonary toxicity
Intervention	Nivolumab administered intravenously (IV) over 30 minutes at 3 mg/kg every 2 weeks (Q2W) combined with ipilimumab administered IV over 30 minutes at 1 mg/kg every 6 weeks (Q6W) for up to 2 years
Comparator(s)	Pemetrexed (500 mg/m^2) combined with either cisplatin (75 mg/m^2) or carboplatin (area under the curve 5) all on day one every 3 weeks for six cycles or until disease progression or unacceptable toxicity.
Follow-up time	Medium follow-up: 29.7 months
Is the study used in the health economic model?	Yes

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Trial name: CheckMate 743	NCT number: NCT02899299
Primary, secondary and exploratory endpoints	**Primary** • Overall survival **Secondary** • Objective response rate • Disease control rate • Composite correlation of PD-L1 expression level and efficacy • Progression Free Survival
Method of analysis	Approximately 600 patients were to be randomized into the two treatment groups in a 1:1 ratio, with 606 patients actually randomized. The sample size was based on the comparison of the primary endpoint of OS between treatment groups. Demographics and baseline laboratory results were summarized by treatment arm as randomized using descriptive statistics for all randomized subjects. The primary endpoint analysis of OS was performed using all randomized subjects by treatment group as randomized. The distribution of OS was compared in two randomized arms at the interim and final analysis via a two-sided, log-rank test stratified by histology and gender with an overall significance level of 0.05. The HR and the corresponding two-sided 100x (1-adjusted α) % CI was estimated in a stratified Cox proportional hazards model using the randomized arm as a single covariate (Bristol-Myers Squibb 2019). For OS, approximately 473 events (i.e. deaths), observed among the 606 randomized subjects, provides 90% power to detect an average HR of 0.72 with a type 1 error of 0.05 (two-sided) (Bristol-Myers Squibb 2019). There was one planned interim analysis of OS for superiority at approximately 85% of total events, i.e. 403 deaths. A group sequential testing procedure was applied to OS to control the overall type I error for interim and final analyses (Bristol-Myers Squibb 2019). The HR, median, and survival rate at 6, 12, 18, 24, 36, 48 months and 5 years were estimated for OS. Associated two-sided 95% CIs were calculated using the Greenwood formula (using log-log transformation). The secondary endpoints i.e., ORR, DCR, and the distribution of PFS were assessed by BICR. ORRs or DCRs and their corresponding 95% exact CIs were calculated using the Clopper-Pearson method for each treatment group (Bristol-Myers Squibb 2019). The PFS curves for each randomized arm were estimated using the Kaplan-Meier product-limit method. Two-sided, 95% CIs for median PFS were computed by Brookmeyer and Crowley method (using log-log transformation). PFS rates at 6, 12, 18, 24, 36, 48 months and 5 years were estimated using Kaplan-Meier estimates on the PFS curve for each randomized arm provided minimum follow-up was longer than timepoint to generate the rate (Bristol-Myers Squibb 2019). Associated two-sided 95% CIs were calculated using the Greenwood formula (using log-log transformation). The safety analysis was performed in all treated subjects. Descriptive statistics of safety were presented using the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) version 4.0 by treatment arm. Analyses of EQ-5D and LCSS-Meso data were also descriptive.
Subgroup analyses	Prespecified descriptive subgroup analyses for overall survival was summarised using HRs (with 95% CIs) calculated using an unstratified Cox proportional hazards mode
Other relevant information	N/A

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

The baseline characteristics of patients are presented in Section 7 above.

15.1 Comparability of patients across studies

The treatment (nivolumab plus ipilimumab) is compared with the comparator directly in the trial CheckMate 743, and baseline characteristics are balanced between the treatment arms.

15.2 Comparability of the study populations with Danish patients eligible for treatment

Differences between the study populations and the Danish patient population and how this affects transferability of results to Danish clinical practice are described in Section 8 above.

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16. Appendix D: Efficacy and safety results per study

16.1 Definition, validity and clinical relevance of included outcome measures

Overall survival (OS) is the gold standard primary end point to evaluate the outcome of any drug, biologic, intervention, or procedure that is assessed in oncologic clinical trials. OS is universally recognized as being unambiguous, unbiased, with a defined end point of paramount clinical relevance, and positive results provide confirmatory evidence that a given treatment extends the life of a patient.

Progression-free survival (PFS), the time from treatment initiation until disease progression or worsening, may be used as a direct or surrogate measure of clinical benefit for drug approvals, depending on the disease and response observed, while overall survival (OS), the duration of patient survival from the time of treatment initiation, is a universally-accepted direct measure of clinical benefit. As noted in Section 7.1.2.1.2, since MPM is a heterogeneous tumour and may not be well-delineated and lack clearly demarcated margins (Sureka 2013), radiographic assessment of tumour margins—used in PFS as well as ORR assessment—in MPM, is faced with inherent challenges due to the natural history of this disease and location of lesions (FDA 2018).

As for PFS, the outcomes centred around tumour progression—objective response rate (ORR), time to response (TTR), duration of response (DOR), and disease control rate (DCR)—can face the same challenges when it comes to the assessment of tumor margins.

- ORR defined as the percentage of randomized participants who achieve a best overall response of complete response or partial response per Blinded Independent Central Review (BICR) assessments (Per adapted m-RECIST for pleural mesothelioma and RECIST 1.1, confirmation of response required).
- TTR is defined as the time from randomization until objective tumor progression; TTP does not include deaths
- DOR is defined as the time between the date of first response to the date of the first documented tumour progression, or death due to any cause, whichever occurred first.
- DCR is defined as the percentage of all randomized participants whose Best Overall Response was Complete Response, Partial Response, Stable Disease or Non-CR/Non-PD per adapted m-RECIST and RECIST 1.1 as assessed by Blinded Independent Central Review (BICR)

While improvements in OS clearly demonstrate clinical benefits that are meaningful to patients, PFS, depending on the magnitude, may have high value as well. By design, PFS and OS will be related, as OS is comprised of PFS plus post-progression survival**.**

The tables below presents the results from the CheckMate 743 trial.

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16.2 Results per study

The main results of CheckMate 743 (NCT02899299) clinical trial, which is described in Table 51 below.

Table 51: Results of CheckMate 743

Results of CheckMate 743												
				Estimated absolute difference in effect			Estimated relative difference in effect			Description of methods used	References
Outcome	**Study arm**	**N**	**Result (CI)**	**Difference**	**95% CI**	***P* value**	**Difference**	**95% CI**	***P* value**		
Overall survival (median months)	Nivo + ipi	303	18.1 (16.8-21.4)	5.0	96.6% CI: 1.4-9.4		HR: 0.74	96.6% CI: 0.60-0.91	0.002	Median survival is based on the KM estimator. The HR and the corresponding two-sided 100x (1-adjusted α) % CI was estimated in a stratified Cox proportional hazards model using the randomized arm as a single covariate.	(Baas 2021)
	chemo	302	14.1 (12.4-16.2)								
Progression free survival (median months)	Nivo + ipi	303	6.8 (5.6–7.4)	0.0	96.6% CI: -1.2-1.6		HR: 1.00	0.82-1.21	0.8*	The PFS curves for each randomized arm were estimated using the Kaplan-Meier product-limit method. Two-sided, 95% CIs for median PFS were computed by	(Baas 2021)
	chemo	302	7.2 (6.9–8.0)								

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									Brookmeyer and Crowley method (using log-log transformation).	
Objective response rate (n)	Nivo + ipi	303	120 (34.1-45.4)	9.7	96.6% CI: -14-39.4	RR: 0.93	0.77-1.12	0.458	ORRs or DCRs and their corresponding 95% exact CIs were calculated using the Clopper-Pearson method for each treatment group.	(Baas 2021)
	chemo	302	129 (37.1-48.5)							
Disease control rate (n)	Nivo + ipi	303	232 (71.4-81.2)	28.6	96.6% CI: 7.1-51.9	RR: 0.90	0.83-0.97	<0.01	ORRs or DCRs and their corresponding 95% exact CIs were calculated using the Clopper-Pearson method for each treatment group.	(Baas 2021)
	chemo	302	257 (80.6-88.9)							
Duration of response (months)	Nivo + ipi	120	11.0 (8.1-16.5)	4.3	95% CI: 0.02-8.59	HR: 0.53*	0.39-0.73*	<0.001*		(Baas 2021)
	chemo	129	6.7 (5.3-7.1)							
Time to response (months)	Nivo + ipi	232	2.7 (IQR 1.45-3.27)	4.0	95% CI: 3.77-4.23					(Baas 2021)
	chemo	257	6.7 (IQR 1.41-3.02)							

Abbreviations: CI, confidence interval; ipi, ipilimumab; IQR, interquartile range; nivo, nivolumab; ORR, objective response rate; OS, overall survival; PFS, progression free survival.
*Obtained after digitizing the Kaplan-Meier curves and reconstructing individual patient data with the Guyot algorithm (Guyot 2012) and subsequently running Cox regression.

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

The safety data for the intervention and the comparators are described in Section 7 above.

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18. Appendix F: Comparative analysis of efficacy and safety

As the treatment (nivolumab plus ipilimumab) are compared to the comparator directly in the clinical trial CheckMate 743, the comparative analysis is reported in the per trial results section.

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19. Appendix G: Extrapolations

19.1 Estimating transition between health states

The partitioned survival method requires simulation of PFS and OS over the course of the time horizon of the evaluation. The cumulative survival probabilities for PFS and OS were used to estimate the number of patients occupying the PF, PD, and death states using the following equations:

$$PF = P(PFS)$$

$$Death = 1 - P(OS)$$

$$PD = P(OS) - P(PFS)$$

Abbreviations: OS: overall survival; PD: progressed disease; PF: Progression-free; PFS: Progression-free survival

The primary data for the economic model was from the April 2020 database lock of CheckMate 743. At this time point, the minimum follow-up for all patients was 22.1 months. This follow-up period is shorter than the required length of the economic analysis (a lifetime of up to 20 years) and 23% and 15% of patients were still alive at the end of trial period, with expected ongoing benefit on nivolumab and ipilimumab and pemetrexed and cisplatin/carboplatin, respectively. To estimate the cumulative PFS and OS over the 20-year time horizon, parametric survival curves were fitted to CheckMate 743 patient-level data and used to extrapolate survival beyond the study time horizon.

The process for fitting parametric survival curves to patient-level data was based on methods guidance from the Decision Support Unit at the National Institute for Health and Care Excellence (NICE)(Latimer 2013, Rutherford 2020), and guidelines from the Danish Medicines Council (Medicinrådet 2020b). Figure 37 provides a visual depiction of the process for identifying the parametric survival model for PFS and OS.

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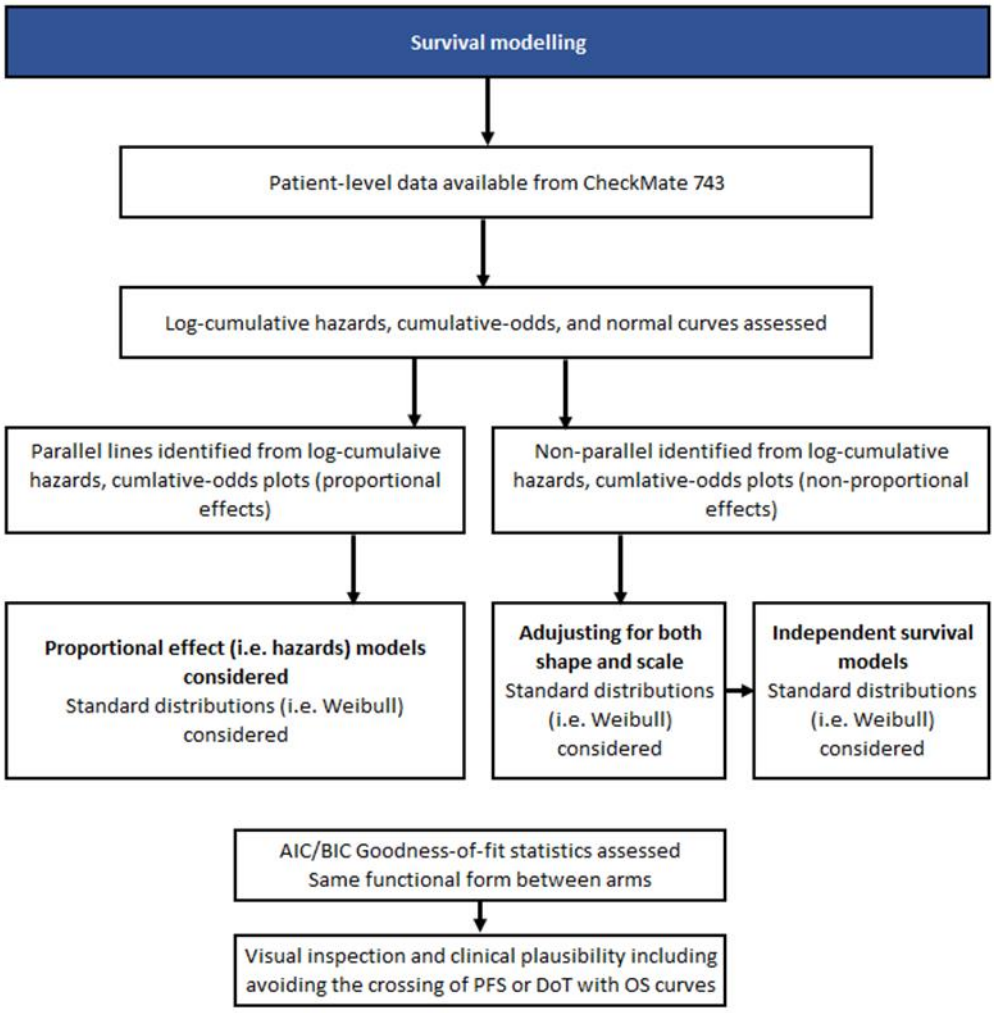
Figure 37: Identifying the parametric survival curves for the economic model



Abbreviations: AIC: Akaike information criterion; BIC: Bayesian information criterion

Aligned with Figure 37, the following process was used to determine the most appropriate curve fits for PFS and OS in the model:

- Testing the proportional effects assumption – the log cumulative hazards, log cumulative odds, and standardized normal curve plots were assessed to determine if the data from CheckMate 743 indicate proportional effects. This assessment was done both by testing the significance of the Grambsch and Therneau's correlation test between Schoenfeld residuals and log of time and visual inspection to determine if the survival curves of nivolumab and ipilimumab and platinum doublet chemotherapy arms were parallel.
- In the event proportional effects holds, a range of dependent standard parametric and spline-based survival distributions were explored. A summary of the survival distributions used in the parametric modelling is provided in Table 52. Where proportional effects did not hold, independent standard parametric and spline-based models were considered.
- Akaike Information Criterion (AIC) and Bayesian Information Criterion (BIC) goodness-of-fit statistics were assessed to identify the best fitting survival models.
- The final choice of parametric survival distributions for the base case model was based on:
- the best fitting survival models measured by the lowest AIC statistic, measuring goodness-of-fit (compared to the KM data from CheckMate 743), prioritizing it over BIC measure
- the visual inspection of the model's goodness-of-fit (compared to the KM data from CheckMate 743)
- For OS: Clinical plausibility of survival extrapolations were assessed until 19 years using conditional survival estimates from the Surveillance, Epidemiology and End Results (SEER) programme of the National Cancer Institute in the US (SEER 2021) and the MAPS study (Zalcman 2016).

It is important to consider goodness-of-fit because it measures the model fit against the available trial data. In addition, it is equally important to assess the clinical plausibility of the extrapolated portion of the curves as it is the area with the highest uncertainty due to lack of trial data.

When the proportional effects assumption did not hold, only independent survival models were assessed. Following this assessment, the same approach — goodness of fit, visual inspection, and clinical plausibility — was used to identify the base case survival curve for the model.

A summary of the survival distributions used in the parametric modelling is provided in Table 52.

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Table 52: Definition of distributions in the economic model

Distribution name	Survival function	Characteristic
Exponential	$S(t) = \exp(-\lambda x)$	Constant hazard function; proportional hazards mode
Weibull	$S(t) = \exp\left(-\left(\frac{x}{b}\right)^{a}\right)$	Hazard function can increase or decrease monotonically over time; proportional hazards (or accelerated failure time)
Gompertz	$s(t) = \exp\left(-\frac{b}{a}(\exp(ax) - 1)\right)$	Hazard function can increase or decrease monotonically over time; proportional hazards
Lognormal	$s(t) = 1 - \Phi\left(\frac{\log(x) - \mu}{\sigma}\right)$	Hazard function increases initially to a maximum, before decreasing over time
Log-logistic	$s(t) = 1 - \frac{1}{1 + \left(\frac{x}{\alpha}\right)^{-\beta}}$	Hazard function can be non-monotonic with respect to time; accelerated failure time. Log-logistic models often result in long tails in the survivor function
Generalized gamma	$f(x) = \lvert Q\rvert (Q^{-2})^{Q^{-2}} \frac{1}{\sigma x \Gamma(Q^{-2})} \exp\left(Q^{-2}(Qw - e^{Qw})\right)$ $x = \exp(\mu + \sigma w)$	Flexible 3-parameter model, and can be generalized to the Weibull, exponential, and lognormal distributions
Gamma	$f(t) = \frac{1}{(b^a\,\Gamma(a))} t^{(a-1)} e^{-\left(\frac{t}{b}\right)}$	Hazard function can increase or decrease monotonically over time; proportional hazards
Proportional odds spline model	$\ln H(x) = s(x,\gamma) + \beta$ $S(x,\gamma) = \gamma_0 + \gamma_1 x + \gamma_2 V_1(x) + \cdots \gamma_{m+1} V_m(x)$ $V(x) = (x - k_j)_+^3 - \lambda_j (x - k_{min})_+^3 - (1 - \lambda_j)(x - k_{max})_+^3$ $\lambda_j = \frac{k_{max} - k_j}{k_{max} - k_{min}}$ $(x - a)_+ = \max(0, x - a)$	Up to 3-knot models were fitted to the trial data – for the base case, the knots were evenly distributed over the time horizon of the study follow-up, based on the default settings of the flexsurv package
Proportional hazards spline model	$\ln O(x) = s(x,\gamma) + \beta$ $S(x,\gamma) = \gamma_0 + \gamma_1 x + \gamma_2 V_1(x) + \cdots \gamma_{m+1} V_m(x)$ $V(x) = (x - k_j)_+^3 - \lambda_j (x - k_{min})_+^3 - (1 - \lambda_j)(x - k_{max})_+^3$ $\lambda_j = \frac{k_{max} - k_j}{k_{max} - k_{min}}$ $(x - a)_+ = \max(0, x - a)$	
Spline model with a probit link function	$-\Phi^{-1}[S(x)] = s(x,\gamma) + \beta$ $S(x,\gamma) = \gamma_0 + \gamma_1 x + \gamma_2 V_1(x) + \cdots \gamma_{m+1} V_m(x)$ $V(x) = (x - k_j)_+^3 - \lambda_j (x - k_{min})_+^3 - (1 - \lambda_j)(x - k_{max})_+^3$ $\lambda_j = \frac{k_{max} - k_j}{k_{max} - k_{min}}$ $(x - a)_+ = \max(0, x - a)$	

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19.2 Extrapolation methods

All survival modelling was conducted using the FlexSurv package in R and modelled using the FlexSurvReg function. The proportion of patients in PF, PD, and death states beyond the trial follow-up were estimated by fitting parametric and spline-based survival functions to the observed PFS and OS data from the CheckMate 743 trial.

The following parameters were modelled:

- Overall survival (OS)
    - Used to estimate proportion of patients alive at each cycle of the model and in the PD health state
- Progression-free survival (PFS)
    - Used to calculate proportion of patients in the PF and PD health state
- Duration of treatment (DoT)
    - Used to estimate actual primary treatment costs

For OS and PFS, seven parametric models were considered for the extrapolation of 'all-comers' patient-level data (exponential, Weibull, Gompertz, log-normal, log-logistic, gamma, and generalized gamma) as well as spline models (odds spline model, hazards spline model and spline model with a probit link function). For DoT, Kaplan-Maier (KM) data from the study was used directly for this analysis, i.e. no modelling extrapolation was utilized.

Proportional hazards were assessed by a visual inspection of log-cumulative hazards plots, a Grambsch and Therneau's correlation test, and a visual inspection of a Schoenfeld residuals plot. Curve selection was based on NICE DSU guidance. The process involved using goodness-of-fit as assessed by the Bayesian Information Criteria (BIC) and the Akaike Information Criteria (AIC), visual fit to observed Kaplan-Meier data, clinical plausibility, and by validating against external evidence where plausible.

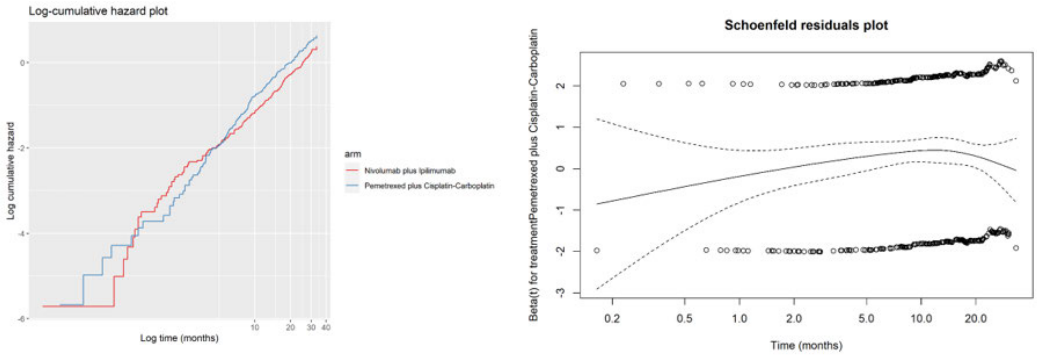
19.3 Overall survival

19.3.1 Testing of proportional hazards assumption

Visual inspection of the log-cumulative hazards and Schoenfeld residuals plots were undertaken to assess proportionality of treatment effects over time. The Grambsch and Therneau's correlation test between Schoenfeld residuals and log of time failed to reject the proportional hazards assumption (p=0.34), however, visual inspection of the Schoenfeld residuals plot provides some evidence of non-proportionality (Figure 39).

While statistical tests failed to reject the proportional hazards assumption, key opinion leaders (KOLs) from the global advisory board agreed that there was evidence of non-proportionality in the log-cumulative hazards plot and the Schoenfeld residuals plot, and considered independent models to be more appropriate to model OS given the contrasting mechanism of action and survival kinetic of immunotherapy compared with chemotherapy. However, given the inconclusive nature of the assessment of proportional hazards, dependent curves were still assessed for visual fit and external validation.

Figure 39: Log-cumulative hazard plot and Schoenfeld residuals plot for nivolumab and ipilimumab vs. pemetrexed and cisplatin/carboplatin for OS



19.3.2 Pemetrexed and cisplatin/carboplatin

A summary of the goodness-of-fit statistics for the OS endpoint of pemetrexed plus cisplatin/carboplatin is presented in Table 53. This shows the AIC and BIC for standard parametric models as well as the spline-based models, up to 3 knots. The difference in AIC values between the top 10 distributions was minimal, suggesting that they may provide a reasonable fit to the trial data.

Table 53: Statistical goodness-of-fit indicators (AIC/BIC) values for independent parametric models fitted to OS data for pemetrexed and cisplatin/carboplatin

Independent model	AIC rank	AIC	BIC
Gamma	1	1737.23	1744.65
Log-logistic	2	1737.31	1744.73
Spline on odds, 1 knot	3	1737.75	1748.89
Spline on normal, 1 knot	4	1737.85	1748.98
Generalised gamma	5	1738.71	1749.84
Spline on hazard, 1 knot	6	1738.81	1749.94
Weibull	7	1739.22	1746.64
Spline on normal, 2 knots	8	1739.28	1754.12
Spline on hazard, 2 knots	9	1739.67	1754.51
Spline on odds, 2 knots	10	1739.70	1754.54
Spline on odds, 3 knots	11	1740.23	1758.78
Spline on hazard, 3 knots	12	1741.60	1760.15
Spline on normal, 3 knots	13	1743.09	1761.64
Gompertz	14	1749.37	1756.79
Log-normal	15	1749.58	1757.00
Exponential	16	1756.98	1760.69

Abbreviation: AIC: Akaike information criterion; BIC: Bayesian information criterion; OS: Overall survival

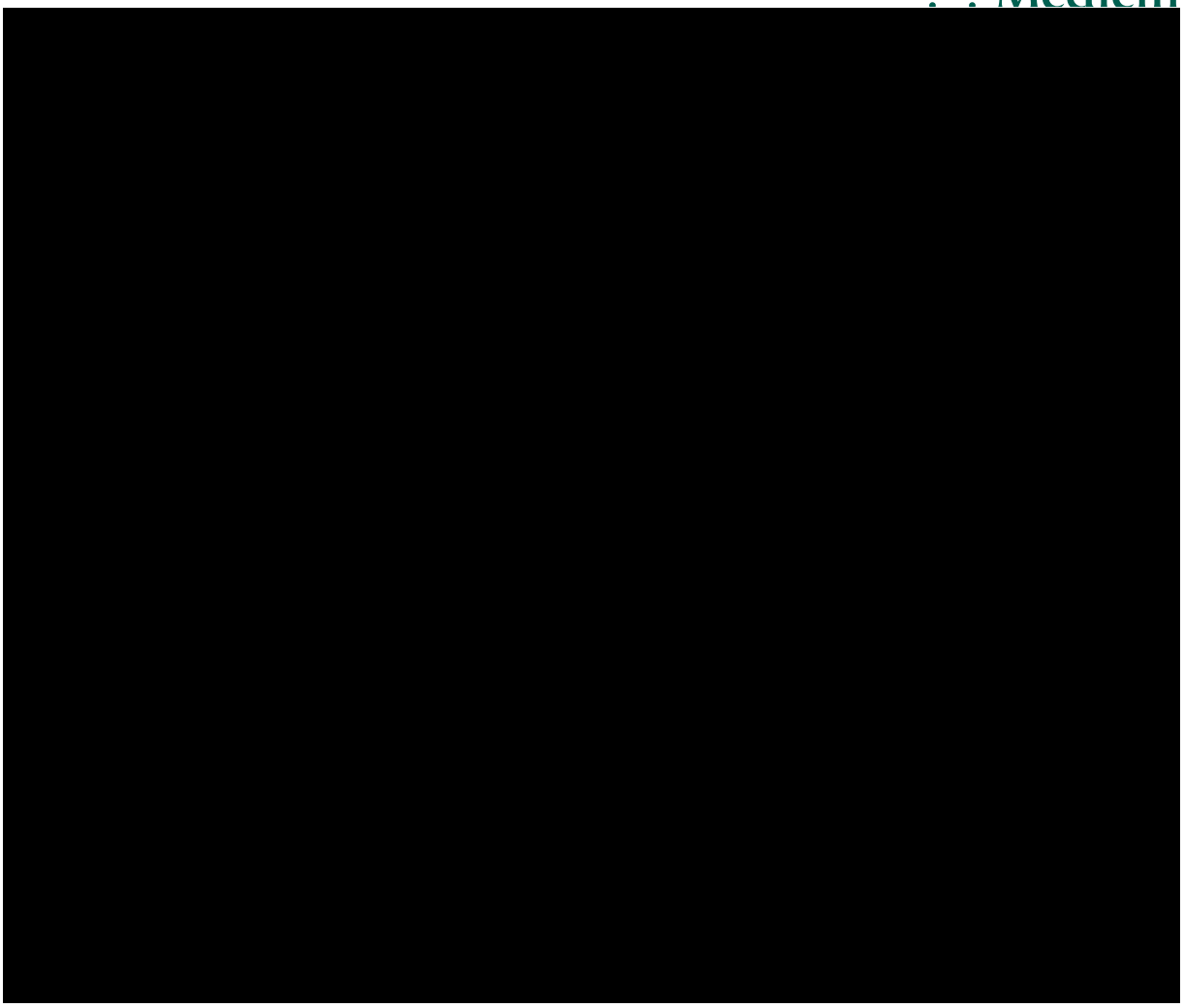
In order to appropriately select the base case curve for OS in the pemetrexed and cisplatin/carboplatin arm, external sources of long-term data were utilized in order to assess the clinical plausibility of the different distributions. This was conducted by analysing the survival models for OS against a piecewise curve constructed using data from:

- CheckMate 743 (pemetrexed and cisplatin/carboplatin arm)
- MAPS trial data (pemetrexed and cisplatin arm). The patients in the MAPS trial were relatively younger and had a slightly different histology mix than was the case in CheckMate 743 (Median age 66 vs 69 and epithelioid proportion 81% vs 75% for MAPS vs Checkmate 743 respectively), thus representing an upper limit of the long term OS (Zalcman 2016).
- SEER data (MPM patients). Survival data for MPM patients with mixed treatment history were obtained from SEER cancer registry (SEER 2021).

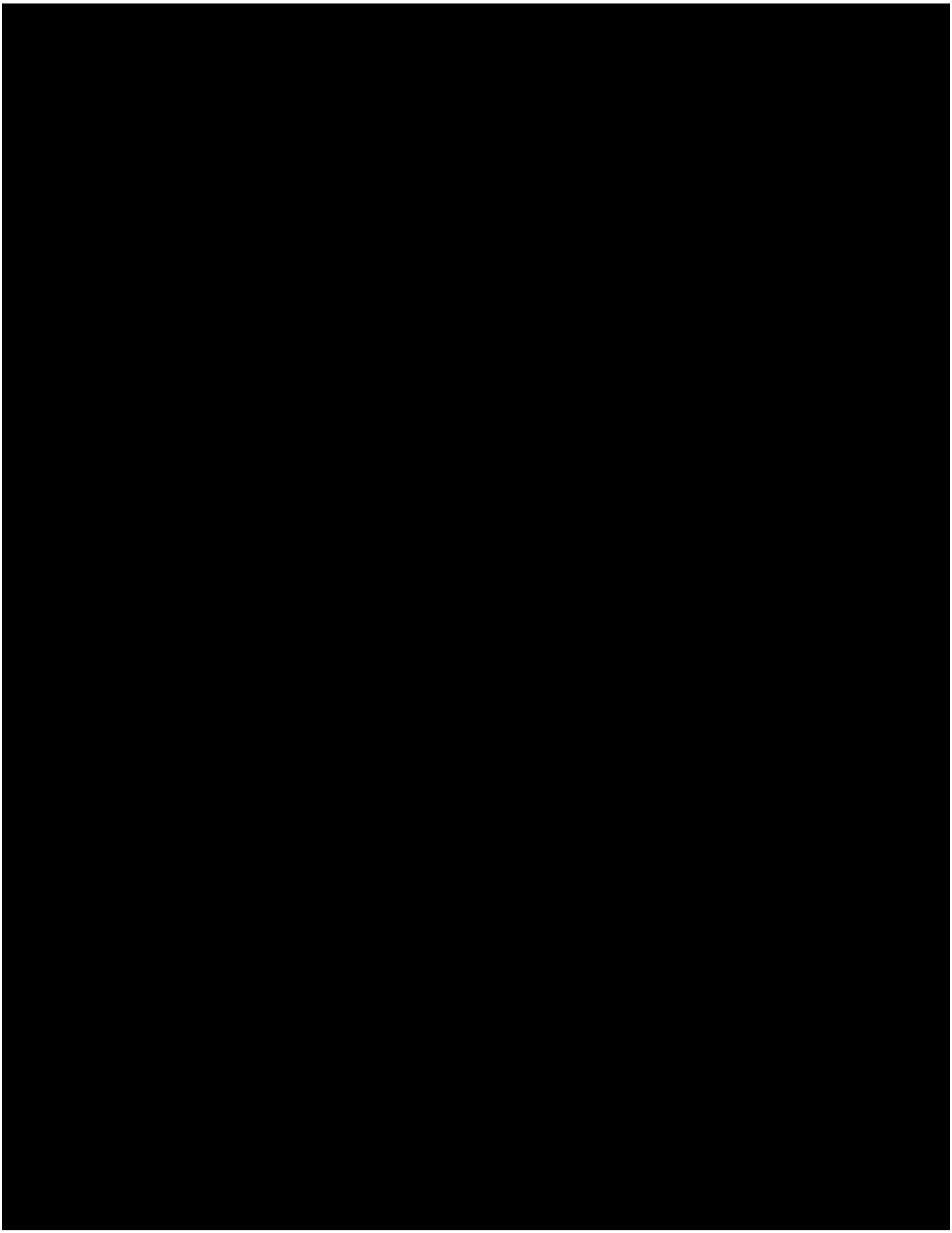
Upon finalization of the dossier an additional source of long-term outcomes was published (Waterhouse 2021). Information regarding long term OS outcomes from this source was included in the smoothed hazard plots included in I (section 21) but was not applied to inform the constructed curve below. The Waterhouse et al overall curve (overall survival for all included treatment regimens) does not fit the trial based data very well but do indicate the same long term trend of a decreasing hazard over time that is also observed for the trial based data.

The constructed curve was produced in 3 steps (see Figure 40 and Figure 41 for an illustration):

- The absolute survival at year 2 was derived from the nivolumab and ipilimumab arm in CheckMate 743. The minimum follow-up of the CheckMate 743 data was 22.1 months. Survival up to two years was used due to the low number of patients at risk beyond 2 years in the pemetrexed and cisplatin/carboplatin arm of CheckMate 743.
- Data from the pemetrexed and cisplatin arm of the MAPS trial was used to calculate conditional survival from years 2 to 6, as the MAPS trial has a follow-up of 80 months (Zalcman 2016).
- The conditional survival estimates from year 6 to 19 were calculated from SEER cancer registry. Data on 5 937 patients with MPM were available for this exercise (SEER 2021)



This approach allowed the used of previous trials and registry data with longer follow up to validate the long-term extrapolation of survival curves. The landmark results for the OS of pemetrexed and cisplatin/carboplatin are reported in Table 54. The majority of the spline-based models showed a better fit to the trial data in years 1 and 2. However, the selection was narrowed down to the log-normal, log-logistic, spline on odds 1 knot and spline on odds 2 knots, given the long-term predictions were closer to the constructed KM curve. In addition, looking at the smoothed hazard plots, of the standard parametric models, only the log-normal and log-logistic models reflect the expected decreasing hazard over time, as observed in the external and long term data sources, effectively disqualifying the other standard parametric models (see Appendix I (section 21)). For the spline-based models, the spline on odds models 1 and 2 knots models matches closest the decreasing hazard over time vs the observed long-term sources. Figure 42 shows the log-normal, log-logistic, spline on odds 1 knot and spline on odds 2 knots curves. This showed they provide a close fit to the constructed curve, with both the log-logistic and spline on odds (1 knot) curves showing good statistical fit according to AIC and BIC (Table 53). The spline on odds (1 knot) considered to have the best fit to the trial data and was selected as the base case OS distribution for pemetrexed and cisplatin/carboplatin.



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19.3.3 Nivolumab and ipilimumab

The goodness-of-fit statistics for the nivolumab and ipilimumab OS endpoints are shown in Table 55. The Weibull and Gamma distributions were statistically the best fitting distributions. In terms of the AIC values, the difference between the distributions is minimal (aside from the log-normal), suggesting that they provide reasonable predictions of the trial data.

Table 55: Statistical goodness-of-fit indicators (AIC/BIC) values for independent parametric and spline models fitted to OS data for nivolumab and ipilimumab

Independent model	AIC rank	AIC	BIC
Weibull	1	1703.26	1710.68
Gamma	2	1703.74	1711.17
Gompertz	3	1704.14	1711.57
Generalised gamma	4	1705.11	1716.25
Spline on hazards, 1 knot	5	1705.23	1716.37
Spline on normal, 2 knots	6	1705.75	1720.61
Spline on odds, 2 knots	7	1706.39	1721.24
Spline on hazards, 2 knots	8	1706.54	1721.40
Spline on normal, 3 knots	9	1706.55	1725.12
Spline on hazards, 3 knots	10	1706.89	1725.46
Spline on odds, 3 knots	11	1707.47	1726.04
Spline on normal, 1 knot	12	1707.77	1718.91
Spline on odds, 1 knot	13	1708.74	1719.88
Exponential	14	1709.84	1713.55
Log-logistic	15	1710.87	1718.30

Log-normal	16	1720.36	1727.79

Abbreviations: Akaike information criterion; BIC: Bayesian information criterion; OS: Overall survival

Given there are no existing IO therapies available for patients with MPM, external validation of the OS curves for nivolumab and ipilimumab was challenging. The experts from the virtual advisory board agreed that MAPS and SEER data should be used as a benchmark for selecting the nivolumab and ipilimumab curves beyond the trial. This was justified as a conservative approach in the absence of other relevant long-term data; the expectation was that this data would provide lower-bound estimates for survival, although the survival would in reality be expected to be higher for nivolumab and ipilimumab. It was suggested to select the curves that provided estimates higher than the pemetrexed and cisplatin arm of the MAPS trial at year 5. From the landmark survival estimates presented in Table 56, eight of the distributions had survival higher than MAPS at 5 years. These were the exponential, log-logistic, log-normal, spline on odds 1-knot, spline on odds 2 knots, spline on odds 3 knots, spline on normal link 1 knot and spline on normal link 3 knots. After selecting these distributions, they were assessed against the constructed curve for pemetrexed and cisplatin/carboplatin. This showed that only the spline on odds 1 knot, log-logistic and log-normal distributions had survival predictions greater than the constructed curve. Figure 43 illustrates the curves plotted alongside the CheckMate 743 data for nivolumab and ipilimumab as well as the MAPS pemetrexed and cisplatin curve and the constructed curve for pemetrexed and cisplatin/carboplatin. This showed that the spline on odds 1 knot distribution overlaps with the constructed curve for chemotherapy.

To further choose between the alternatives, smoothed hazard plots were produced (presented in Appendix I section 21), key plots are presented in section 21.2), showing that only the log-logistic and log-normal standard parametric models and the spline on odd 1 reflects the decreasing hazard over time as suggested by the long term overall survival data used for the validation of the chemotherapy arm. From the above analyses, log-normal distribution was determined to be the most clinically plausible and selected as the base case. The spline on odds 1 knot and log-logistic were selected for scenario analyses.

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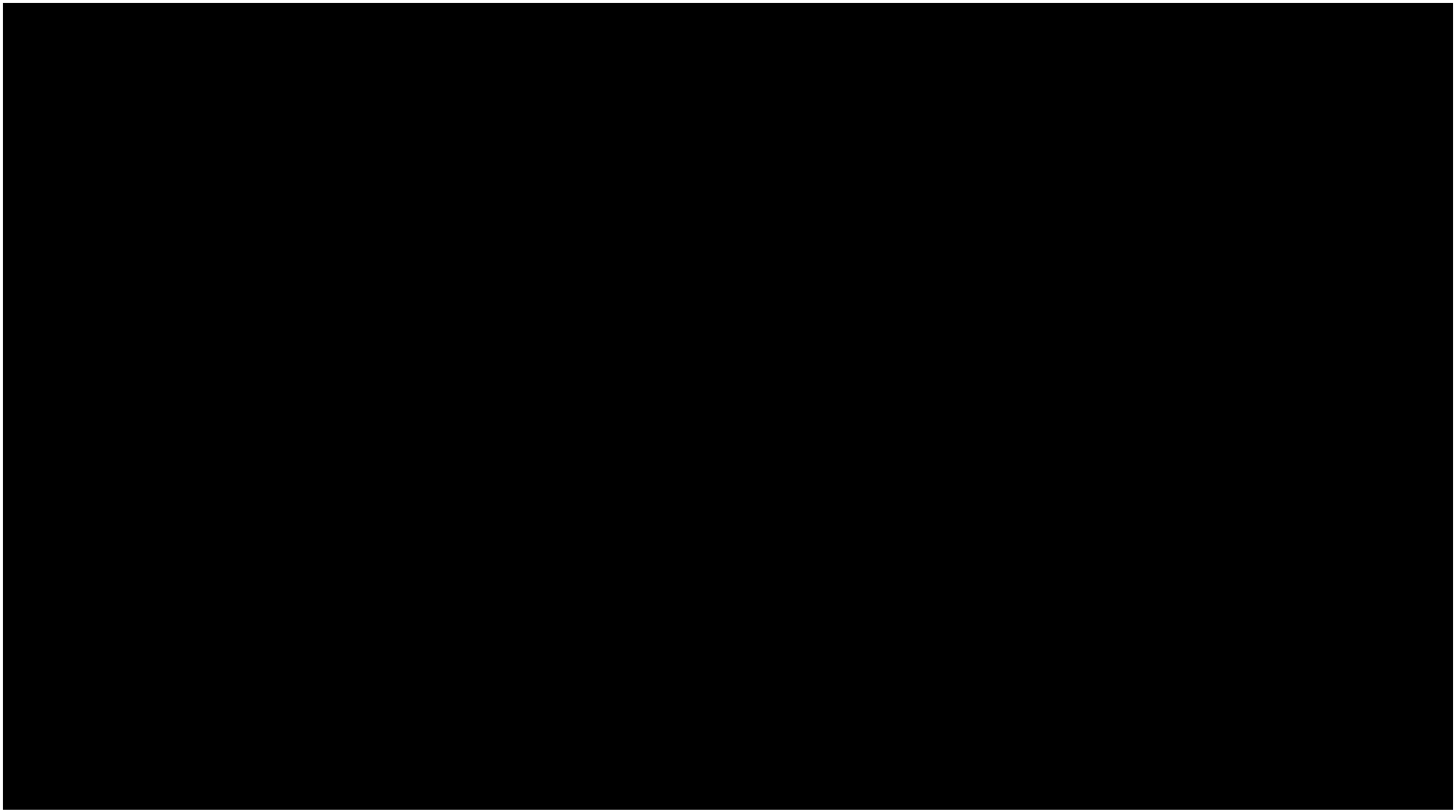

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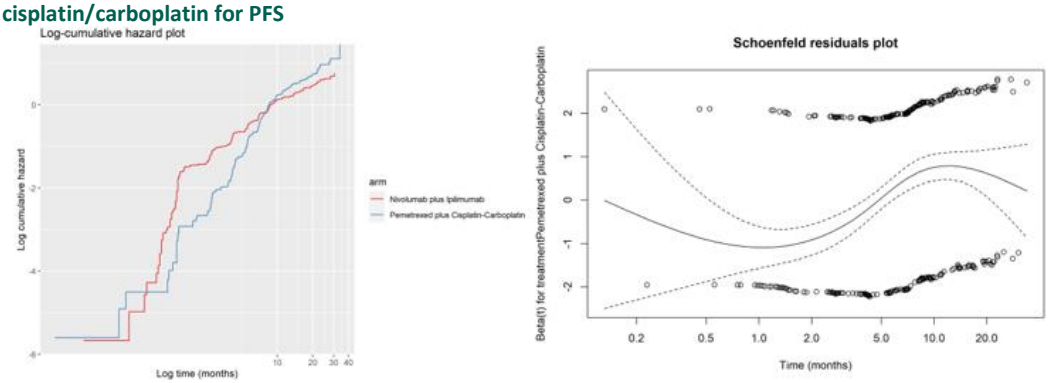
19.4 Progression-free survival

[redacted]

19.4.1 Testing of proportional hazards assumption

Visual inspection of the log-cumulative hazards and Schoenfeld residuals plots was undertaken to assess proportionality of treatment effects over time. Visually it appears that the proportional hazards assumption does not hold given the non-linearity and crossover seen in the log-cumulative plot (Figure 45). A Grambsch and Therneau's correlation test between Schoenfeld residuals and log of time use was utilized which confirmed the rejection of the null hypothesis of proportional hazards ($p < 0.001$). Therefore, independent parametric curves were used to model PFS in the base case.

Figure 45: Log-cumulative hazard plot and Schoenfeld residuals plot for nivolumab and ipilimumab vs. pemetrexed and cisplatin/carboplatin for PFS



19.4.2 Pemetrexed and cisplatin/carboplatin

Table 57 shows the goodness-of-fit statistics for the independent parametric distributions according to AIC/BIC criteria for the pemetrexed and cisplatin/carboplatin arm of CheckMate 743. The ranges between the AIC values is quite large, suggesting that not all models would be a reasonable fit to the data. The spline on odds 2 knots is the best fitting distribution according to AIC and BIC, followed by the spline on hazard, 2 knots.

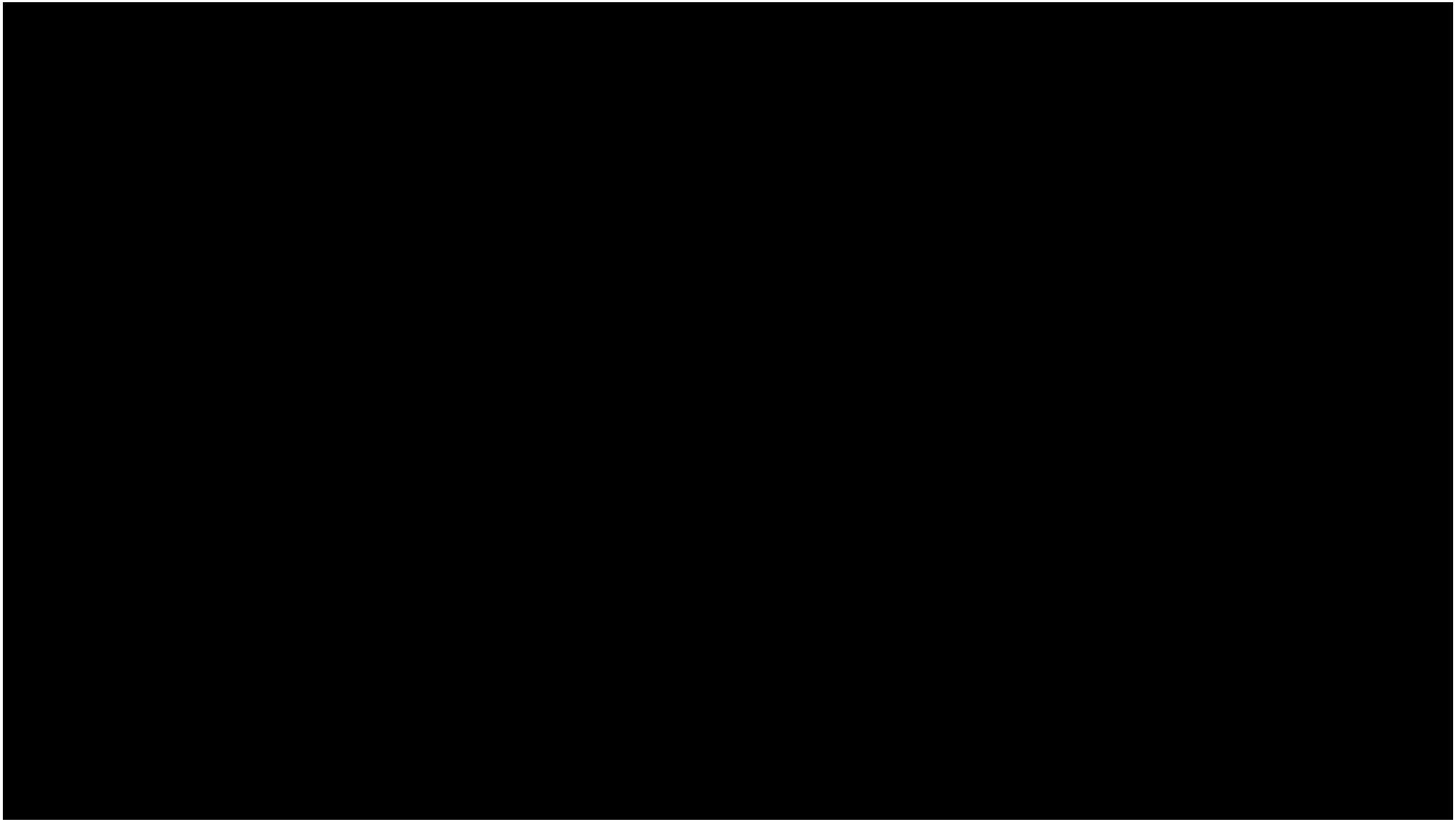
Table 57: Statistical goodness-of-fit indicators (AIC/BIC) values for independent parametric models fitted to PFS data for pemetrexed + cisplatin/carboplatin

Independent model	AIC rank	AIC	BIC
Spline on odds, 2 knots	1	1331.46	1346.30
Spline on hazards, 2 knots	2	1332.28	1347.12
Spline on normal, 2 knots	3	1332.35	1347.20
Spline on odds, 3 knots	4	1333.52	1352.07
Spline on hazards, 3 knots	5	1333.82	1352.38
Log-normal	6	1355.49	1362.91
Spline on normal, 3 knots	7	1333.90	1352.46
Log-logistic	8	1336.30	1343.73
Spline on odds, 1 knot	9	1337.63	1348.76
Spline on hazards, 1 knot	10	1345.44	1356.57
Spline on normal, 1 knot	11	1347.37	1358.50
Gamma	12	1353.93	1361.35
Generalised gamma	13	1349.79	1360.92
Weibull	14	1365.31	1372.73
Spline on odds, 2 knots	15	1393.66	1401.08
Spline on hazards, 2 knots	16	1400.95	1404.66

Abbreviations: AIC: Akaike information criterion; BIC: Bayesian information criterion; PFS: Progression-free survival

Table 58 shows the survival estimates at different landmark points for the distributions for PFS in the pemetrexed and cisplatin/carboplatin arm, and an estimate from the survival from MAPS. There were some differences between survival at 2 years between CheckMate 743 and MAPS. The spline odds on 2 knots is the best fitting distribution, and shows similar survival compared to CheckMate 743 at 6 months ant 1 year. However, it may slightly overestimate progression-free survival at 2 years compared to CheckMate 743. The next best fitting curves also slightly overestimate PFS at year 2. The independent log-logistic had a small differential in survival compared to the CheckMate 743 and MAPS data points up until year 1. At year 2, the log-logistic distribution provided an estimate in between the CheckMate 743 and MAPS estimates. As a result, the log-logistic distribution was selected for the base case.

Figure 46 shows the independent parametric models for pemetrexed and cisplatin/carboplatin over a longer time horizon. The majority of the curves fit the within trial period for CheckMate 743 and MAPS reasonably well apart from the exponential and Gompertz distributions.



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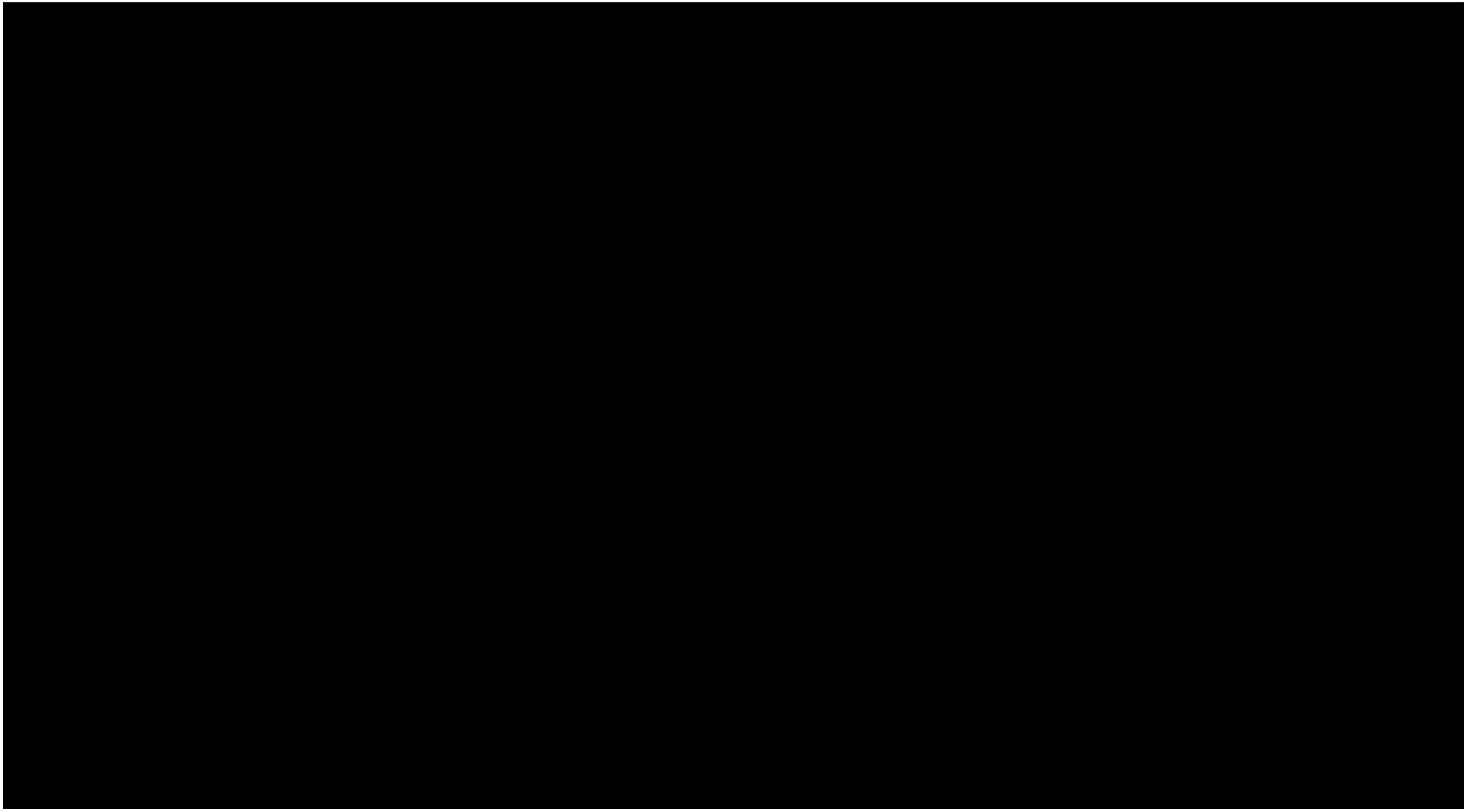

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19.4.3 Nivolumab and ipilimumab

Table 59 provides a summary of the AIC and BIC goodness-of-fit statistics reported for the parametric distributions of the independent survival model fit to the nivolumab plus ipilimumab arm of CheckMate 743. This shows that the range between AIC values is quite large, suggesting not all models would be a reasonable fit to the data. The spline on odds 3 knots is the best fitting distribution, followed by the spline on hazards 3 knots.

Table 59: Summary of goodness-of-fit of curves fitted to chemotherapy and fitted to nivolumab and ipilimumab

Distribution	AIC ranked	AIC	BIC
Spline on odds, 3 knots	1	1432.95	1451.52
Spline on hazards, 3 knots	2	1434.20	1452.76
Spline on normal ,3 knots	3	1439.42	1457.99
Generalised gamma	4	1446.96	1458.10
Spline on normal, 2 knots	5	1447.50	1462.35
Spline on normal, 1 knot	6	1447.76	1458.90
Spline on odds, 2 knots	7	1449.31	1464.17
Spline on hazards, 2 knots	8	1451.71	1466.57
Log-normal	9	1453.04	1460.46
Spline on hazards, 1 knot	10	1453.52	1464.66
Spline on odds, 1 knot	11	1453.66	1464.81
Log-logistic	12	1461.66	1469.09
Gompertz	13	1479.02	1486.45
Exponential	14	1491.68	1495.40
Weibull	15	1492.67	1500.10
Gamma	16	1493.68	1501.10

Abbreviations: AIC: Akaike information criterion; BIC: Bayesian information criterion; PFS: Progression-free survival

Table 60 shows PFS at different landmark points using the different distributions. This shows that the most optimistic curve is the Gompertz, which would be clinically implausible given that the PFS estimates were higher than OS at year 15 and 20. Figure 47 shows the top 6 distributions (according to AIC) overlaying the CheckMate 743 Kaplan-Meier curve, showing that they provide a good fit to the trial data and some variation in the long-term extrapolation. The spline on odds 1 knot is the best ranked distribution, however, it is the second most optimistic and also considered too high in comparison to the selected OS curve. As a result, the generalized gamma was selected in the base case as it gave slightly lower estimates than the spline on odds 1 knot distribution and provided a close fit to the CheckMate 743 trial data.

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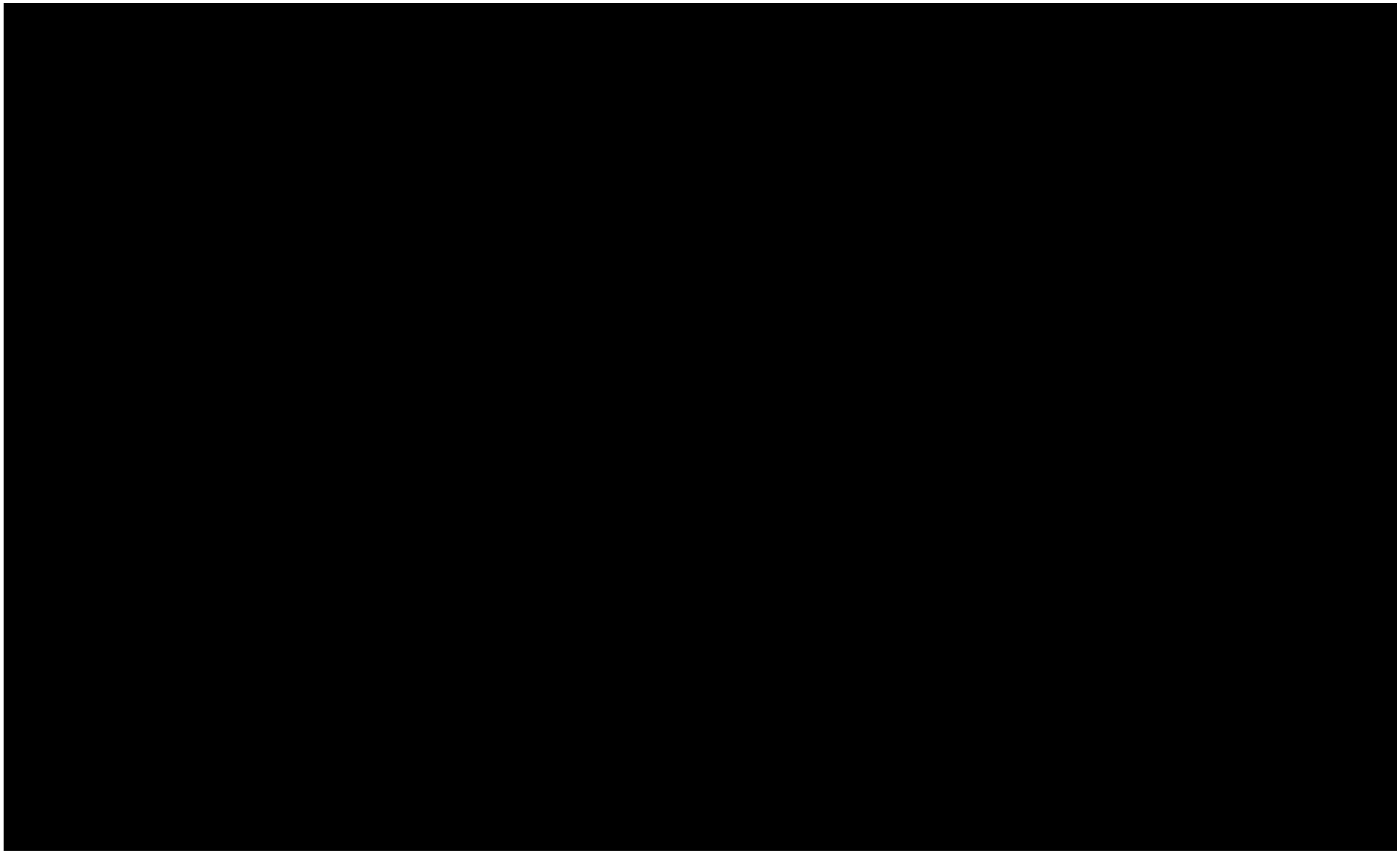

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Additional adjustment of the survival curves beyond the time of follow-up in the trials was also performed to ensure that the resulting survival estimates were plausible and externally valid. For example, if the PFS was greater than OS at any timepoint, the PFS was assumed to be equivalent to OS in order to avoid a clinically implausible scenario.

19.5 Hazard ratio adjustment for histology

The proportion of patients with epithelioid subtype is estimated to be around 60% in Denmark. This is lower than in CheckMate 743 where the proportion was 75.4%. That the proportion of epithelioid patients is lower in Danish clinical practice than in CheckMate 743 was confirmed to be the case through interviews with Danish clinical experts (Danish Clinical Expert 2021a, Danish Clinical Expert 2021b). This also aligns with data from Denmark (Laaksonen 2019, Cancer in Norway 2020) where the share of epithelioid patients was 59.5% (Panou 2021). Table 61 shows the proportion of patients by histology in the CheckMate 743 trial and the expected share in Danish clinical practice, respectively.

Table 61: Histology subtype in CheckMate 743 compared to Danish clinical practice

Histology subtype	Epithelioid	Non-epithelioid	Source
CheckMate 743	75.4%	24.6%	CheckMate 743 trial data (Bristol-Myers Squibb 2020d, Baas 2021)
Danish clinical practice	60.0%	40.0%	Danish KOL interviews (Panou 2021, Danish Clinical Expert 2021a, Danish Clinical Expert 2021b) (Laaksonen 2019, Cancer in Norway 2020, Danish Clinical Expert 2021a, Danish Clinical Expert 2021b)

Abbreviations: KOL: key opinion leader

In the CheckMate 743 trial, patients treated with nivolumab and ipilimumab experienced similar overall and progression-free survival irrespective of epithelioid status. However, among patients treated with pemetrexed and cisplatin/carboplatin, the relative survival of non-epithelioid patients was considerably lower than for epithelioid patients. As a consequence, the relative difference in clinical efficacy between treatment arms was greater among non-epithelioid patients. The overall survival by histology subgroup for nivolumab and ipilimumab compared to pemetrexed and cisplatin/carboplatin are shown in Figure 48 and Figure 49.

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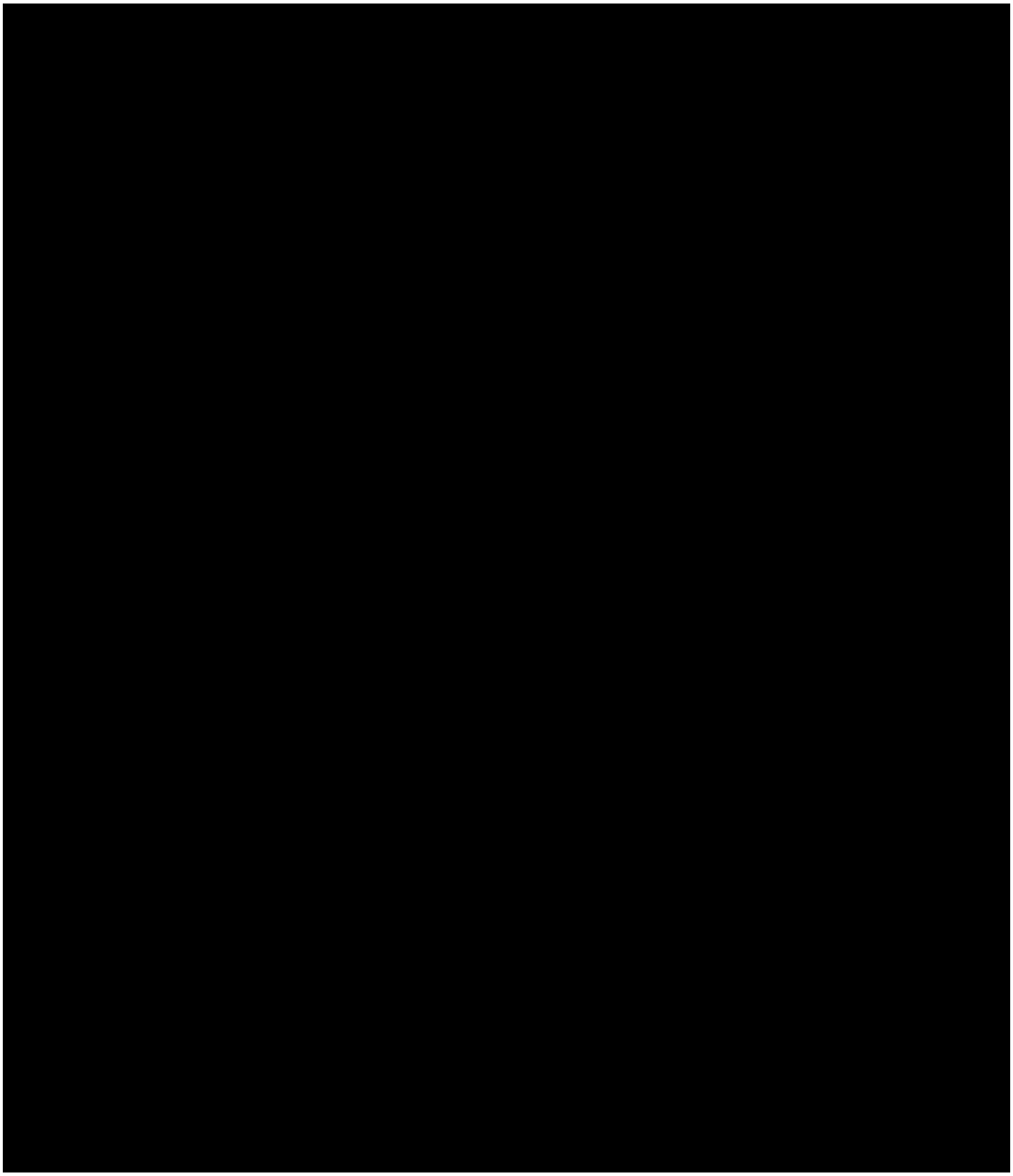

If survival extrapolations would be based upon ITT data from CheckMate 743, without factoring in the higher proportion of non-epithelioid patients in Danish clinical practice, the expected increased mortality among patients treated with pemetrexed and cisplatin/carboplatin would not be accurately captured. To overcome this, an approach using hazard ratios to adjust the survival curves and re-weight them was explored. The proportional hazards test was conducted for OS and PFS in epithelioid subgroup versus the non-epithelioid subgroup (within the same treatment group). An alternative approach would involve conducting survival analysis on the trial data for the epithelioid and non-epithelioid subtypes to obtain curve estimates. However, published long-term data for the subtypes was not identified in order to

validate and select the most appropriate estimates. Given the lack of data and the fact the proportional hazards assumption did hold, applying hazard ratio adjustments based on the ITT curve was considered the most appropriate approach.

Table 62 shows the hazard ratios that were obtained as well as the p-value for the proportional hazards test, showing that the proportional hazards did hold in all cases. Therefore, this analysis created two additional curves for each treatment and endpoint, by applying the hazard ratio to the selected base case curves for the ITT population (as outlined in section 8.3). Importantly, these histology-specific survival curves were not generated through new parametric extrapolations, but only through applying hazard ratio adjustments to the previously generated curves.

Specifically, the derivation of the subgroup survival probabilities required solving the following simultaneous equations:

- $S_1(t) = S_2(t)^{hr}$ – i.e. the subgroup survival probabilities respect the proportional hazards assumption; and
- $w_1 S_1(t) + w_2 S_2(t) = S(t)$ – i.e. in aggregate the subgroup survival probabilities combine to match the ITT survival probabilities when weighted according to their proportions in the ITT population.

The following steps were taken in the model to calculate the survival (using OS in week 52 for pemetrexed and cisplatin/carboplatin as an example):

- At week 52, overall survival was calculated as 0.641936 in the epithelioid group and 0.397056 in the non-epithelioid group;
- The hazard ratio at this time is calculated as $\log_e (0.397056) / \log_e (0.641936) = 2.084$, as per [redacted];
- Weighted OS was 0.581206 (=641936 * 75.2% + 0.397056 * 24.8%);
- For comparison, OS was 0.581206 without the weighted approach (independent log-normal), as required;

This calculation was performed in every cycle (using the corresponding survival for that cycle), to preserve the hazard ratio and the weighted mean OS matching the ITT model.

Through these operations, the survival curves used for the economic model were a function of the proportion of epithelioid patients. The curves were constructed so that they align with the ITT curves when the proportion of epithelioid patients is identical to that in the CheckMate 743 study [2].

[redacted]

As shown in Table 62, the difference in survival between epithelioid and non-epithelioid patients in CheckMate 743 was small for the nivolumab and ipilimumab arm. A Cox proportional hazards test showed that the difference in survival by histology was only statistically significant in the comparator arm. Since the difference in survival by histology was not significant for the nivolumab and ipilimumab arm, hazard ratio adjustment was only performed for treatment with pemetrexed and cisplatin/carboplatin in the base case.

[2] The proportion of epithelioid patients differed slightly between treatment arms in CheckMate 743: 75.6% for nivolumab and ipilimumab, and 75.2% for pemetrexed and cisplatin/carboplatin. In the economic analysis, this proportion is identical between the arms, to avoid biasing the cost-effectiveness analysis.

The impact of the adjustments is shown as scenarios in the results section of the report (see section 8.7.3).

Figure 56 shows the impact of the adjustment of overall survival with the model base case settings. The adjustment results in a slight downward shift in the overall survival of the comparator arm, accounting for the slightly higher proportion of non-epithelioid patients in clinical practice compared to the CheckMate 743 trial.

19.6 Duration of treatment by histology

A primitive analysis of time-to-treatment discountinuation (TTD) by histology was performed to explore whether it would be motivated to include this type of funcitonality within the economic model. The results are presented in Table 63. These result suggest that there is no statistically significant difference in TTD by histology. Based upon this

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analysis it was decided that the TTD for the ITT population could be used for the analysis, i.e. that no weighting by histology was needed for the duration of treatment.

Setting	Nivolumab and ipilimumab	Pemetrexed and cisplatin/carboplatin
Epithelioid	[redacted]	
Mean duration, months		
Median duration, months (Q1, Q3)		
Patients still treated after 3 months (%)		
Patients still treated after 6 months (%)		
Patients still treated after 9 months (%)		
Patients still treated after 12 months (%)		
Non-epithelioid		
Mean duration, months		
Median duration, months (Q1, Q3)		
Patients still treated after 3 months (%)		
Patients still treated after 6 months (%)		
Patients still treated after 9 months (%)		
Patients still treated after 12 months (%)		

Abbreviations: Q: quartile

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20. Appendix H: Literature search for HRQoL data

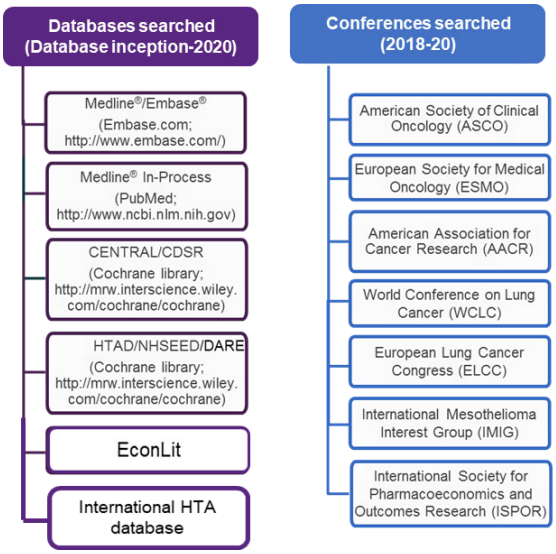
Identifying data of HRQoL of patients receiving first line treatment for MPM was part of the objective of a non-clinical SLR, focusing on QoL, guidelines, economic evaluations, costs, and resource use. For a comprehensive description of the SLR, please see the attached SLR document in Appendix 26A.

The literature search identified 17 studies evaluating QoL. The instruments identified were cancer-specific (n=5; EORTC QLQ-C30, VAS, SF-36, GHQ, and RSCL) and lung cancer-specific (n=3; EORTC LC13, LCSS, and LCSS Meso).

20.1 Search strategy

Figure 51 presents a summary of electronic searches conducted for systematic reviews.

Figure 51: Electronic searches conducted for all the literature reviews



Searches were carried out on the following key biomedical databases: Excerpta Medica Database (Embase®), Medical Literature Analysis and Retrieval System Online (MEDLINE®), MEDLINE in-process, Cochrane Central Register of Controlled Trials (CENTRAL), and Cochrane Database of Systematic Reviews (CDSR), EconLit, and International HTA database.

MEDLINE® and Embase® were searched using the embase.com interface, while the MEDLINE in-process was searched via PubMed. CENTRAL and CDSR were searched using the Cochrane Library. EconLit® was searched via the AEAweb.org interface.

It should be noted that the National Health Service Economic Evaluation Database (NHS EED) and The Database of Abstracts of Reviews of Effects (DARE) ceased to be updated after March 31, 2015, due to the discontinuation of NIHR (National Institute for Health Research) funding. However, the bibliographic records published until March 31, 2015, are archived until at least 2021 in the Centre for Reviews and Dissemination (CRD) York Database.

Also, from March 31, 2018, the HTA database (HTAD) remains available, but CRD is no longer adding new records. The International Network of Agencies for Health Technology Assessment (INAHTA) took over production and the next phase of the database development from CRD. The new platform for the international HTA database was launched in June 2020.

- As a part of the original review (conducted from database inception to May 9, 2018), NHS EED and DARE were searched from Cochrane Library. Since there are no further updates after 2015, we have not separately re-run the search on CRD York Database

In addition to searching for biomedical databases, supplementary searches of conference proceedings were conducted to ensure the inclusion of all relevant literature. Abstracts from the following seven conference proceedings from 2018 to 2020 were searched:

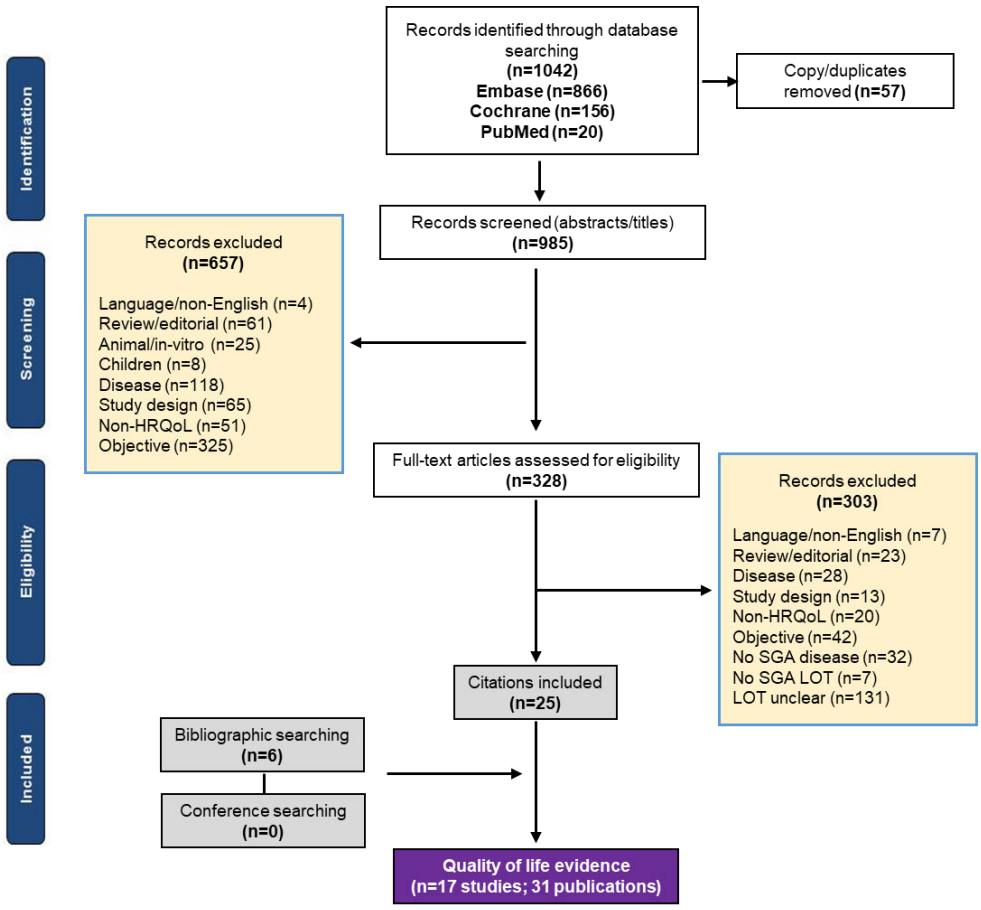
- American Society of Clinical Oncology
- European Society for Medical Oncology
- American Association for Cancer Research
- International Society for Pharmacoeconomics and Outcomes Research
- World Conference on Lung Cancer
- European Lung Cancer Congress
- International Mesothelioma Interest Group

We also conducted bibliographic searching of included studies and relevant literature reviews to supplement the evidence retrieved from the biomedical databases.

The studies were included based on a pre-specified protocol: for a detailed overview, please refer the attached Appendix 26 document. The patient population of interest in the review comprised adult patients with MPM of any race, ethnicity, or gender. The review did not limit the inclusion of studies based on the interventions being evaluated. There was no restriction based on the study design. Studies that were likely to report information in line with the objectives of the reviews were considered for inclusion. The searches were conducted from database inception until October 5, 2020. Searches were restricted to the English language.

Figure 52 presents the flow of studies included in the review. Searches of literature databases yielded 1042 separate references. Due to the overlap of coverage between the different databases, 57 duplicates were found. Following the first pass of the citations, 328 potentially relevant references were identified. Detailed examination of the full-texts led to the inclusion of 25 references. Six additional references were identified following the bibliographic searching of relevant literature.

Figure 52: Flow of studies through the systematic review process



HRQoL: Health-related quality of life; LOT: Line of therapy; SGA: Subgroup analysis

The literature search identified 17 studies reporting evidence specific to the QoL of patients with MPM, treated with 1L treatments. Overall, eight different health-related quality of life (HRQoL) instruments were identified:

- European Organization for Research and Treatment of Cancer (EORTC) Quality of Life Questionnaire-Core 30 (QLQ-C30): 7 studies - Arnold 2015; Nowak 2002; Arrieta 2012; Arrieta 2014; O'Brien 2006, Eberst 2019, Brims 2019
- EORTC Lung Cancer 13 (LC13): 3 studies - Arnold 2015; Nowak 2002, Eberst 2019
- EORTC QLQ-C30 and EORTC LC13 (combined data of relevant items reported from both scales): 4 studies - Van Haarst 2002; Van Meerbeeck 2002; Muers 2008; Bottomley 2006
- The Rotterdam Symptom Checklist (RSCL): 3 studies - Steele 2010; Fennel 2005; Weder 2007
- Lung Cancer Symptom Scale (LCSS): 1 study - Hollen 2004
- Lung Cancer Symptom Scale-mesothelioma (LCSS-Meso): 1 study - Fennel 2019
- Visual analog scale (VAS): 1 study - Ceresoli 2019
- 36-Item Short form health survey (SF-36): 1 study – Brims 2019
- 12-item General health questionnaire (GHQ): 1 study – Brims 2019

All the studies except one were published as journal articles (10 phase II, 4 phase III, and for 3 studies, phase was not reported). The majority of the evidence was retrieved from single-arm studies (n=8), while 6 were randomized controlled studies, 2 were prospective observational studies, and 1 was a longitudinal validation study.

Several studies reflected a small sample size and were not powered to present any significant conclusions regarding the impact of treatment on QoL. Eight studies enrolled <50 patients (Arrieta 2012; Arrieta 2014; O'Brien 2006; Van Haarst 2002; Van Meerbeeck 2002; Steele 2010; Fennel 2005; Weder 2007), whereas three studies enrolled 50-100 patients (Arnold 2015; Nowak 2002; Ceresoli 2019) and six studies enrolled ≥250 patients.

20.2 Quality assessment and generalizability of estimates

The different available measurement and time trade off tools used for the HRQoL affect the generalizability and transferability of results.

20.3 Unpublished data

The unpublished data used in this submission are all sourced from the CheckMate 743 clinical trial.

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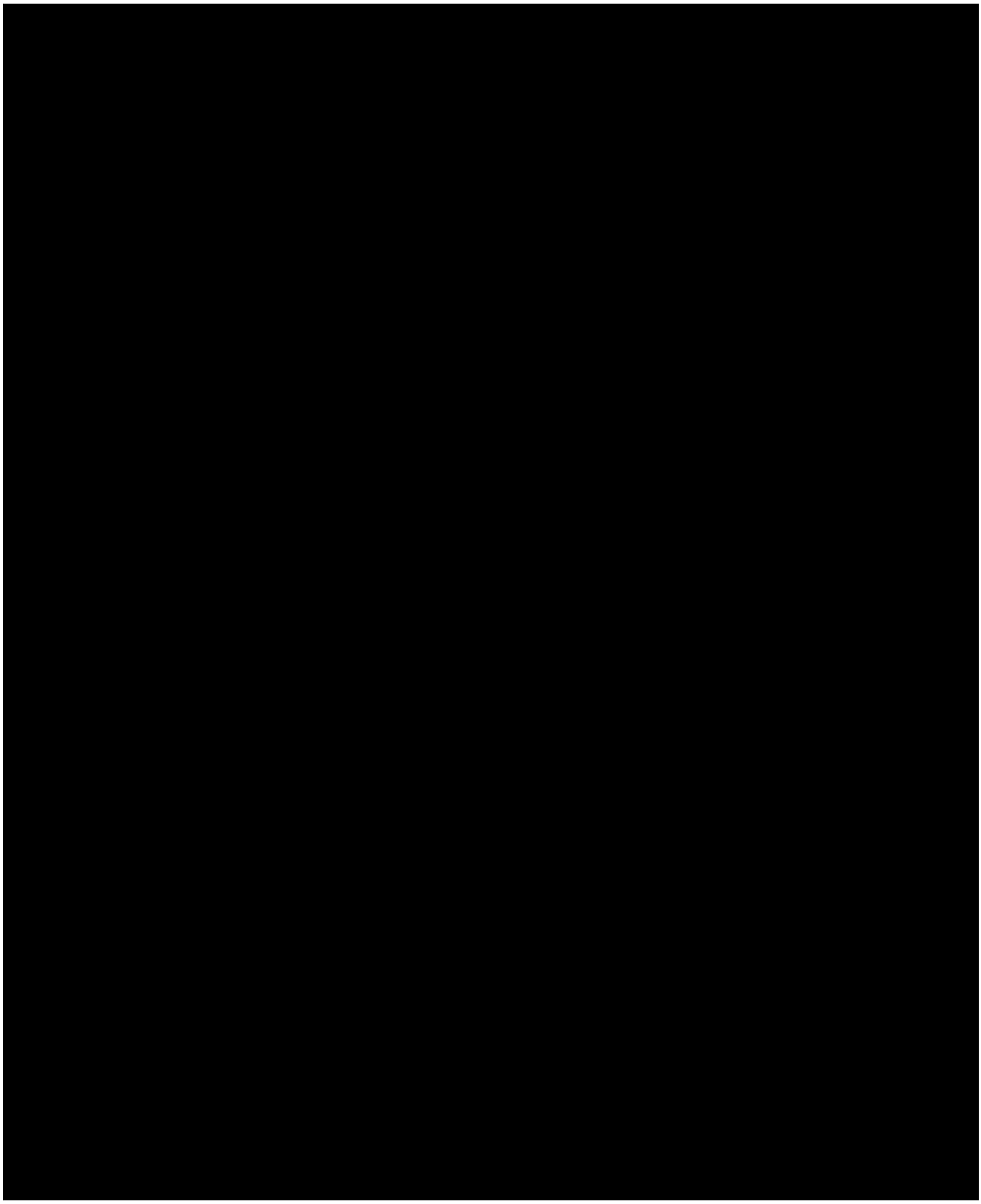

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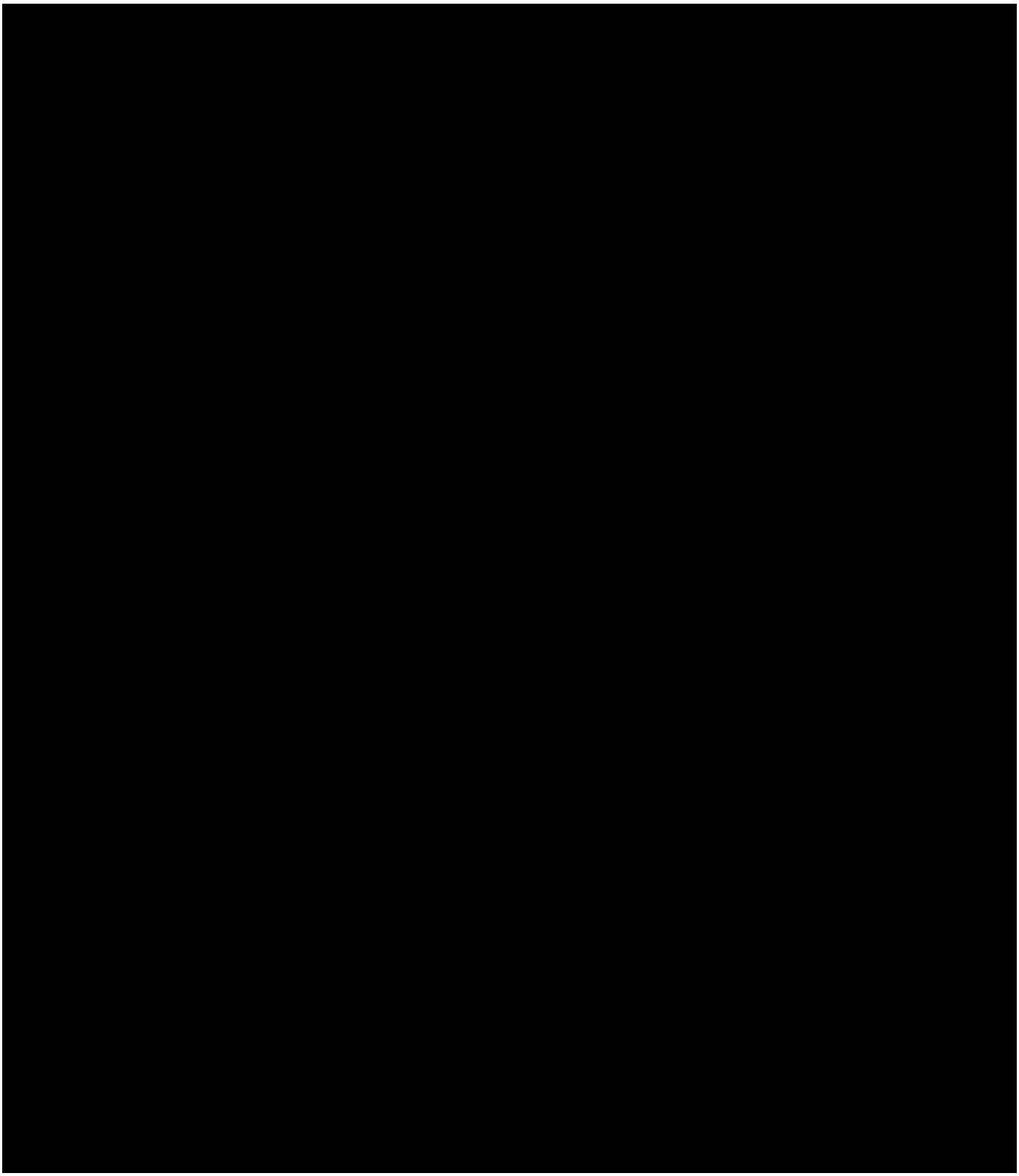

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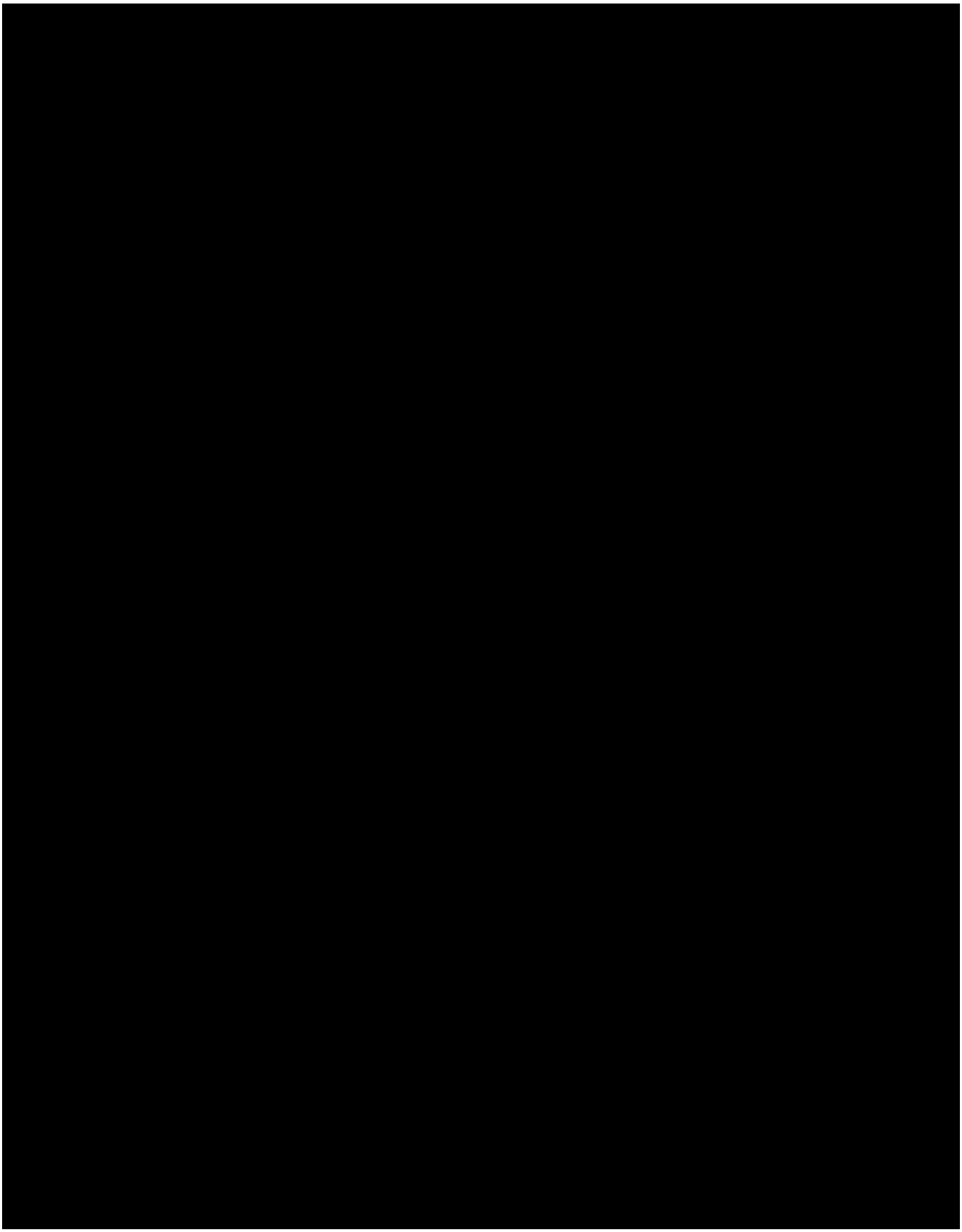

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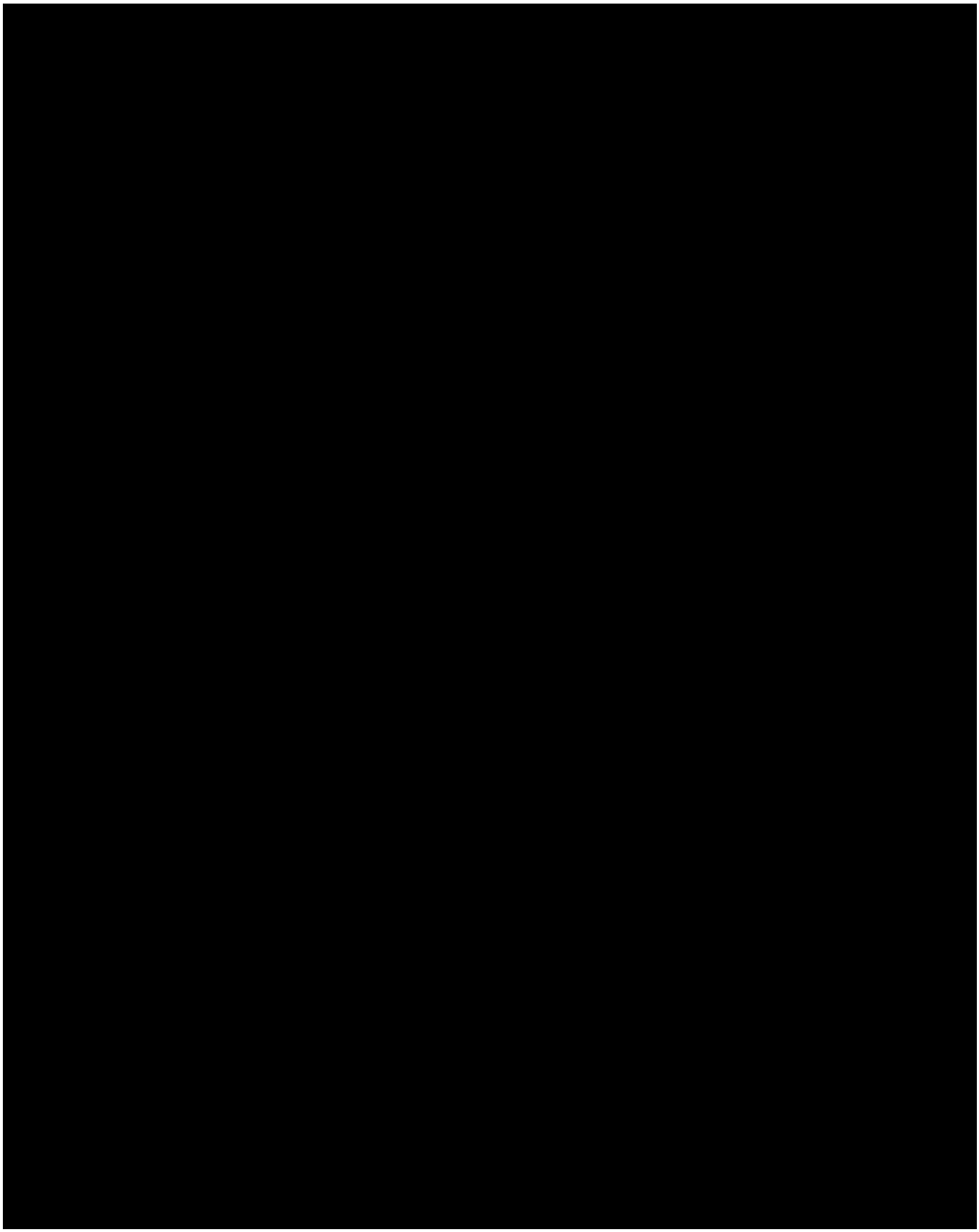

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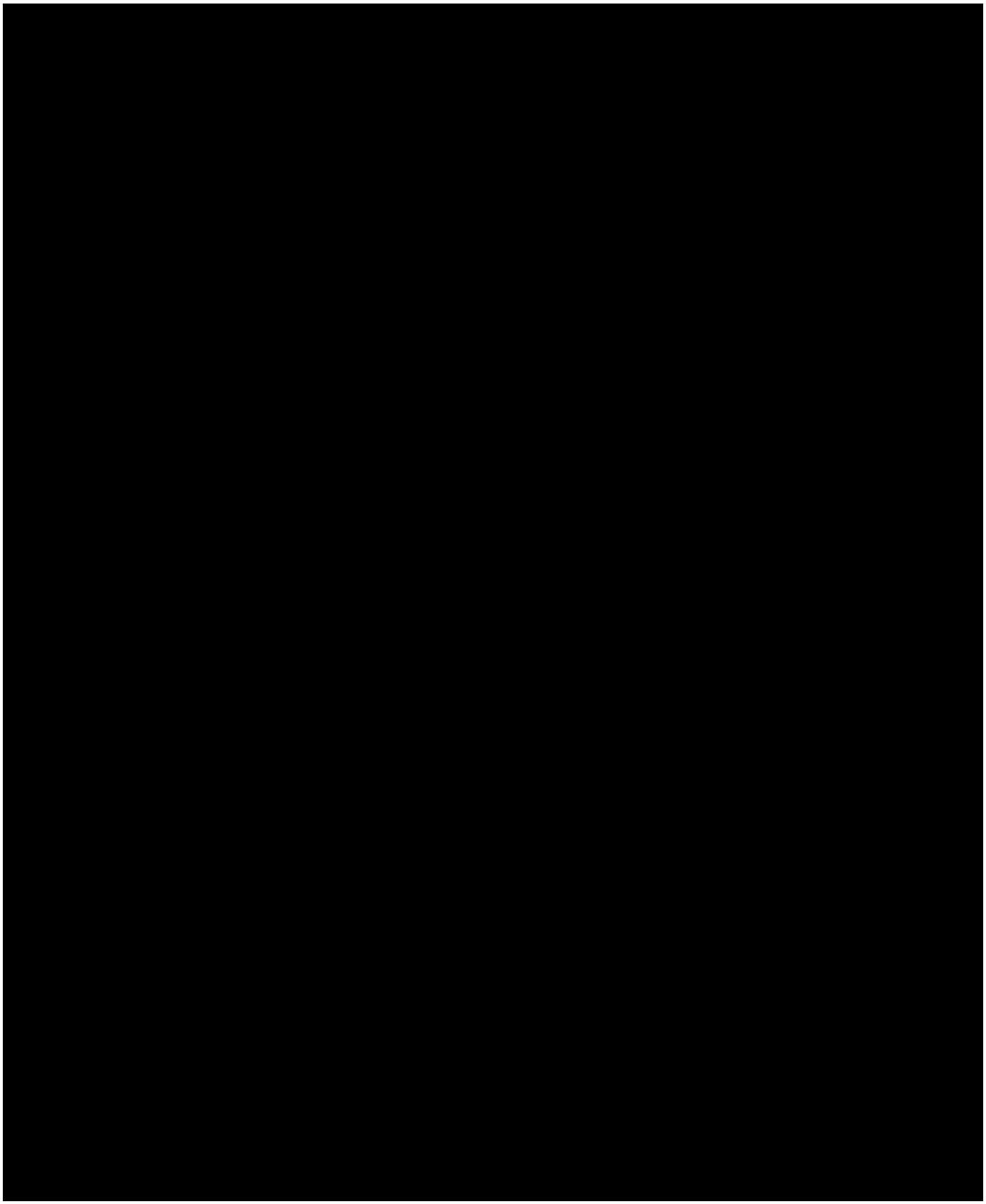

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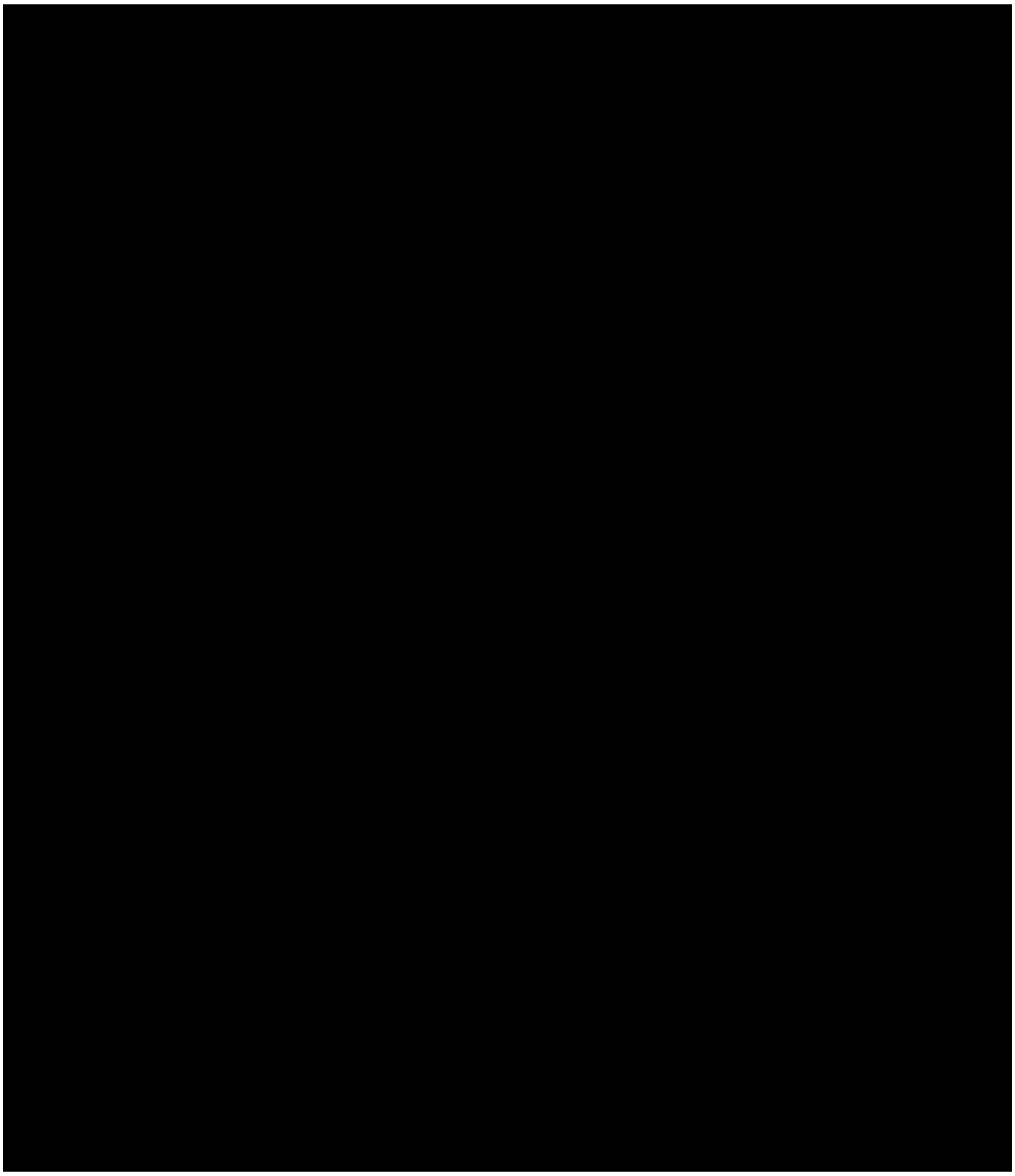

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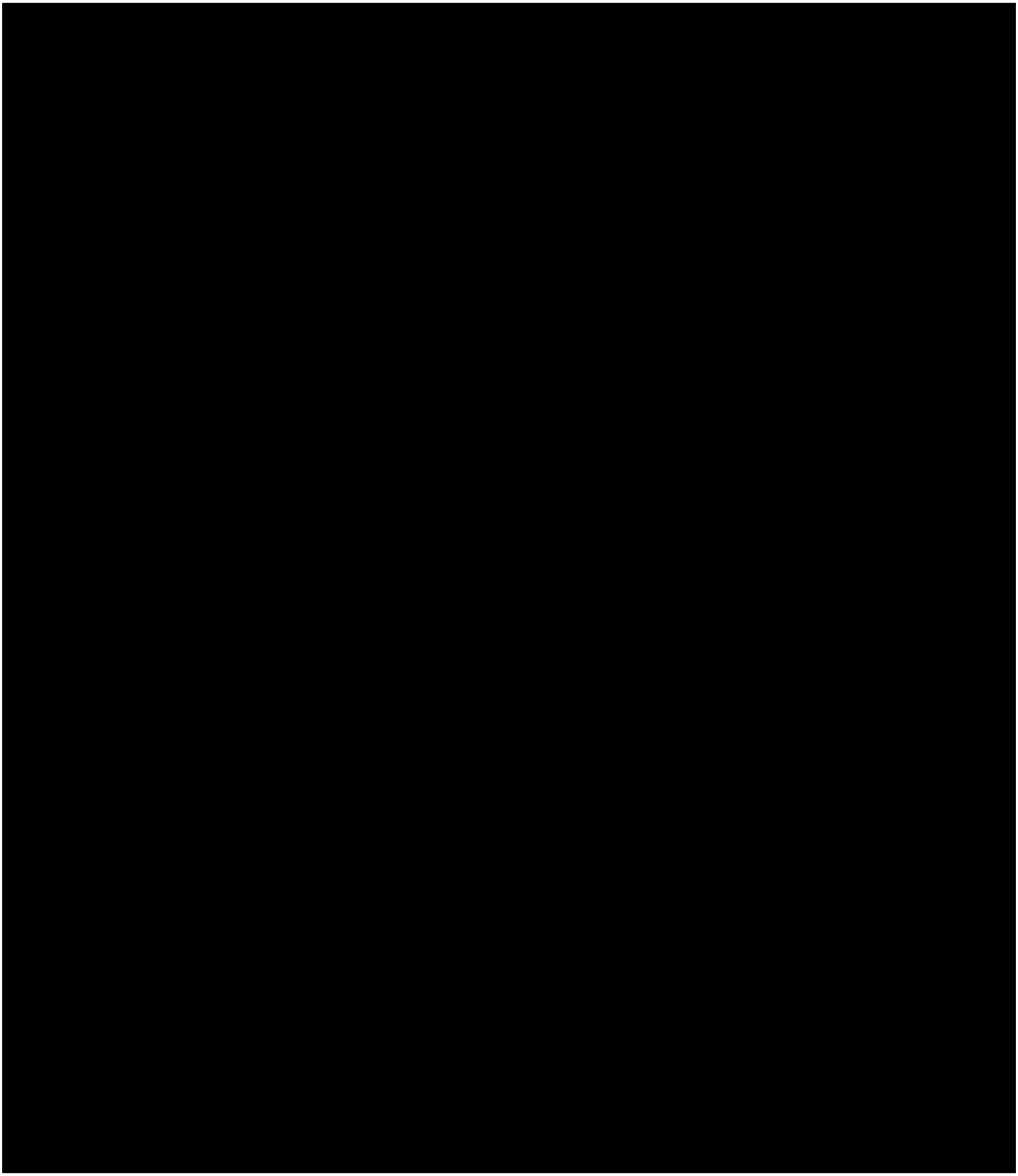

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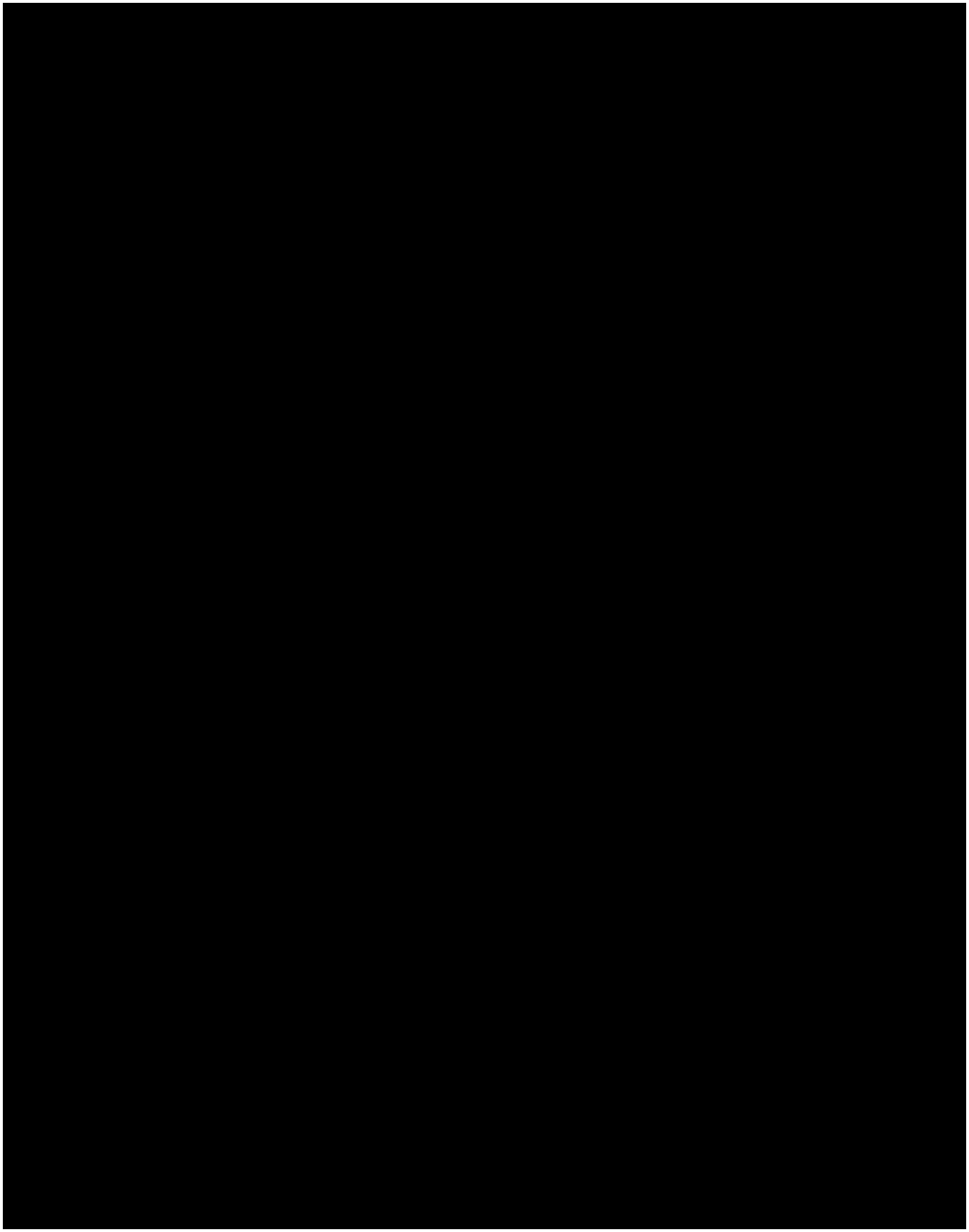

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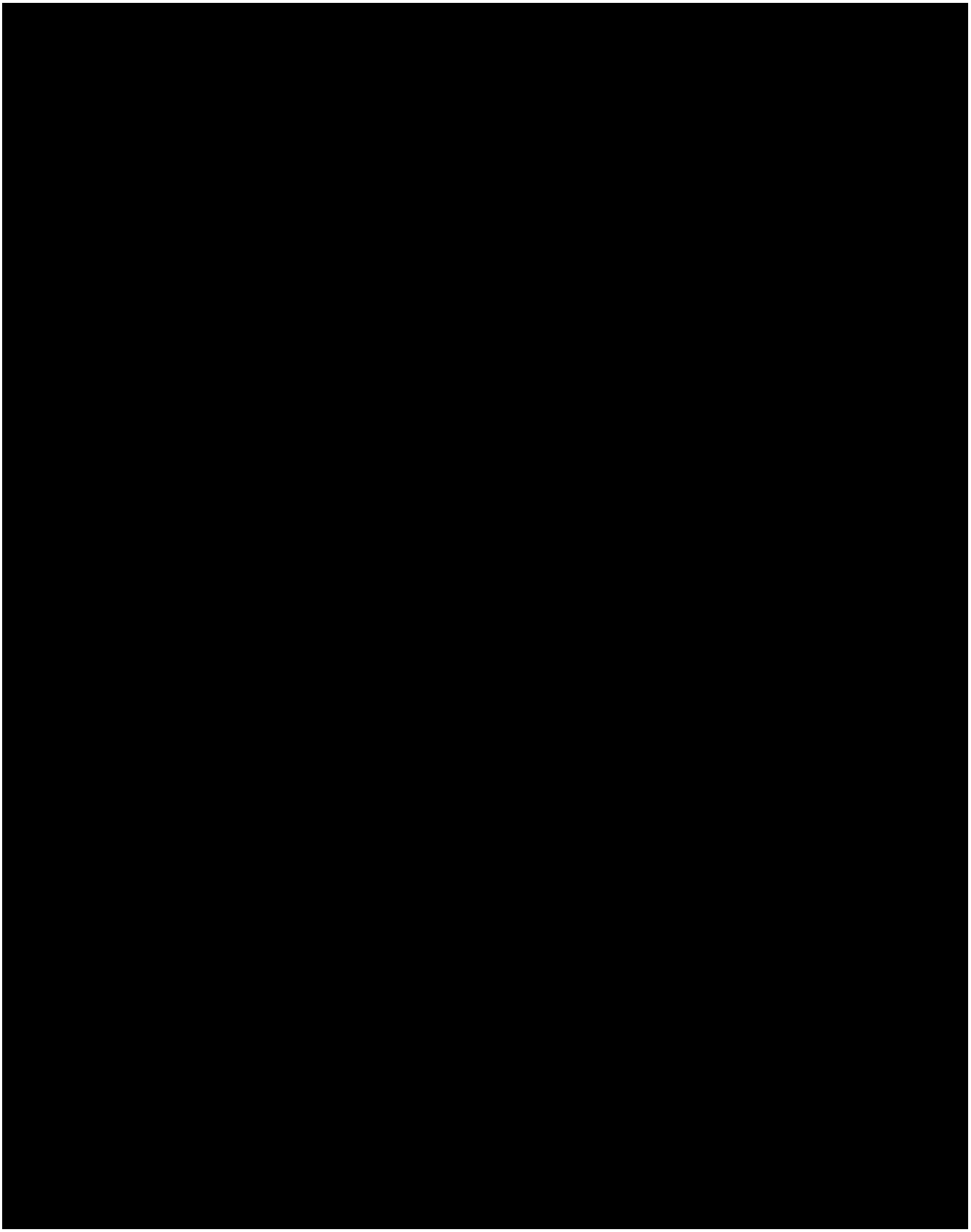

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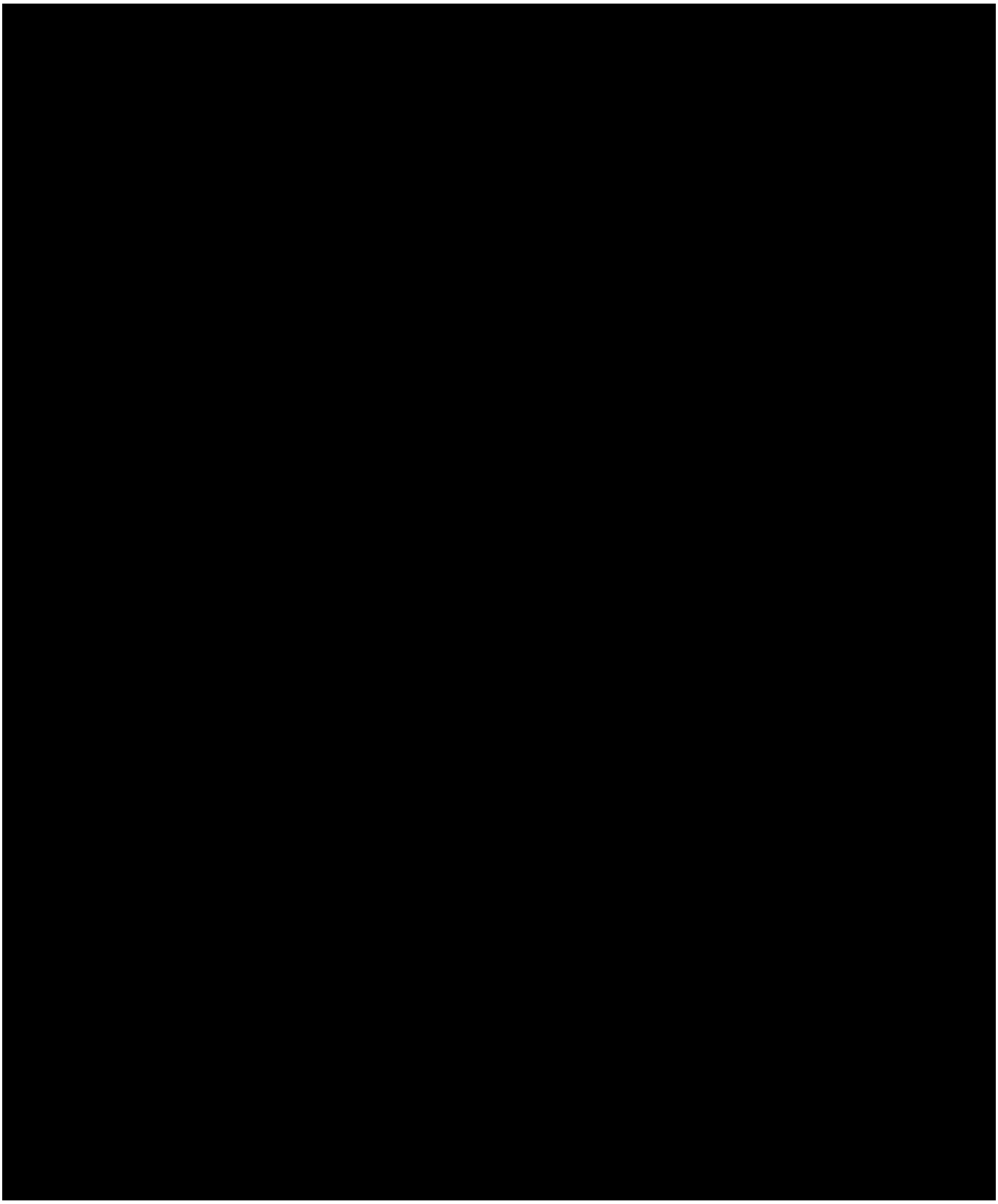

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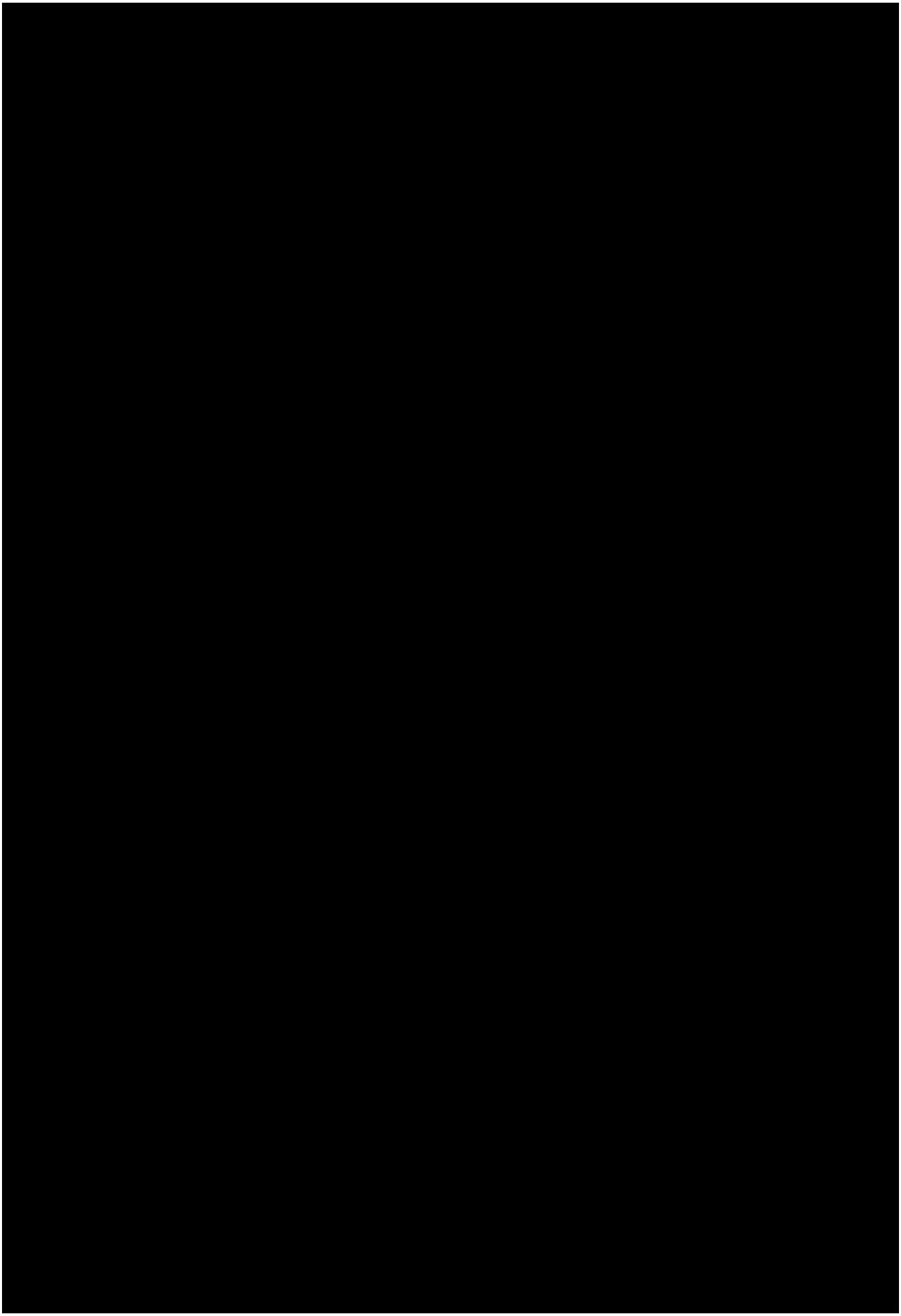

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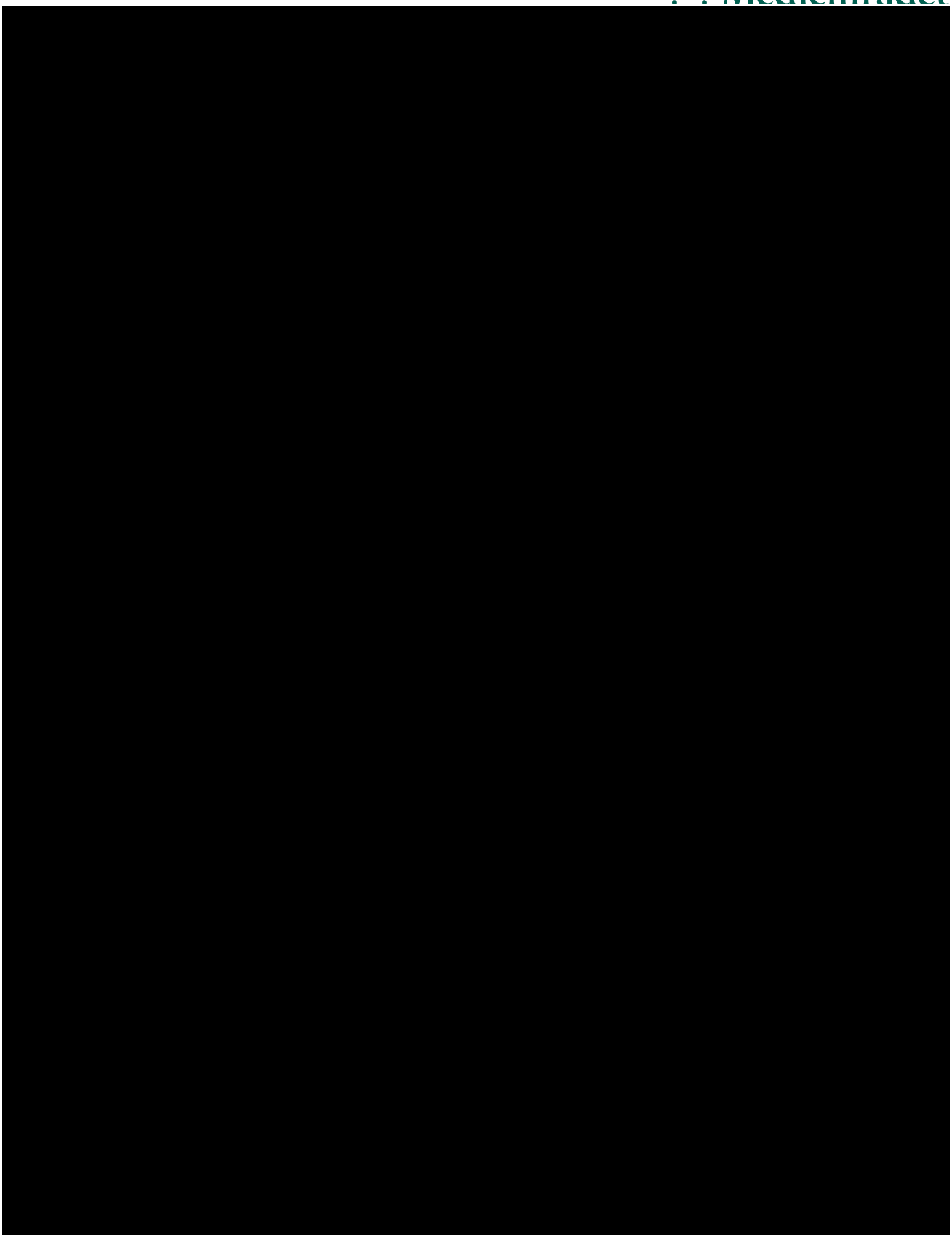

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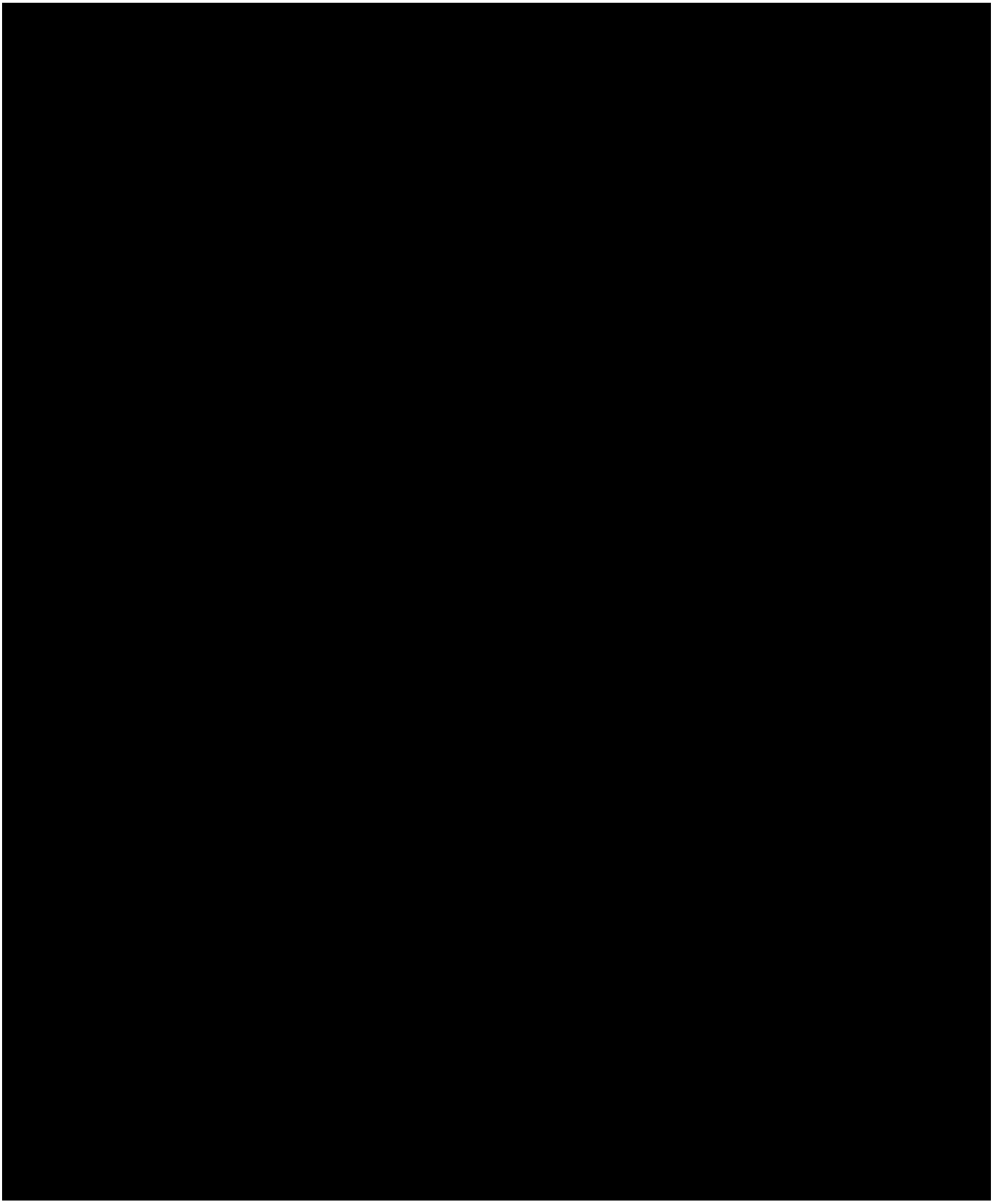

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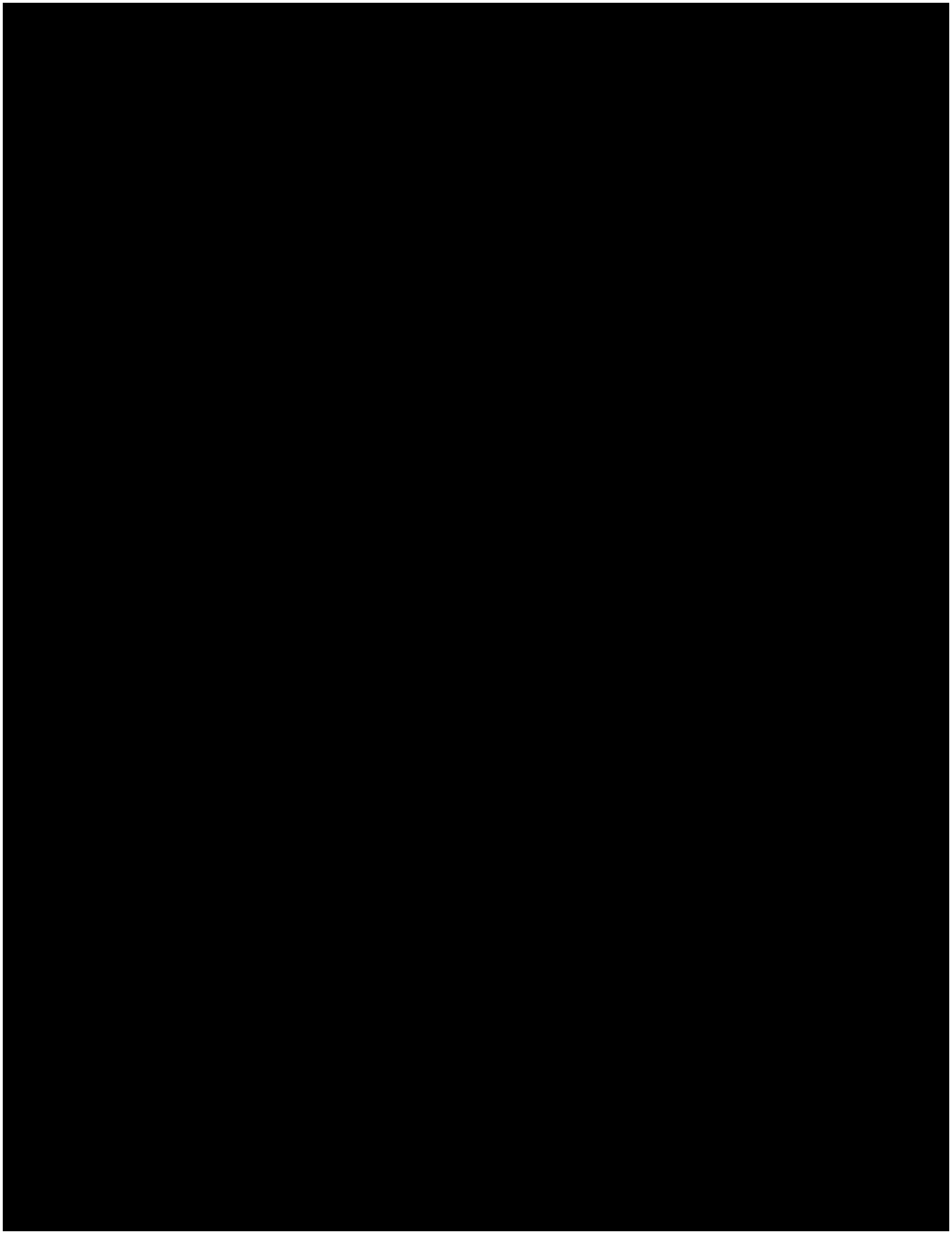

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22. Appendix J: Mapping of HRQoL data

As the CheckMate 743 trial collected EQ-5D-3L data as an exploratory endpoint of HRQoL, the HRQoL results required mapping to EQ-5D-5L. As such, the EQ-5D-3L responses were mapped by the means of a validated mapping method (van Hout 2021). The mapping was done according to the preferred method, which was an ordinal logistic regression that disregarded age and gender and accounted for unobserved heterogeneity using a latent factor.

See Table 64 to Table 69 for the mapping results.

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[redacted]

Model		Overall	Nivo+Ip.	Pem+C.
Num.	Desc.	[redacted]		
1	Intercept only			
2	Prog.			
	Overall			
	Pre-Prog.			
	Post-Prog.			
3	Prog.-Response			
	Overall			
	Pre-Prog. and Resp.			
	Pre-Prog. and Non-Resp.			
	Post-Prog.			
3a	Prog.-Response Sens.			
	Overall			
	Pre-Prog. and Resp.			
	Pre-Prog. and Non-Resp.			
	Post-Prog. and Resp.			
	Post-Prog. and Non-Resp.			
4	Time-to-Death			
	Overall			
	>52 Weeks			
	27-52 Weeks			

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Model		Overall	Nivo+Ip.	Pem+C.
	5-26 Weeks	[redacted]		
	<=4 Weeks			

[a] Based on pre-progression.
[b] Based on > 52 weeks.
Abbreviations: Nivo+Ip. is Nivolumab plus Ipilimumab and Pem+C. is Pemetrexed plus Cisplatin or Carboplatin.

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[redacted]

Model		Overall	Nivo+Ip.	Pem+C.
Num.	Desc.	[redacted]		
5	Time-to-Death by Prog.			
	Overall			
	Pre-Prog. and >52 Weeks			
	Pre-Prog. and 27-52 Weeks			
	Pre-Prog. and 5-26 Weeks			
	Pre-Prog. and <=4 Weeks			
	Post-Prog. and Overall			
	Post-Prog. and >52 Weeks			
	Post-Prog. and 27-52 Weeks			
	Post-Prog. and 5-26 Weeks			
6	Combined Scenario 1			
	Overall			
	>52 Weeks[a]			
	27-52 Weeks[a]			
	5-26 Weeks[a]			
	<=4 Weeks[a]			
7	Combined Scenario 2			
	Overall			
	Pre-Prog.[b]			
	Post-Prog.[b]			

[a] Based on pre-progression [b] Based on > 52 weeks.
Abbreviations: Nivo+Ip. is Nivolumab plus Ipilimumab and Pem+C. is Pemetrexed plus Cisplatin or Carboplatin.

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[redacted]

Model		Model without Treatment	Model with Treatment
Num.	Desc.	[redacted]	
1	Intercept only		
2	Prog.		
	Overall		
	Pre-Prog.		
	Post-Prog.		
3	Prog.-Response		
	Overall		
	Pre-Prog. and Resp.		
	Pre-Prog. and Non-Resp.		
	Post-Prog.		
3a	Prog.-Response Sens.		
	Overall		

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Model		Model without Treatment	Model with Treatment
	Pre-Prog. and Resp.	[redacted]	
	Pre-Prog. and Non-Resp.		
	Post-Prog. and Resp.		
	Post-Prog. and Non-Resp.		

[1] Post-Progression decrement was calculated as the LS mean for post-progression minus the LS mean for pre-progression.[2] <=52 weeks decrement was calculated as the LS mean for TTD <=52 weeks minus the LS mean for TTD >52 weeks.
[a] Based on pre-progression [b] Based on > 52 weeks.Nivo+Ip. is
Abbreviations: Nivolumab plus Ipilimumab and Pem+C. is Pemetrexed plus Cisplatin or Carboplatin.

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[redacted]

Model		Model without Treatment	Model with Treatment
Num.	Desc.	[redacted]	
4	Time-to-Death		
	Overall		
	>52 Weeks		
	27-52 Weeks		
	5-26 Weeks		
	<=4 Weeks		
5	Time-to-Death by Prog.		
	Overall		
	Pre-Prog. and >52 Weeks		
	Pre-Prog. and 27-52 Weeks		
	Pre-Prog. and 5-26 Weeks		

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Model		Model without Treatment	Model with Treatment
	Pre-Prog. and <=4 Weeks	[redacted]	
	Post-Prog. and >52 Weeks		
	Post-Prog. and 27-52 Weeks		
	Post-Prog. and 5-26 Weeks		
	Post-Prog. and <=4 Weeks		

[1] Post-Progression decrement was calculated as the LS mean for [redacted] ks.
[a] Based on pre-progression. [b] Based on > 52 weeks.
Abbreviations: Nivo+Ip. is Nivolumab plus Ipilimumab and Pem+C. is Pemetrexed plus Cisplatin or Carboplatin.

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Table 68 EQ-5D-3L Utility Index (Denmark Van Hout Cross-Walk Weights) Least Squares Estimates for Health States: LS (SE) (95% CI) (All Randomized Subjects)

Model		Model without Treatment	Model with Treatment
Num	Desc.	[redacted]	
6	Combined Scenario 1		
	Overall		
	>52 Weeks[a]		
	27-52 Weeks[a]		
	5-26 Weeks[a]		
	<=4 Weeks[a]		
	Post-Prog. dec.[1]		
7	Combined Scenario 2		
	Overall		
	Pre-Prog.[b]		
	Post-Prog.[b]		
	<= 52 weeks dec.[2]		

[1] Post-Progression decrement was calculated as the LS mean for post-progression minus the LS mean for pre-progression. [2] <=52 weeks decrement was calculated as the LS mean for TTD <=52 weeks minus the LS mean for TTD >52 weeks.
[a] Based on pre-progression. [b] Based on > 52 weeks.
Abbreviations: Nivo+Ip. is Nivolumab plus Ipilimumab and Pem+C. is Pemetrexed plus Cisplatin or Carboplatin.

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[redacted]

Model		Model without Treatment[1]	Model with Treatment[2]
Num.	Desc.	[redacted]	
1	Intercept only		
2	Progression		
3	Progression-Response		
3a	Progression-Response Sens.		
4	Time-to-Death		
5	Time-to-Death by Progression		
6	Combined Scenario[3]		
7	Combined Scenario[4]		

[1] For AIC/BIC, a smaller value means better model fit. [2] In models with treatment, the interaction terms between treatment and all other variables in the model without treatment were included. [3] Models for Combined Scenario 1 were the same as TTD by Progression [4] Models for Combined Scenario 2 included progression status, time-to-death <=52 weeks and their interaction as fixed effects.
Abbreviations: Nivo+Ip. is Nivolumab plus Ipilimumab and Pem+C. is Pemetrexed plus Cisplatin or Carboplatin.

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23. Appendix K: Probabilistic sensitivity analyses

The results of the probabilistic sensitivity analyses are described in Section 8.7.2 above.

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24. Appendix L: Ongoing and supporting studies for the intervention

This submission focuses on nivolumab + ipilimumab for the treatment of MPM. The efficacy and safety data are mainly based on the phase 3 trial, Checkmate 743.

Table 70: Ongoing and supporting studies for nivolumab and ipilimumab in malignant mesothelioma

Title of the study and RCT	Objective of the study	Intervention	Comparator	End-points	Start date	Expected end date
NIPU CA209-7H4 (NCT04300244) Nivolumab and Ipilimumab +/- UV1 Vaccination as Second Line Treatment in Patients With Malignant Mesothelioma (NIPU)	To induce a meaningful progression-free survival benefit in patients with MPM after progression on first line standard platinum doublet chemotherapy, by treating with nivolumab and ipilimumab with or without UV1 vaccine	Ipilimumab and nivolumab + UV1	Ipilimumab and nivolumab	• Progression free survival • Response rate • Patient reported outcomes • Safety	JUN 2020	Estimated Primary Completion Date: MAR 2024 Estimated Study Completion Date: MAR 2027
MAPS2 (NCT02716272) Nivolumab Monotherapy or Nivolumab Plus Ipilimumab, for Unresectable Malignant Pleural Mesothelioma (MPM) Patients (MAPS2)	To prospectively assess the outcomes of anti-PD-1 monoclonal antibody alone or in combination with anti-cytotoxic T-lymphocyte protein 4 (CTLA-4) antibody in patients with malignant pleural mesothelioma	Experimental arm monotherapy Nivolumab at 3mg/kg every 2 weeks Experimental arm combination Nivolumab at 3mg/kg every 2 weeks, combined with Ipilimumab at 1mg/Kg every 6 weeks	N/A	• Disease Control rate • Treatment-related adverse events • Progression-Free Survival • Overall Survival • Quality of Life • Prognosis impact of blood biomarkers (exploratory studies)	MAR 2016	Primary Completion Date: FEB 2018 Actual Completion Date: JUN 2019
MERIT/JapicCTI163247* Clinical Efficacy and Safety of Nivolumab: Results of a Multicenter, Open-label, Single-arm, Japanese Phase	Evaluated the efficacy and safety of nivolumab, an immune checkpoint inhibitor, for the treatment of advanced or metastatic MPM	Nivolumab 240 mg intravenously every 2 weeks	N/A	• Objective response rate • Duration of response • Disease control rate • Progression free survival • Safety	MAR 2018	Primary Completion Date: MAR 2016 Actual Completion Date: MAR 2018

II study in Malignant Pleural Mesothelioma (MERIT)						
NivoMES (NCT02497508) Nivolumab in Patients With Recurrent Malignant Mesothelioma (NivoMes)	Evaluate nivolumab in previously treated patients with MPM who are considered candidates for immunotherapy and repeat thoracoscopies/transthoracic biopsies	Nivolumab administered 3 mg/kg every 2 weeks	N/A	• Disease control rate • Progression free survival • Overall survival • Time to progression • Overall response rate • Safety	JUN 2015	Actual Completion Date: JUL 2017
CONFIRM (NCT03063450) CheckpOiNt Blockade For Inhibition of Relapsed Mesothelioma (CONFIRM)	Evaluate the Efficacy of Nivolumab in Relapsed Mesothelioma	ARM 1: Nivolumab 240mg flat dose Q2W over 30 minutes IV until disease progression, to a maximum of 12 months	ARM 2: Sterile 0.9% sodium chloride Q2W over 30 minutes IV until disease progression, to a maximum of 12 months	• Overall survival • Progression free survival • Overall response rate • Quality of life • Toxicity • Cost effectiveness	MAR 2017	Actual Completion Date: JUL 2021
INITIATE (NCT03048474) Ipilimumab and Nivolumab in the Treatment of Malignant Pleural Mesothelioma (INITIATE)	Evaluate nivolumab and ipilimumab in patients with unresectable MPM, who experience disease progression or recurrence after at least one previous line of platinum-based systemic treatment	Nivolumab administered of 240 mg every 2 weeks for a maximum period of 2 years. Nivolumab will be given in combination with ipilimumab on week 1, 7, 13 and 19. Ipilimumab will be administered at the dose of 1 mg/Kg.	N/A	• Disease control rate • Safety • Progression free survival • Overall survival • Overall response rate	SEP 2016	Primary Completion Date: DEC 2017 Actual Completion Date: DEC 2019
DART (NCT02834013) Nivolumab and Ipilimumab in Treating Patients With Rare Tumors	Evaluate nivolumab and ipilimumab in treating patients with rare tumors	Nivolumab and ipilimumab	N/A	• Progression free survival • Overall survival • Overall response rate • Safety • Best response • Clinical benefit rate	AUG 2021	Primary Completion Date: N/A Actual Completion Date: N/A
LUN15-299 (NCT03502746)	To study the combination of ramucirumab with nivolumab in mesothelioma	Nivolumab 240mg IV + Ramucirumab 8mg/kg IV	N/A	• Response rate • Safety • Progression free survival	JU 2018	Primary Completion Date: JUN 2022

Phase II Nivolumab and Ramucirumab for Patients With Previously-Treated Mesothelioma				• Overall survival		
JME-001 (UMIN000030892; Japanese ISR Trial)	To assess efficacy and safety of the first-line combination therapy of cisplatin, pemetrexed and nivolumab for advanced or metastatic malignant pleural mesothelioma which is untreated and unresectable	Cisplatin, pemetrexed and nivolumab	N/A	• Safety • Response rate • Disease control rate • Overall survival • Progression free survival • Curation of response • Time to response • Best overall usrival • Quality of life	JAN 2018	Primary Completion Date: N/A Actual Completion Date: N/A
NICITA (NCT04177953) Nivolumab With Chemotherapy in Pleural Mesothelioma After Surgery	Evaluate Time-to-next-treatment (TNT), as well as safety and tolerability, in patients with malignant pleural mesothelioma stage I-III who have undergone cytoreductive surgery with curative intend consisting of extended pleurectomy / decortication (eP/D) with or without hyperthermic intrathoracic chemoperfusion	Carboplatin AUC 5, Cisplatin 75mg/m^2, Pemetrexed 500mg/m^2, Nivolumab	Chemotherapy: Carboplatin AUC 5, Cisplatin 75mg/m2, Pemetrexed 500mg/m2	• Time to next treatment • Safety • Progression free survival • Overall survival • Treatment beyond progression • Treatment beyond progression • Quality of life • ECOG performance	FEB 2019	Primary Completion Date: JUN 2023
NCT03918252 Neoadjuvant Immune Checkpoint Blockade in Resectable Malignant Pleural Mesothelioma	Evaluate the safety and feasibility of neoadjuvant nivolumab +/- ipilimumab in resectable MPM	ARM A Nivolumab, 240mg IV ARM B Nivolumab, 3mg/kg IV + ipilimumab 1mg/kg IV	N/A	• Safety • Feasibility • Pathological Response • Radiographic Response • Toxicity	OCT 2019	Primary Completion Date: JUN 2025
NCT04162015	Test whether giving nivolumab in combination with pemetrexed and either cisplatin or carboplatin before surgery is	Nivolumab 360 mg, pemetrexed 500 mg/m^2, and cisplatin 75 mg/m^2 or carboplatin AUC=5	N/A	• Patients going to operating room for surgical resection	NOV 2019	Primary Completion Date: NOV 2022

A Study of Nivolumab and Chemotherapy Followed by Surgery for Mesothelioma	a safe and effective approach to treating resectable mesothelioma without delaying surgery.					
NCT02341625 A Study of BMS-986148 in Patients With Select Advanced Solid Tumors	Determine the safety, tolerability, pharmacokinetics, immunogenicity, antitumor activity and pharmacodynamics of BMS-986148 administered alone and in combination with nivolumab in patients with mesothelioma, non-small cell lung cancer, ovarian cancer, pancreatic cancer and gastric cancer	PART 1: BMS-986148 PART 2: BMS-986148 PART 3A and B: BMS-986148 Nivolumab	N/A	• Safety • Observed serum or plasma concentration of BMS-986148 • Area under the concentration-time curve of BMS-986148 • Terminal serum or plasma half-life of BMS-986148 • Total body clearance of BMS-986148 • Volume of distribution of BMS-986148 • Accumulation index of BMS-986148 • Concentration over a dosing interval of BMS-986148 • Best overall response • Objective Response rate • Duration of response • Progression free survival • Overall response • Changes in QTcF of BMS-986148 • Immunogenicity of BMS-986148	JUL 2015	AUG 2022

Amgros I/S
Dampfærgevej 22
2100 København Ø
Danmark

T +45 88713000
F +45 88713008

Medicin@amgros.dk
www.amgros.dk

Forhandlingsnotat

Dato for behandling i Medicinrådet	23.03.2022
Leverandør	Bristol-Myers Squibb (BMS)
Lægemiddel	Nivolumab (opdivo) + ipilimumab (yervoy)
EMA-indikation	Nivolumab i kombination med ipilimumab til behandling af ikke-resektabel lungehindekræft

Amgros har følgende pris på nivolumab og ipilimumab:

Tabel 1: Forhandlingsresultat

Lægemiddel	Styrke/dosis	Pakningsstørrelse	AIP (DKK)	Nuværende SAIP (DKK)	SAIP (DKK) pr. 01.04.2022	Rabatprocent ift. AIP
Nivolumab	240 mg/24 ml	1 stk.	22.003,74	[redacted]	[redacted]	[redacted]
Nivolumab	100 mg/10 ml	1 stk.	9.168,23	[redacted]	[redacted]	[redacted]
Nivolumab	40 mg/4 ml	1 stk.	3.690,68	[redacted]	[redacted]	[redacted]
Ipilimumab	5 mg/ml	10 ml.	25.653,53	[redacted]	[redacted]	[redacted]
Ipilimumab	5 mg/ml	40 ml.	102.385,55	[redacted]	[redacted]	[redacted]

[redacted]

Årlige lægemiddelpriser

Følgende tabel viser lægemiddelpriserne for 7,8 måneders behandling med nivolumab i kombination med ipilimumab.

[redacted]

Tabel 2: Udregning af prisen for 7,8 måneders behandling med nivolumab i kombination med ipilimumab med fast dosis af nivolumab

Lægemiddel	Dosis	Frekvens	Antal behandlinger i 7,8 måneder	Pris for behandling i 7,8 måneder SAIP (DKK)
Nivolumab*	360 mg	Hver 3. uge	[redacted]	[redacted]
Ipilimumab	1 mg/kg	Hver 6. uge	[redacted]	[redacted]
Total pris for 7,8 måneders behandling med fast dosis nivolumab				[redacted]
Nivolumab**	3 mg/kg	Hver 2. uge	[redacted]	[redacted]
Ipilimumab	1 mg/kg	Hver 6. uge	[redacted]	[redacted]
Total pris for 7,8 måneders behandling med vægtbaseret dosis nivolumab				[redacted]

*Fast dosis

**Vægtbaseret dosis 3mg/kg. 72,75 kg

Status i andre lande

Under behandling i Norge[1].

Under behandling i UK[2].

Konklusion

[redacted]

[redacted]

[1] https://nyemetoder.no/metoder/ipilimumab-yervoy-nivolumab-opdivo-indikasjon-vii

[2] https://www.nice.org.uk/guidance/indevelopment/gid-ta10498

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

Virum, 25. februar 2022.

Til Medicinrådet

Bristol Myers Squibbs tilbagemelding på udkast til vurderingsrapport for nivolumab (Nivo) i kombination med ipilimumab (Ipi) til Førstelinjebehandling af ikke-resekterbar malignt pleuralt mesotheliom (1L MPM)

Bristol Myers Squibb (BMS) imødeser Medicinrådets (MR) anbefaling vedr. behandling med Nivo+Ipi til 1L MPM planlagt til 23. marts 2022, og således 10 måneder efter MR modtog ansøgningen (12 ugers validering og 26 ugers evaluering). BMS takker hermed for muligheden for at give en tilbagemelding på vurderingsrapporten, og benytter lejligheden til at gøre opmærksom på fire faktorer, som, hvis ignoreret, må antages at give anledning til – i bedste fald – en anbefaling hvilende på et forkert grundlag og – i værste fald – en fejlagtig anbefaling. Dette skyldes, at de fire faktorer har ført til en bias i den sundhedsøkonomiske afrapportering, da MR både har undervurderet den kliniske gevinst *og* overvurderet omkostningen forbundet med behandlingen.

For det første overestimerer MR behandlingsomkostningerne ved at antage, at Nivo vil blive administreret som en fast dosering. Nivolumab har været markedsført i Danmark siden 2015, og har været brugt til behandling af en række kræftformer. Alligevel har en dansk patient – os bekendt – stadig til gode at blive behandlet med fast dosering, da man i Danmark har valgt at behandle patienter med en vægtbaseret dosering. Ved at lave beregningerne med udgangspunkt i en fast dosering overvurderer man således omkostningerne i klinisk praksis. Derudover bryder man med tidligere praksis i MR – senest demonstreret ved vurderingen af pembrolizumab på rådsmødet i januar 2022, hvor man også regnede med en vægtbaseret dosering i stedet for den EC-godkendte faste dosering. I BMS' sundhedsøkonomiske analyse af ITT-populationen reduceres ICER'en med ca. syv procent ved vægtbaseret dosering, og øger dermed sandsynligheden for, at Nivo+Ipi er omkostningseffektiv.

For det andet underestimerer MR langtidsoverlevelsen, bl.a. fordi man i sin analyse ser bort fra de seneste studiedata. Ét af de mest afgørende parametre i en sundhedsøkonomisk analyse er at estimere langsigts-effekter som ligger ud over opfølgningstiden fra de kliniske studier. For bedre at informere disse estimater, og for at reducere beslutningsusikkerheden, har BMS delt seneste data-opdatering fra det pivotale fase 3-studie; CheckMate 743, med MR. Det senest opdaterede data for overlevelse (OS) har en minimumopfølgningstid på 35,5 måneder (og en medianopfølgningstid på 43,1 måneder). Data fra seneste opdatering blev delt i august 2021 inden dag 0 (20. september 2021), og er siden blevet publiceret i peer-reviewed tidsskrift, men disse data er desværre ikke blevet taget i betragtning i evalueringen.

Overlevelsesanalysen i den seneste dataopdatering bekræfter en af nøgleantagelserne i BMS' sundhedsøkonomiske analyse; nemlig at sandsynligheden for at dø (hasarden) først stiger og dernæst falder. Dette er et kendt statistisk forhold, som er observeret indenfor et utal af bl.a. registerstudier og randomiserede-studier af immunterapi til behandling af en række forskellige kræftformer. Når man skal vælge en ekstrapolationskurve til at estimere den langsigtede overlevelse, er det af afgørende betydning, at man vælger en kurve med de samme statistiske egenskaber. Dette er ikke tilfældet i den udførte evaluering. Her har MR valgt en ekstrapolationskurve, hvor sandsynligheden for at dø (hasarden) er stigende. Ikke kun i starten, men over hele tidsperioden. Det ses tydeligt af figur 1A og 1B i Appendiks A, at MR's valg af kurve *ikke* er i overensstemmelse med hverken nyeste data fra CheckMate 743 eller fra andre studier indenfor MPM. Ligeledes er det heller ikke i overensstemmelse med tidligere studier af immunterapi indenfor andre kræftformer. At MR på denne måde ser bort fra summen af evidensen virker ikke rimeligt.

I praksis antager MR nemlig, at det er mere sandsynligt at dø af sin kræft fem *år* efter diagnosen, end det er fem *måneder* efter diagnosen. En antagelse der, som nævnt, hverken synes klinisk plausibel eller er

funderet i studiedata. Implikationen af denne antagelse er, at patienter i MR's model dør tidligere end i både klinisk praksis og i de kliniske studier. Dermed undervurderer MR overlevelses- og QALY-gevinsten ved en livsforlængende behandling, og der introduceres altså endnu en bias i den sundhedsøkonomiske afrapportering.

For det tredje underestimerer MR langtidsoverlevelsen ved at begrænse tidshorisonten til 10 år. Denne begrænsning medfører, at sundhedsgevinster (og omkostninger) der indtræffer 10 år efter behandlingsstart ignoreres. Dette er et problem, fordi studier har vist, at der er MPM-patienter (med epitheloid histologi), som er i live mere end 10 år efter behandlingsstart[1]. MR's valg af ekstrapolationskurve anerkender ikke dette. Hvis man skal evaluere en livsforlængende behandling, men afskærer sig selv fra at måle på slutningen af livet, vil man automatisk undervurdere gevinsten. Potentialet ved Nivo+Ipi-behandling til MPM ift. at øge langtidsoverlevelse understreges af, at der er patienter behandlet med Nivo+Ipi, som opnår et komplet respons i CheckMate 743 (2,6 procent (8 patienter) vs. 0,0 procent af patienter behandlet med kemoterapi)[2]. I BMS-analysen viser en 10-års tidshorisont, at ICER'en stiger med 15 procent, og MR's valg af tidshorisont vil derfor på et fejlagtigt grundlag markant reducere sandsynligheden for, at Nivo+Ipi fremstår som en omkostningseffektiv behandling.

For det fjerde ignorerer MR behandlings-"cross-over", som tydeligt indikerer, at gevinsten ved Nivo+Ipi underestimeres ift. dansk klinisk praksis. I CheckMate 743 blev 21,5 procent af de patienter, som var randomiseret til kemoterapi behandlet med immunterapi efter behandlingssvigt. Behandlingen med immunterapi forbedrede overlevelsen for denne patientgruppe i studiet, men er *ikke* en del af dansk klinisk praksis. Analyserer man alene de patienter i CheckMate 743, som ikke efterfølgende får immunterapi, falder overlevelsen for gruppen behandlet med kemoterapi. Det betyder at hasardraten mellem Nivo+Ipi og kemoterapi falder fra 0.73 til [redacted]. Dermed må behandlingsgevinsten i Danmark forventes at være noget større end de beskrevne forskelle i MR's afrapportering, og den ICER som præsenteres er derfor et overestimat.

Samlet set har ovenstående fire faktorer en markant påvirkning på resultaterne af analysen. Hvis de tre førstnævnte bias rettes i den sundhedsøkonomiske model, vil man få en inkrementel gevinst på 1,32 QALY, på 1,57 leveår og en ICER baseret på listepriser på 450 000 kr./QALY for patienter med non-epitheloid histologi. Udføres analysen på nettopriser bliver resultatet [redacted] kr./QALY, hvilket, i de lande Danmark normalt sammenlignes med, ville betragtes som en omkostningseffektiv behandling. Bemærk også, at BMS-analysen med en QALY-gevinst på 1,32 (i modsætning til MR's beregnede gevinst på 0,74) er bemærkelsesværdigt tæt på estimatet fra fx de hollandske HTA-myndigheder på 1,28 QALY.[3] **MR-sekretariatets afrapportering må derimod betragtes som et biased og delvist fejlbehæftet oplæg til prisforhandling, og det reelle ICER-estimat må formodes at ligge *markant* under det i vurderingsrapporten beskrevne estimat.**

BMS opfordrer dog afslutningsvist MR til at fastholde ambitionen om en rådsanbefaling på rådsmødet i marts, idet vi henleder opmærksomheden på, at en gruppe danske patienter — 10 måneder efter modtagelsen af vores ansøgning — endnu ikke har adgang til behandling med nivolumab i kombination med ipilimumab. I modsætning til en række sammenlignelige lande. Det udækkede medicinske behov for danske patienter er åbenlyst og sygdommen skyldes næsten udelukkende eksponering for asbest i erhvervsmæssig sammenhæng[4,5], og det bemærkes i den sammenhæng, at behandling med nivolumab i kombination med ipilimumab har et både livs*forlængende* og livs*forbedrende* perspektiv[2,6]. Behandlingen er efter BMS' overbevisning dokumenteret omkostningseffektiv i Danmark — baseret på gængs og videnskabelig velfunderet sundhedsøkonomisk metode. BMS opfordrer derfor på det kraftigste MR til ordentlighed og redelighed udi metodetilgang og det er vores klare vurdering, at rapporten som den foreligger — med eller uden intention — ikke bare er konservativ, men i tillæg rejser stor bekymring om den aktuelle faglige standard og erfaring i MR ift. implementering af cost/QALY-metoden nu 14 måneder efter metoden officielt blev standard.

Det er også et centralt princip i de prisloftsaftaler, der indgås mellem Lægemiddelindustriforeningen (Lif), Danske Regioner og Regeringen, at priser i Danmark skal være på niveau med et gennemsnit af priserne i ni sammenlignelige lande. Ikke at de skal være under. Hvis MR konsekvent, og måske ligefrem med intention,

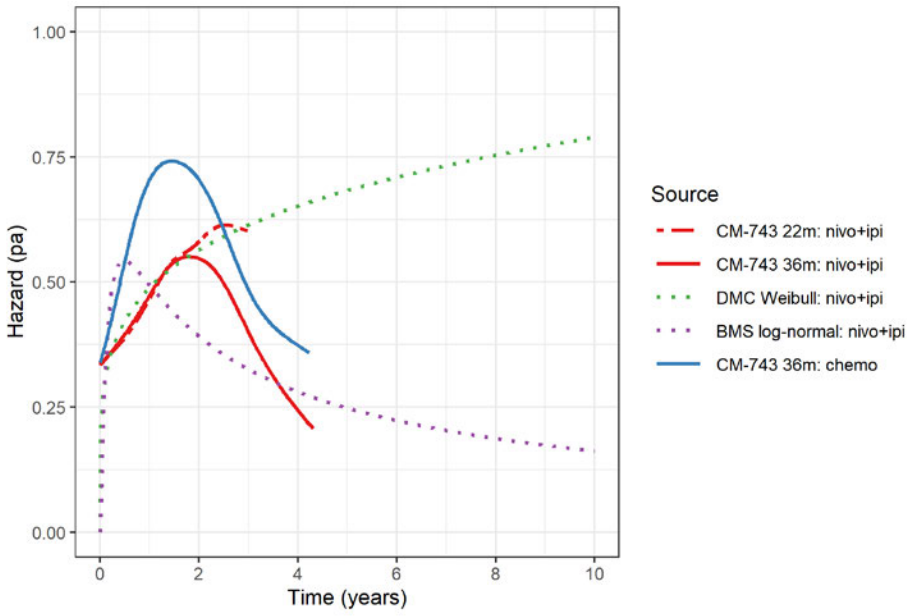
nedjusterer sundhedsgevinster kunstigt i sine analyser med henblik på at opnå kunstigt lave priser, da risikerer vi — ikke mindst for patienterne — helt uanstændige forsinkelser (som her), men måske ligefrem scenarier for fremtiden, hvor medicinske behandlingstilbud over en længere periode kun vil være tilgængelig uden for landets grænser eller i privat regi. Det har ingen interesse i.

Med venlig hilsen,

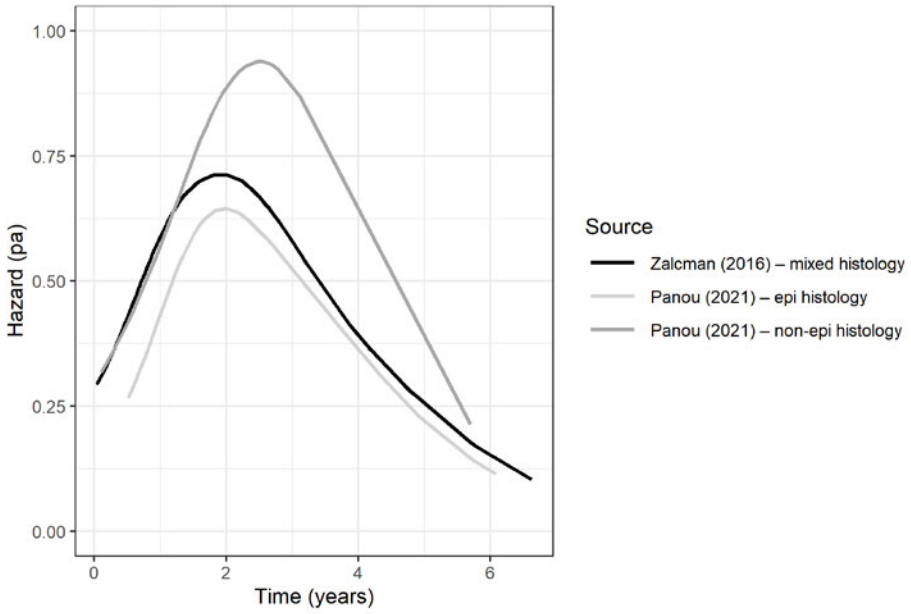
Anders Thelborg
Adm. direktør
Bristol Myers Squibb, Denmark

Appendiks A | Figurer

Figur 1A: Sandsynligheden for at dø over tid i CheckMate 743 og de sundhedsøkonomiske modeller



Figur 1B: Sandsynligheden for at dø over tid i andre MPM studier[4,7]



Note: Figuren viser sandsynligheden for at dø over tid (*smoothed* hazards) for patienter med MPM. Figur 1A viser sandsynligheden for nivo+ipi for begge CheckMate 743 datasæt samt de valgte kurver af hhv. MR og BMS. Det fremgår, at Weibull-kurven valgt af MR har en konstant stigende sandsynlighed. Log-normal kurven valgt af BMS har derimod en stigning i starten og et efterfølgende fald, hvilket er i overensstemmelse med nivo+ipi kurven fra det kliniske studie. Figur 1B viser lignende kurveforløb for to andre studier, hvoraf det ene er et dansk registerstudie. Der er ikke noget der tyder på, at sandsynligheden for at dø er stigende på sigt, som antaget af MR i den sundhedsøkonomiske analyse.

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