Medicinrådet

Bilag til Medicinrådets anbefaling vedr. nivolumab plus relatlimab til behandling af fremskredent melanom hos PD-L1-negative patienter

Vers. 1.0

Bilagsoversigt

1. Ansøgers notat til Rådet vedr. nivolumab + relatlimab
2. Forhandlingsnotat fra Amgros vedr. nivolumab + relatlimab
3. Ansøgers endelige ansøgning vedr. nivolumab + relatlimab

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Virum, 24. november 2023.

Til Medicinrådet

Bristol Myers Squibbs tilbagemelding på udkast til vurderingsrapport for Opdualag (nivolumab i kombination med relatlimab) til behandling af patienter over 12 år med inoperabel eller metastatisk malignt melanom med PDL1<1%

Bristol Myers Squibb (BMS) imødeser Medicinrådets anbefaling vedr. Opdualag (nivolumab i kombination relatlimab) til behandling i første linie af fremskredent malignt melanom med PDL1<1% planlagt til d. 13. december 2023.

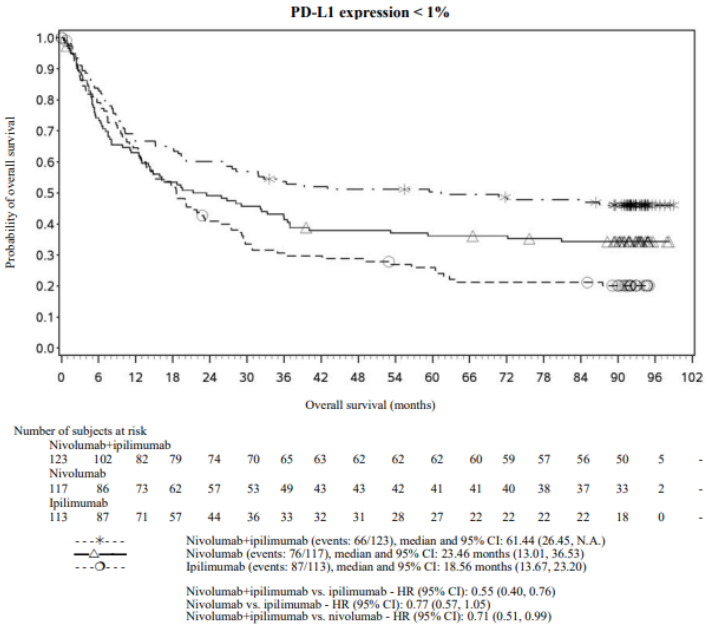
Indledningsvis glæder det BMS, at Medicinrådet i hovedanalysen er enig i størstedelen af BMS' antagelser.

BMS stiller sig dog uforstående over for Medicinrådets metode i forhold til sensitivitetsanalysen, som bliver unødig konservativt uden rimelige argumenter. I sensitivitetsanalysen benyttes *independent fit* til fremskrivning af samlet overlevelse (OS) trods det, at man anerkender, antagelsen om proportional hazards ikke kan afvises. I sensitivitetsanalysen fremskrives komparatorarmen med det mere optimistiske scenarie *Gompertz*, mens interventionsarmen fremskrives med det mere pessimistiske scenarie *Generalized Gamma*.

Der er flere aspekter at anfægte ved den tilgang:

- Immunterapiens virkningsmekanisme samt det faktum, at der er nivolumab i begge behandlingsarme, understøtter antagelsen om proportional hazards. Dette er påvist i Checkmate-067 studiet, hvori der indgår immunterapi og dobbeltimmunterapi. Heri ses netop en vedvarende effekt og parallelle kurver (i.e. parallelforskudt plateau i OS KM-kurverne for de tre immunterapibehandlinger i studiet, se nedenfor).
- Rent biologisk er det også usandsynligt, at Opdualag har en positiv effekt på overlevelsen frem til år 4, hvorefter virkningen skulle ophøre og tilmed ophæve den tidligere positive effekt, således, at kurverne kan konvergere ved år 10. For blot denne ene komponent af Opdualag, nivolumab, kendes en vedvarende effekt frem til minimum 7 år (jf. nedenstående).

Figure 7: Overall survival by PD-L1 expression: 1% cut off (CA209067) - Minimum follow-up of 90 months



Kilde: Opdivo EPAR

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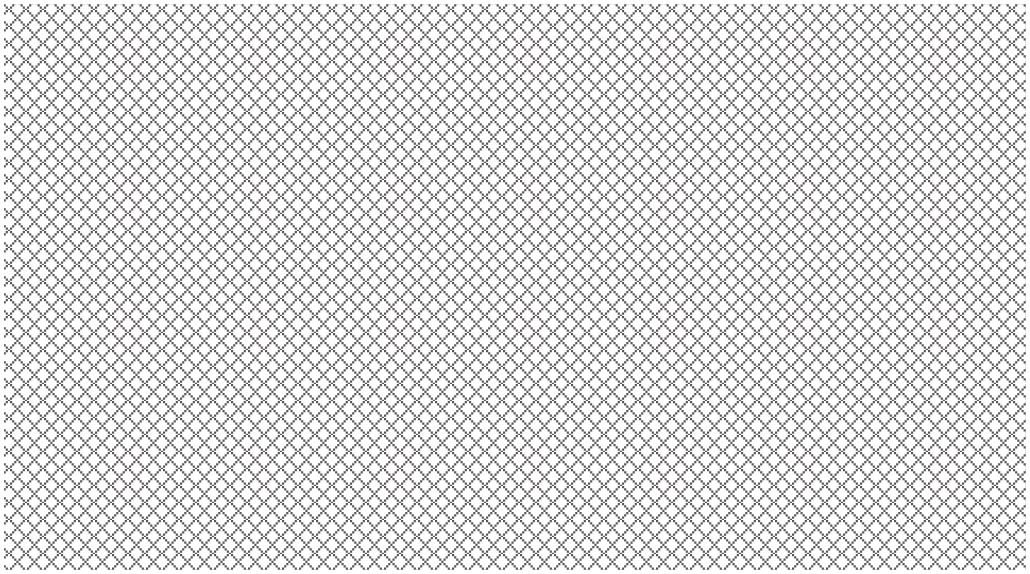
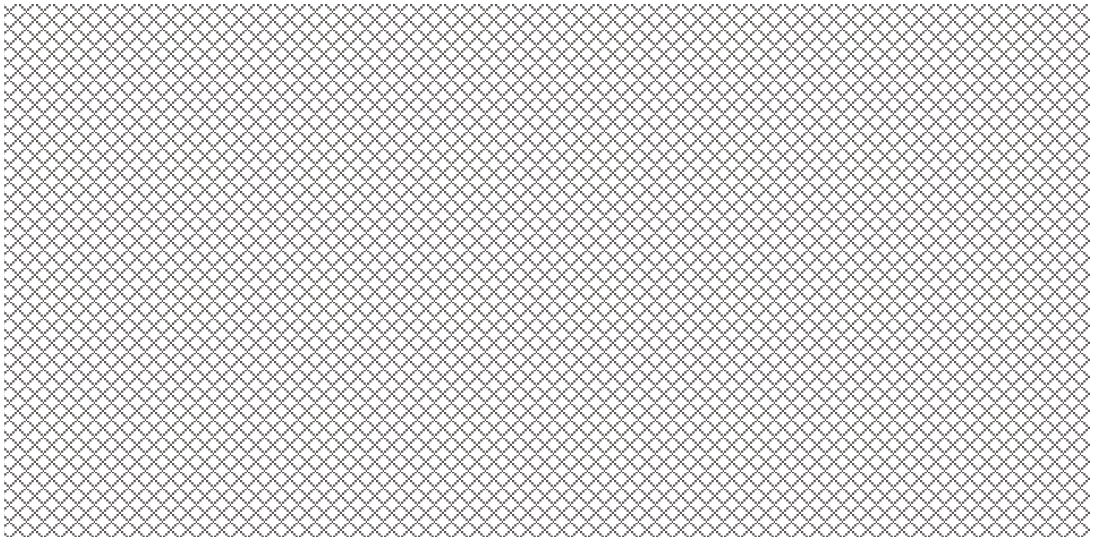
BMS anerkender, at nuværende opfølgningstid kan give anledning til nogen usikkerhed omkring OS. Derfor vedlægger vi OS-data på ITT-populationen såvel som PDL1<1% fra et helt nyt datacut (oktober 2023), som netop er færdigbehandlet og strengt fortroligt.





Kilde: BMS, Data on File (Database Lock October 2023)

Det er værd at bemærke, at OS HR konfidensinterval [redacted] ITT-populationen. For PDL1<1% [redacted] sammenlignet med datacuttet fra oktober 2022, som præsenteres i ansøgningen.

Det nye datacut bestyrker Medicinrådets hovedanalyse; at der er en relevant og betydningsfuld OS gevinst ved Opdualag.

Vi takker for et godt og effektivt samarbejde med sekretariatet.

Med venlig hilsen,

Anders Thelborg
Adm. direktør
Bristol Myers Squibb, Denmark

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Forhandlingsnotat

01.12.2023
CAF/DBS

Dato for behandling i Medicinrådet	13.12.2023
Leverandør	Bristol Myers Squibb
Lægemiddel	Nivolumab + relatlimab (Opdualag)
Ansøgt indikation	Nivolumab + relatlimab er indiceret til førstelinjebehandling af fremskredent (inoperabelt eller metastatisk) melanom hos voksne og unge i alderen 12 år og ældre med PD-L1-tumorcelleekspression < 1 %
Nyt lægemiddel / indikationsudvidelse	Nyt lægemiddel

Prisinformation

Amgros har fået følgende tilbudspris på Opdualag (nivolumab + relatlimab):

Tabel 1: Forhandlingsresultat betinget af en anbefaling i Medicinrådet

Lægemiddel	Styrke	Pakningsstørrelse	AIP (DKK)	Forhandlet SAIP (DKK)	Rabatprocent ift. AIP
Opdualag	240 mg nivolumab + 80 mg relatlimab	1 stk.	56.250	[redacted]	[redacted]

Prisen er betinget af Medicinrådets anbefaling.

Hvis Medicinrådet ikke anbefaler Opdualag, indkøbes lægemidlet til følgende ubetingede pris.

Tabel 2: Forhandlingsresultat ubetinget af en anbefaling i Medicinrådet

Lægemiddel	Styrke	Pakningsstørrelse	AIP (DKK)	Forhandlet SAIP (DKK)	Rabatprocent ift. AIP
Opdualag	240 mg nivolumab + 80 mg relatlimab	1 stk.	56.250	[redacted]	[redacted]

Aftaleforhold

Amgros har ved forhandling fået ovenstående pris (tabel 1) fra leverandøren, som er betinget af Medicinrådets anbefaling af Opdualag til den ansøgte indikation. Da flere leverandører har udtrykt, at de kan levere Opdualag har Amgros publiceret et udbud med tilbudsfrist den 20.12.2023. Originalleverandøren byder ind med prisen i tabel 1 i udbuddet, hvis Medicinrådet anbefaler Opdualag.X

Aftalen kan starte den 01.03.2024 med mulighed for prælevering så snart aftalen er underskrevet af leverandøren. Det betyder, at der kan leveres Opdualag til den forhandlede pris umiddelbart efter den 02.01.2024. Aftalen varer indtil den 31.12.2025 med mulighed for at forlænge i 2 gange 12 måneder. Leverandøren har mulighed for at sætte prisen ned i hele aftaleperioden.

Konkurrencesituationen

Nuværende behandling af patienter med fremskredent melanom, som ikke har modtaget tidligere systemisk behandling, er PD-L1 negative og ikke har aggressiv sygdom (defineret ved lille tumorbyrde og langsom sygdomsvækst) er monoterapi med en PD-L1 hæmmer, Opdivo (nivolumab) eller Keytruda (pembrolizumab).

Tabel 2: sammenligning af lægemiddeludgifter pr. patient for et års behandling

Lægemiddel	Styrke	Paknings størrelse	Dosering	Pris pr. pakning (SAIP, DKK)	Lægemiddeludgift (SAIP, DKK)
Opdualag	240 mg nivolumab + 80 mg relatlimab	1 stk.	480 mg nivolumab og 160 mg relatlimab administreret intravenøst over 30 minutter hver 4. uge.	[redacted]*	[redacted]
Opdivo	240 mg/24 ml	1 stk.	6 mg/kg hver 4. uge**	[redacted]	[redacted]
Keytruda	25 mg/ml	4 ml	4 mg/kg hver 6. uge**	[redacted]	[redacted]

*Betinget pris
**Gennemsnitsvægt 79,7 kg jf. Medicinrådets vurderingsrapport
*** pris pr. 01.01.2024

Status fra andre lande

Tabel 4: Status fra andre lande

Land	Status	Link
Norge	Under vurdering	Link til vurdering
Sverige	Under vurdering	Link til vurdering
England	Under vurdering	Link til vurdering

Konklusion

[redacted]

Application for the assessment of Opdualag™ (nivolumab + relatlimab) for previously untreated metastatic or unresectable melanoma in adults and adolescents 12 years of age and older with tumour cell PD-L1 expression < 1%

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1. Basic information

Contact information	
Name	Mie-Ran Yoon
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Overview of the pharmaceutical	
Proprietary name	Opdualag™
Generic name	Nivolumab plus relatlimab
Marketing authorization holder in Denmark	Bristol Myers Squibb™
ATC code	L01XY03
Pharmacotherapeutic group	Combinations of antineoplastic agents
Active substances	Nivolumab plus relatlimab
Pharmaceutical form	Concentrate for solution for infusion (sterile concentrate)
Mechanism of action	Nivolumab blocks the PD-1 (also called CD279) receptor expressed by activated T cells and B cells, which prevents binding of the PD-1 receptor with its ligands, PD-L1 and PD-L2. This would otherwise result in the downregulation of the immune response. Inhibition of the interaction between PD-1 and its ligands by nivolumab promotes tumour antigen-specific T-cell responses. Relatlimab is an immunoglobulin G4 LAG-3–blocking monoclonal antibody. Relatlimab acts to restore the effector function of exhausted T cells and to promote cytokine secretion. The combination of nivolumab (anti-PD-1) and relatlimab (anti-LAG-3) results in increased T-cell activation compared to the activity of either antibody alone.
Dosage regimen	The recommended dose for adults and adolescents 12 years of age and older is 480 mg nivolumab and 160 mg relatlimab every 4 weeks administered as one intravenous infusion over 30 minutes; this dose is established for adolescent patients weighing at least 30 kg
Therapeutic indication relevant for assessment (as defined by the European Medicines Agency, EMA)	Nivo+rela is indicated for the 1L treatment of advanced (unresectable or metastatic) melanoma in adults and adolescents 12 years of age and older with tumour cell PD-L1 expression < 1%
Other approved therapeutic indications	n/a
Will dispensing be restricted to hospitals?	Yes
Combination therapy and/or co-medication	n/a

Overview of the pharmaceutical	
Packaging – types, sizes/number of units, and concentrations	One vial of 20 mL contains 240 mg of nivolumab and 80 mg of relatlimab
Orphan drug designation	No

2. Abbreviations

Abbreviation	Definition
1L	First-line
2L	Second-line
AD	Anxiety/depression
AE	Adverse event
AFT	Accelerated failure time
AIC	Akaike information criterion
AJCC	American Joint Committee on Cancer
APC	Antigen-presenting cell
ATC	Anatomical therapeutic chemical
Atezo	Atezolizumab
BIC	Bayesian information criterion
BICR	Blinded independent central review
Bini	Binimetinib
BMS	Bristol-Myers Squibb
carb	Carboplatin
CD	Cluster of differentiation
CE	Cost-effectiveness
CEAC	Cost-effectiveness acceptability curve
CHMP	Committee for Medicinal Products for Human Use
CI	Confidence interval
Cob	Cobimetinib
COVID-19	Coronavirus disease 2019
CT	Computed tomography
CTLA-4	Cytotoxic T-lymphocyte-associated protein-4
Dab	Dabrafenib
Dac	Dacarbazine
DBL	Database lock
DKK	Danish Kroner
DMC	Danish Medicines Council (Medicinrådet)
DRG	Diagnosis-related group
DSA	Deterministic sensitivity analysis
EC	European Commission

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Abbreviation	Definition
ECOG PS	Eastern cooperative oncology group performance status scale
EMA	European medicines agency
Enco	Encorafenib
EQ-5D	Euroqol five dimensions
EQ-5D-3L	Euroqol 5-dimension 3-level
EQ-5D-5L	Euroqol 5-dimension 5-level
EQ-(5D) VAS	Euroqol 5-dimension visual analogue scale
FACT-M	Functional Assessment of Cancer Therapy – Melanoma
FDC	Fixed-dose combination
FPNMA	Fractional polynomial network meta-analysis
HR	Hazard ratio
HRQoL	Health-related quality of life
HSUV	Health state utility values
HTA	Health technology assessment
ICER	Incremental cost-effectiveness ratio
IFNγ/-R	Interferon-gamma/receptor
Ipi	Ipilimumab
IQR	Interquartile range
ITT	Intention-to-treat
IV	Intravenous
KM	Kaplan-Meier
LAG-3	Lymphocyte activation gene-3
LDH	Lactate dehydrogenase
LY	Life year
Max	Maximum
MEK	Mitogen-activated protein kinase
MHC	Major histocompatibility complex
MID	Minimum important difference
Min	Minimum
MO	Mobility
NA	Not applicable/available
NF-κB	Nuclear factor kappa B
NICE	National institute for health and care excellence
NIVO	Nivolumab
Nivo+rela	Nivolumab plus relatlimab
NMA	Network meta-analysis
NR	Not reached
ONS	Office of National Statistics
ORR	Objective response rate

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Abbreviation	Definition
OS	Overall survival
Pac	Paclitaxel
PD	Progressed disease
PDI	Pain/discomfort
PD-1	Programmed death -1
PD-L1	Programmed death-ligand 1
PD-L1/2	Programmed death ligand-1/2
Pembro	Pembrolizumab
PET-CT	Positron emission tomography computerised tomography
PF	Progression-free
PFS	Progression-free survival
PI3K	Phosphoinositide 3-kinase
PS	Performance status
PSA	Probabilistic sensitivity analysis
PSM	Partitioned survival model
Q4W	Every four weeks
QoL	Quality of life
QALY	Quality-adjusted life-year
RECIST	Response evaluation criteria in solid tumours
RELA	Relatlimab
SAE	Serious adverse event
SC	Selfcare
SD	Standard deviation
SE	Standard error
Shp-2	Src homology-2 domain-containing protein tyrosine phosphatase-2
SLR	Systematic literature review
TCR	T-cell receptor
Tem	Temozolomide
TM	Trademark
Tra	Trametinib
TRAE	Treatment-related adverse event
TD	Time to death
TTD	Time to discontinuation
UA	Usual activities
UK	United kingdom
VAS	Visual analogue scale
VAT	Value-added tax
Vs.	Versus
WTP	Willingness to pay

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4. Resume

BMS ansøger om godkendelse af nivolumab + relatlimab (nivo+rela, Opdualag™) som mulig standard behandling til førstelinjebehandling (1L) af fremskredent (inoperabelt eller metastatisk) melanom hos patienter i alderen fra 12 år og op med PD-L1-tumorcelleekspression <1%. Ansøgningen er baseret på resultater fra det pivotale fase II/III studie RELATIVITY-047 (NCT03470922). Opdualag™ blev godkendt af Europa-Kommissionen i september 2022.

Population

Melanom tegner sig for langt de fleste dødsfald blandt kutane kræftformer[1]. Mens overlevelsesraterne er høje for lokaliseret melanom, falder 2-års overlevelsesraten betydeligt til anslåede 18-40% for metastatisk sygdom (stadie IV) [2]. Targeterede behandlinger, immunterapier og især dobbelt immunterapi har signifikant forbedret overlevelsen ved metastatisk sygdom[5], men der fortsat et behov for behandlinger, der har vedvarende respons kombineret med en tolerabel bivirkningsprofil.

I Danmark anbefales immunterapi som førstelinjebehandling af metastatisk melanom til hovedparten af patienter med langsomt progredierende sygdom[6]. For patienter med PD-L1-tumorcelleekspression <1% er nivolumab i kombination med ipilimumab (nivo+ipi) standardbehandling. Dog er der patienter, der ikke er egnede til behandling med nivo+ipi, og som derfor kun kan tilbydes anti-PD1-monoterapi med nivolumab eller pembrolizumab. Det er denne gruppe af patienter, ca. 50 patienter årligt, der vurderes at være kandidater til nivo+rela.

Intervention & Komparator

En direkte sammenligning af nivo+rela med nivolumab monoterapi er mulig via RELATIVITY-047, et globalt, randomiseret, dobbeltblindet, kontrolleret fase 2/3 forsøg. Data og evidens fra RELATIVITY-047 er derfor relevant for dansk klinisk praksis. Nivo+rela modtog en positiv CHMP vurdering i juli 2022 og blev godkendt af Europa-Kommissionen i september 2022 [7].

Resultater

Det primære effektmål i RELATIVITY-047 var progressionsfri overlevelse (PFS), mens sekundære effektmål inkluderede samlet overlevelse (OS) og objektiv responsrate (ORR). Effektdata er vist i Table 1 med medianopfølgning på 25,31 måneder (min, maks: 0,3-51,5) (databaselock 27. oktober 2022) for den forudspecificerede undergruppe for patienter med tumorcelle PD- L1-ekspression <1% [5].

Table 1 Summary of efficacy data for RELATIVITY-047, PD-L1 expression <1% subpopulation

	Nivolumab + relatlimab (N=209)	Nivolumab monotherapy (N=212)	HR
Primary outcomes			
Median PFS, months (95% CI)	[redacted]	[redacted]	0.68 (0.54-0.86)
Secondary outcomes			
Median OS, months (95% CI)	[redacted]	[redacted]	0.83 (0.63-1.08)
ORR, %	[redacted]	[redacted]	-

Abbreviation: CI, confidence interval; HR, hazard ratio; NA, not available; ORR, objective response rate; OS, overall survival; PFS, progression free survival.
Source: [5, 59].

Nivo+rela har dokumenteret PFS-fordel i forhold til nivolumab monoterapi med mere end en fordobling i median PFS - samt adskillelse af PFS Kaplan-Meier-kurverne så tidligt som efter 12 uger. Desuden er median OS og ORR til fordel for nivo+rela versus nivolumab monoterapi. Der var ingen statistisk signifikant forskel i bivirkninger mellem armene af det kliniske forsøg [5].

Sundhedsøkonomisk evaluering:

En partitioned survival model med tre sundhedstilstande blev udviklet til at evaluere omkostningseffektiviteten af nivo+rela sammenlignet med nivolumab monoterapi. Nivo+rela var forbundet med højere antal leveår (LY) og kvalitetsjusterede leveår (QALY) sammenlignet med nivolumab monoterapi over den modellerede tidshorisont, hvilket medførte en LY gevinst på [redacted] LY og en QALY gevinst på [redacted] QALY vs. nivolumab monoterapi. Anvendelsen af nivo+rela medførte forskel i omkostninger på [redacted] DKK. sammenlignet med nivolumab monoterapi. Omkostningerne pr. opnået QALY i forbindelse med behandling med nivo+rela vs nivolumab monoterapi var [redacted] DKK. Budgetpåvirkningen i år 5 efter introduktion af nivo+rela i Danmark er estimeret til [redacted] DKK. Alle priser er listepriser.

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

5.1 The medical condition and patient population

5.1.1 Disease description

5.1.1.1 Unresectable or metastatic melanoma

Melanoma is a neoplasm originating from melanocytes—the pigment-producing cells of the skin. It is one of the three main types of skin cancer—along with basal cell carcinoma and squamous cell carcinoma—and accounts for approximately 5% of all skin cancers [8]. Melanoma commonly arises from melanocytes present in cutaneous primary locations, and those are considered cutaneous melanoma.

Melanoma has two main stages of progression: the radial growth phase and the vertical growth phase. Lesions in the latter growth phase are the ones with the capacity to metastasize [9]. In some cases, melanoma is diagnosed as metastatic without a known primary site, which is called unknown primary melanoma [10]. The most frequent cause of mortality in patients with melanoma is distant metastasis, which occurs in a rapid and overwhelming progression due to a combination of factors involving inherited genetics and tumourigenesis [11].

5.1.1.2 Diagnostic assessment and staging

It is critical that diagnosis and staging of melanoma is conducted by a dermatologist or a pathologist experienced with pigmented lesions. Diagnosis and staging include core biopsy, excisional, or incisional biopsy depending on disease location [9]. The melanoma staging system categories from the 8th edition of the American Joint Committee on Cancer (AJCC)'s Cancer Staging Manual and is outlined in Table 2 [12].

Table 2: Clinical stage groups according to the AJCC's Cancer Staging Manual, 8th edition

Clinical stage group	T	N	M
0	Tis	N0	M0
IA	T1a	N0	M0
IB	T1b	N0	M0
	T2a	N0	M0
IIA	T2b	N0	M0
	T3a	N0	M0
IIB	T3b	N0	M0
	T4a	N0	M0
IIC	T4b	N0	M0
III	Any T	≥ N1	M0
IV	Any T	Any N	M1

Abbreviations: AJCC, American Joint Committee on Cancer; M, presence of metastases; N, number of lymph nodes; T, tumour.
Sources: Adapted from Keung and Gershenwald, 2018 [12] (The original and primary source for this information is the AJCC Cancer Staging Manual, 8th Edition [2017], published by Springer International Publishing [13])

Cases of cutaneous melanomas are typically categorized as either localized disease with no evidence of regional or distant metastases (stages 0–II), regional nodal/in-transit disease (stage III), or as distant metastatic disease (stage IV). Nordic data identifying the proportion of patients in each melanoma stage is available for Norway: the distribution of melanoma by AJCC 8th edition stage at diagnosis suggests that around 5% of patients with melanoma are in the metastatic stage (stage IV) [14]. This rate is comparable to estimates from the Danish melanoma database [3, 4].

5.1.1.3 Mortality and morbidity

Worldwide, most patients with melanoma can expect to survive more than 5 years after diagnosis; this is also seen in the Nordic region. However, the survival rate for patients with an advanced stage disease is lower than for those with earlier stages [15]. Data from Denmark on survival by the AJCC's 8th edition stages confirms that survival rates decrease in the advanced stages of the disease (see Table 3).

Table 3: Melanoma survival rates by AJCC's stages in Denmark

Stage	2-year survival rate	5-year survival rate	10-year survival rate
I	n/a	97%	93%
II	n/a	53%	39%
III	n/a	46%	33%
IV*	With normal LDH: 40% With elevated LDH: 18%	n/a	n/a

Abbreviations: AJCC, American Joint Committee on Cancer; LDH, lactate dehydrogenase levels.
The time period (year date) that the survival rates have been reported for, has not been specified in the sourced document.
* Survival depends on serum LDH values.
Source: [2]

5.1.1.4 Prevalence and incidence in Denmark

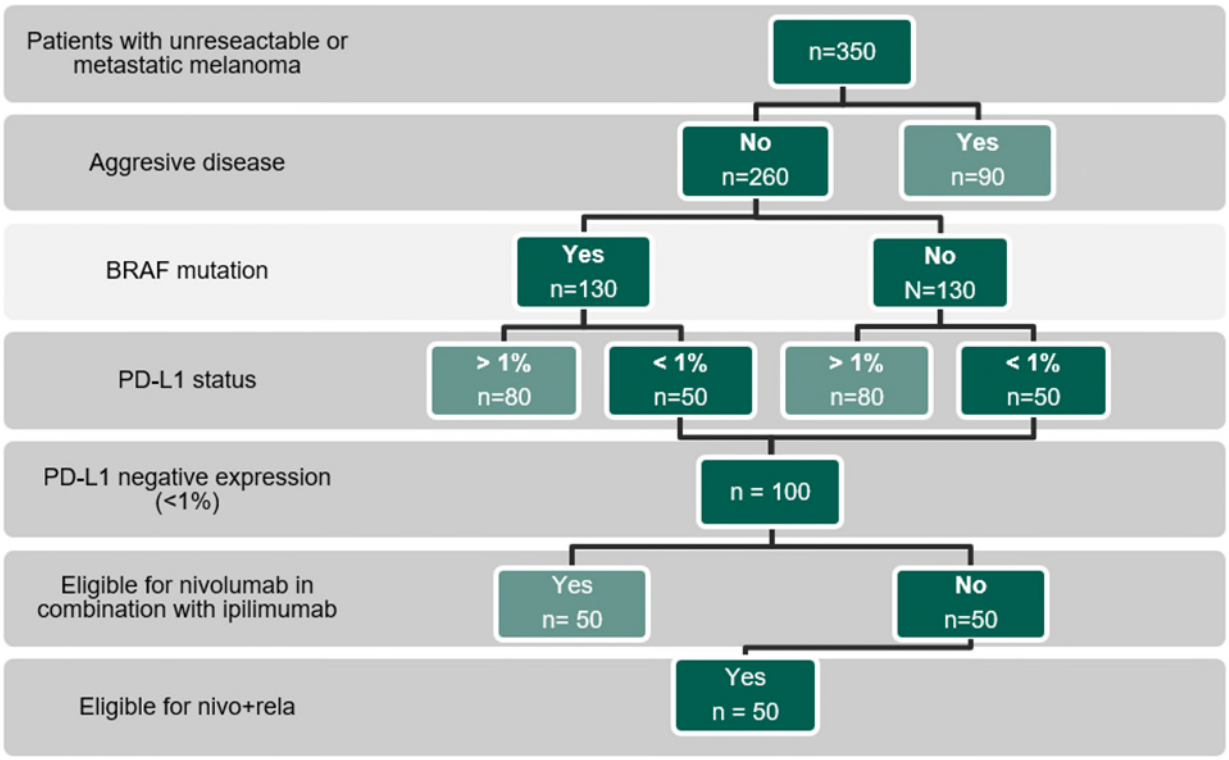
In Denmark, melanoma is the fourth most common cancer in women and the fifth most common in men. The incidence of new melanomas has increased by almost 7% per year over the past ten years, reaching to an average annual incidence between 2016 and 2020 of 1380 new cases in women and 1297 new cases in men. The prevalence of the disease in 2019 was approximately 36 600 patients [1].

5.1.1.5 Patient populations relevant for this application

Treatment with nivo+rela is targeted to patients from 12 years of age with tumour cell PD-L1 expression <1%, regardless of BRAF status, and who are clinically assessed not to have aggressive disease. Nivolumab in combination with ipilimumab is the standard of care for patients with PD-L1 expression <1% in Denmark (see section 5.2.1). Patients who are not considered by clinicians as suitable candidates for nivolumab in combination with ipilimumab (due to tolerability) are therefore treated with an anti-PD1 monotherapy. [redacted]: Overview of number of eligible patients in Denmark

[redacted]

Figure 1: Overview of number of eligible patients in Denmark



Abbreviations: Nivo+rela, nivolumab + relatlimab; PD-L1, programmed death ligand-1.
Note: Dark-coloured boxes refer to parameters relevant for indication. BRAF status is not an influencing factor for eligibility for treatment with nivo+rela.
Source (adapted from): [16]

Table 4: The number of patients eligible for treatment with nivo+rela in Denmark

	2023	2024	2025	2026	2027
Number of patients in Denmark who are eligible to receive nivo+rela, n	50	50	50	50	50

Source: BMS estimations (2023)

5.2 Current treatment options and choice of comparator

5.2.1 Current treatment options

The Danish Medicines Council decided in October 2018 to initiate the process of producing a national treatment guideline for unresectable or metastatic melanoma [17]. The process is on hold since 2021. However, the Danish Cancer Society and the Danish Multidisciplinary Cancer group provide recommendations for this patient population [6, 18].

For the treatment of metastatic or unresectable melanoma, immunotherapy with **PD-1 inhibitors** (nivolumab monotherapy and pembrolizumab monotherapy), **PD-1 plus CTLA-4 inhibitors** (nivolumab plus ipilimumab) and **BRAF/MEK protein kinase inhibitors** (vemurafenib/cobimetinib, dabrafenib/ trametinib or encorafenib/binimetinib) can be used as first line (1L) therapy. The Danish Cancer Society and the Danish Multidisciplinary Cancer group recommend the following [6, 18]:

- **PD-L1 positive expression (>1%)** and **BRAF wildtype**, a PD-1 inhibitor should be considered (nivolumab monotherapy or pembrolizumab monotherapy); in patients with rapid disease progression, high tumour

burden and/or high lactate dehydrogenase levels (LDH), treatment with combination immunotherapy with PD-1 plus CTLA-4 inhibitors should be considered

- **PD-L1 positive expression (>1%)** and **BRAF mutation**, a PD-1 inhibitor should be considered (nivolumab monotherapy or pembrolizumab monotherapy); in patients with rapid disease progression, high tumour burden and/or high LDH, treatment with combination immunotherapy with CTLA-4 plus PD-1 inhibitors or BRAF plus MEK inhibitors should be chosen
- **PD-L1 negative expression (<1%)** and **BRAF wildtype**, combination immunotherapy with PD-1 plus CTLA-4 inhibitors is preferred; In patients with non-aggressive disease (small tumour burden, slow disease growth, comorbidity and/or fragile general condition), a PD-1 inhibitor monotherapy can be used
- **PD-L1 negative expression (<1%)** and **BRAF mutation**, combination immunotherapy with PD-1 plus CTLA-4 inhibitors is also preferred; In case of aggressive disease (rapid disease progression, high tumour burden and/or high LDH), BRAF plus MEK inhibitors should be considered

For second line (2L) treatment of unresectable or metastatic melanoma, different options are available depending on factors such as: widespread of the disease, physician assessment, patient's health state and preferences. Treatment options include chemotherapy, hyperthermic regional perfusion therapy in arms or legs, or palliative treatment with radiation therapy [6].

5.2.1.1 Unmet need

Metastatic melanoma is the most aggressive skin cancer, and its incidence has been rising. In Denmark, it is the leading cause of death in the form of cutaneous malignancy [1, 2, 11, 19, 20].

In the last few years, novel targeted therapies and immunotherapies have improved overall survival (OS) and progression-free survival (PFS) rates [21]. Unfortunately, some patients are still only experiencing limited OS benefit [21]. Therefore, there is a need for additional novel combinations with an optimized benefit-risk profile to allow more patients to benefit from dual immunotherapies. Despite survival outcomes achieved by current standard of care, such as the dual immunotherapies combinations (PD-1 inhibitor in combination with CTLA-4 inhibitor), there remains an unmet need for more durable responses regardless of BRAF and PD-L1 status, while managing any additive toxicities that may arise with immunotherapy combinations.

5.2.2 Choice of comparator

In accordance with the Danish treatment guidelines for melanoma [6, 18] (see Section 5.2.1), treatment with a PD-1 inhibitor (nivolumab monotherapy or pembrolizumab monotherapy) should be considered as the 1L option for the relevant subgroup of patients with unresectable or metastatic melanoma (non-aggressive disease with tumour cell PD-L1 expression <1%) that don't tolerate treatment with nivolumab in combination with ipilimumab. A direct, in-trial comparison of nivo+rela with nivolumab monotherapy is available through the market authorisation study, RELATIVITY-047. Therefore, the evidence from the RELATIVITY-047 trial is considered relevant for the Danish clinical setting, and nivolumab monotherapy as the relevant comparator for nivo+rela. A comparison against pembrolizumab would require a network meta-analysis, which would increase the complexity of the assessment. [redacted]

Neither of the PD-1 inhibitors with EMA indications for metastatic melanoma (i.e., nivolumab nor pembrolizumab) have been assessed by the DMC for use in metastatic melanoma. However, both products have been assessed by the Norwegian Medicines Agency (NoMA) and the Swedish Dental and Pharmaceutical Benefits Agency (*Tandvårds- och läkemedelsförmånsverket*, TLV) in this indication, and were deemed cost-effective compared to the standard of care at

the time of evaluation (in 2015) [23-26].Further, nivolumab and pembrolizumab have been assessed by the DMC compared to placebo in the adjuvant treatment setting: the DMC approved nivolumab for reimbursement in 2018 [27], and pembrolizumab in 2019 [28]. Based on these previous assessments by the DMC, NoMA and TLV BMS finds it reasonable to assume treatment with PD-1 inhibitors, as per current Danish clinical practice, is cost-effective. Thus, no supplementary analysis against placebo is included in this application.

5.2.3 Description of the comparator

An overview of nivolumab monotherapy is presented in Table 5.

Table 5: Description of nivolumab monotherapy

Product description	
Generic name (ATC-code)	Nivolumab (L01FF01)
Mode of action	Nivolumab blocks the PD-1 (also called CD279) receptor expressed by activated T cells and B cells, which prevents binding of the PD-1 receptor with its ligands, PD-L1 and PD-L2. This results in the downregulation of the immune response. Inhibition of the interaction between PD-1 and its ligands by nivolumab promotes tumour antigen-specific T-cell responses
Pharmaceutical form	Concentrate for solution for infusion (sterile concentrate)
Strength	Nivolumab (10 mg/mL): Single-use vials 40 mg/4 mL 100 mg/10 mL 120 mg/10 mL 240 mg/24 mL
Posology/dosing	Advanced (unresectable or metastatic) melanoma inpatients 12 years of age and older: 480 mg every 4 weeks over 30 minutes*
Method of administration	Intravenous
Should the pharmaceutical be administered with other medicines?	No
Treatment duration/criteria for end of treatment	As long as clinical benefit is observed and/or unacceptable toxicity
Necessary monitoring, both during administration and during the treatment period	For adverse event, and thyroid, renal, and hepatic function
Need for diagnostics or other tests (i.e. companion diagnostics)	Patients should be monitored continuously (at least up to 5 months after the last dose)
Medically approved indications relevant for this indication	Melanoma Nivolumab as monotherapy or in combination with ipilimumab is indicated for the treatment of advanced (unresectable or metastatic) melanoma in adults and adolescents 12 years of age and older. Relative to nivolumab monotherapy, an increase in progression-free survival (PFS) and overall survival (OS) for the combination of nivolumab with ipilimumab is established only in patients with low tumour PD-L1

Note: *In the Danish clinical setting, it is also practice to administer nivolumab monotherapy as a weight-based dose of 6 mg/kg every for 4 weeks.
Source: [29]

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5.3 The intervention

Nivo+rela received a positive opinion from the CHMP in July 2022 and gained approval by the European Commission in September 2022 [7]. Nivo+rela is indicated for the 1L treatment of advanced (unresectable or metastatic) melanoma in adults and adolescents 12 years of age and older with tumour cell PD-L1 expression < 1% [7]. An overview of nivo+rela is presented in Table 6 below.

Table 6: Product description of Nivo+rela

Product description	
Name of preparation/pharmaceutical	Opdualag™
Active ingredient	Nivolumab plus relatlimab
Medically approved indication	Indicated for the 1L treatment of advanced (unresectable or metastatic) melanoma in adults and adolescents 12 years of age and older with tumour cell PD-L1 expression < 1%
Pharmaceutical form	Concentrate for solution for infusion (sterile concentrate)
Strength	One vial of 20 mL contains 240 mg of nivolumab and 80 mg of relatlimab
Recommended dosing	480 mg nivolumab and 160 mg relatlimab every 4 weeks administered as an intravenous infusion over 30 minutes; This dose is established for adolescent patients weighing at least 30 kg
Method of administration	Intravenous
Treatment duration/criteria for end of treatment	As long as clinical benefit is observed or until treatment is no longer tolerated by the patient
Should the pharmaceutical be administered with other medicines?	No
Necessary monitoring, both during administration and during the treatment period	Monitoring for symptoms and signs that may be clinical manifestations of underlying adverse reactions (thyroid function, adrenal function and hormone), signs of infection, glucose in blood
Need for diagnostics or other tests (i.e. companion diagnostics)	PD-L1 tumour cell expression

5.3.1 Mechanism of action

Nivolumab blocks the PD-1 (also called CD279) receptor expressed by activated T cells and B cells, which prevents binding of the PD-1 receptor with its ligands, PD-L1 and PD-L2. This results in the downregulation of the immune response. Inhibition of the interaction between PD-1 and its ligands by nivolumab promotes tumour antigen-specific T-cell responses (Figure 3) [30].

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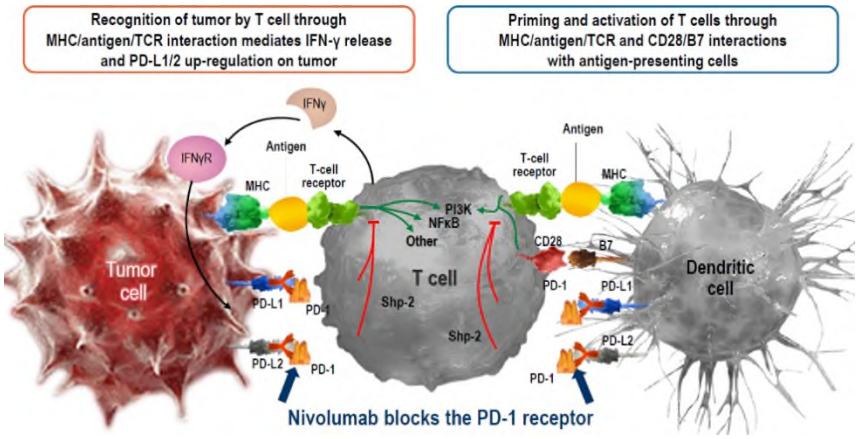
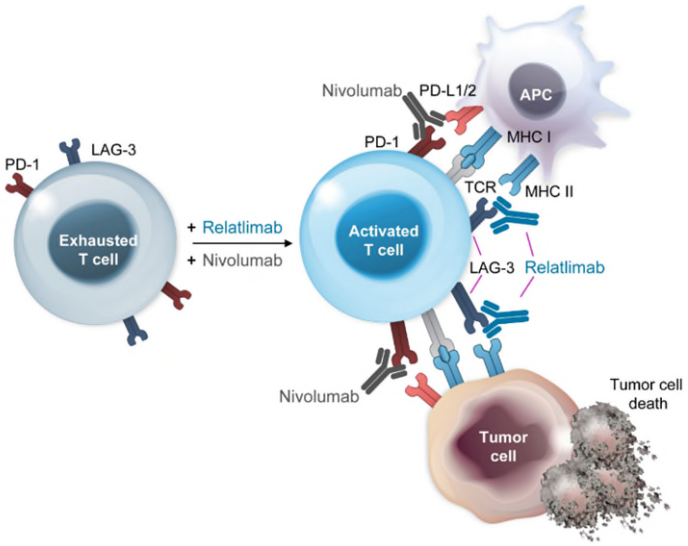
Figure 3: Mechanism of action for nivolumab



Abbreviation: CD28, cluster of differentiation 28; IFNγ/-R, interferon-gamma/receptor; MHC, major histocompatibility complex; NF-κB, Nuclear factor kappa B; PD-1, programmed death-1; PD-L1/2, programmed death ligand-1/2; PI3K, Phosphoinositide 3-kinase; Shp-2, Src homology-2 domain-containing protein tyrosine phosphatase-2; TCR, T-cell receptor.
Source: [30]

Relatlimab is an immunoglobulin G4 LAG-3–blocking monoclonal antibody. Relatlimab acts to restore the effector function of exhausted T cells and to promote cytokine secretion. In combination with nivolumab, relatlimab works to modulate synergistic immune checkpoint pathways that have capacity to enhance antitumour immune responses (Figure 4) [31, 32].

Figure 4: Mechanism of action for nivo+rela



Abbreviations: APC, antigen-presenting cell; LAG-3, lymphocyte activation gene-3; MHC, major histocompatibility complex; PD-1, programmed death-1; PD-L1/2, programmed death ligand-1-2; TCR, T-cell receptor.
Source: [31]

The combination of nivolumab and relatlimab is the first dual immunotherapy fixed-dose combination (FDC) in the metastatic melanoma treatment landscape to include LAG-3 as a new immunotherapy pathway via a synergistic action with nivolumab, a proven standard-of-care PD-1 immune checkpoint inhibitor. LAG-3 and PD-L1 are co-expressed on tumour-infiltrating lymphocytes contributing to tumour-mediated immune suppression.

RELATIVITY-047, a phase 2/3 global, randomised, double-blind, controlled trial, evaluated the efficacy and safety of nivo+rela compared to nivolumab monotherapy in patients with previously untreated metastatic or unresectable

melanoma. Results showed baseline patient characteristics and stratification factors (e.g., LAG-3, PD-L1 expression, BRAF-mutation status, AJCC M stage) that were well-balanced across treatment arms. To date, the safety of nivo+rela is manageable with a favourable risk-benefit profile [31].

5.3.2 Pack size

The strength and pack size for nivo+rela is included in Table 7 below.

Table 7: The strength, pack size, of nivo+rela

Treatment	Strength	Pack size
Nivo+rela (Opdualag)	240 mg / 80 mg	1 vial of 20 ml (12 mg/ml / 4 mg/ml)

Abbreviations: mg, milligram; ml, milliliter; nivo+rela, nivolumab plus relatlimab.

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6. Literature search and identification of efficacy and safety studies

The direct, in-trial comparison available through the RELATIVITY-047 (see Section 7.1) study will be presented to compare nivo+rela against nivolumab monotherapy. As mentioned in Section 5.2, nivolumab monotherapy is considered the relevant comparator for nivo+rela for patients with unresectable or metastatic melanoma who have non-aggressive disease and PD-L1 expression <1%. As such, an SLR is not required for this application

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7. Efficacy and safety of nivo+rela compared to nivolumab monotherapy as 1L treatment of advanced (unresectable or metastatic) melanoma in adults and adolescents 12 years of age and older with tumour cell PD-L1 expression < 1%

7.1 Relevant studies – RELATIVITY-047

RELATIVITY-047 (NCT03470922) is a randomised, double-blind, phase 2/3 study of nivolumab combined with relatlimab versus nivolumab monotherapy in patients with previously untreated metastatic or unresectable stage III or IV melanoma. An overview of the trial is presented in Appendix B Main characteristics of included studies.

As 1L treatment, nivo+rela is the first dual immunotherapy to show a statistically significant and clinically meaningful PFS benefit compared with nivolumab monotherapy in patients with advanced melanoma, which was maintained at longer follow-up (median 25.31 months). Although nivo+rela demonstrated a reduction in the risk of death and a clinically meaningful improvement in OS, it was not statistically significant. Nivo+rela has a safety profile that is generally manageable. This is considered to be the first phase 3 study of a novel fixed dose combination (FDC) to indicate significant benefit by dual inhibition of the LAG-3 and PD-1 pathways [33, 59].

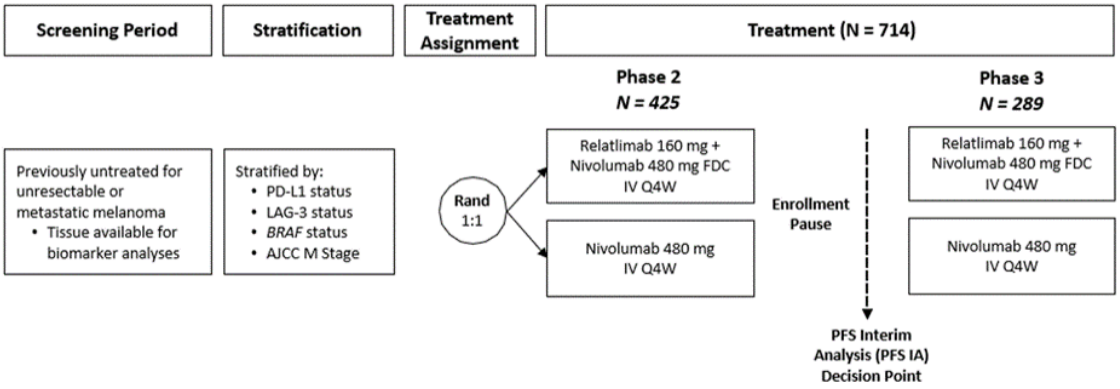
7.1.1 Objective and outcomes

The primary objective of the study was to compare PFS of nivo+rela with nivolumab monotherapy in subjects with previously untreated, unresectable, or metastatic melanoma. The secondary objectives included to compare OS and objective response rate (ORR) in the same population. PFS, OS and ORR were assessed by a blinded independent central review (BICR) using the response evaluation criteria in solid tumours (RECIST) v1.1 in all subpopulations [7].

7.1.2 Study design

Adults and adolescents ≥ 12 years of age with previously untreated metastatic or unresectable stage III or IV melanoma were eligible for enrolment. Subjects were randomised 1:1 to treatment with nivo+rela 480/160 mg in FDC every 4 weeks or nivolumab 480 mg every 4 weeks, administered as 30 minutes IV infusions. Treatment was continued until disease progression, treatment discontinuation, withdrawal of consent, or end of study. Randomisation was stratified by tumour LAG-3 expression (≥ 1% vs < 1%), BRAF mutation (V600 mutation positive vs V600 wild-type), AJCCv8 stage and by tumour cell PD-L1 expression (≥ 1% vs < 1%). The tumour cell PD-L1 expression was defined as the percent of tumour cells with membrane staining in a minimum of 100 evaluable tumour cells. Patients were classified as PD-L1 positive if PD-L1 expression was ≥ 1% and PD-L1 negative if PD-L1 expression was < 1% [7]. An overview of the study design is shown in Figure 5.

Figure 5: RELATIVITY-047 Study design



Abbreviations: AJCC, American Joint Committee on Cancer; FDC, Fixed dose combination; IA, interim analysis; IV, intravenous; PFS, Progression-free survival; Q4W, every 4 weeks.
Source: [7]

Tumour assessments started 12 weeks from randomisation and continued every 8 weeks up to week 52, and every 12 weeks thereafter until BICR-confirmed disease progression or treatment discontinuation. The median duration of follow-up for the intention to treat (ITT) population (defined as randomisation to last known alive date) was 25.31 (min, max: 0.3-51.5) months [redacted]

For the Phase 3 study, type I error control across endpoints was planned to be performed hierarchically. The primary analysis was for the primary endpoint (PFS). If needed, then the secondary endpoints would be tested in the order of OS followed by ORR (upon data maturity) [35].

[redacted]

7.1.4 Overview of key patient characteristics

A total of 714 patients were randomised 1:1 to the two treatment groups. For both treatment arms, the proportion of PD-L1 negative expression (<1%) patients (58.9-59.1%) was higher than for PD-L1 positive patients (40.9-41.1%) [7, 36].

Following the prespecified stratification in the study-protocol a total of 421 patients was grouped as PD-L1 negative. Baseline demographics and disease characteristics for all these patients were balanced across both treatment groups (see Table 48 in Appendix C Baseline characteristics of patients in studies used for the comparative analysis of efficacy and safety). Patients had a median age of 62 years in the nivo+rela group and 64 years in the nivolumab monotherapy group.

[redacted]

7.1.5 Efficacy and safety – results per study

The purpose of the trial was to test the effectiveness and tolerability of nivo+rela compared to nivolumab monotherapy, as treatment for unresectable or metastatic melanoma. RELATIVITY-047 was published in January 2022 with data from the database lock of March 9, 2021 [33]. Data, not yet published, from a more recent and database lock is used in this dossier. [redacted]

7.1.5.1 Primary endpoint: progression-free survival, tumour cell PD-L1 expression <1%

[redacted]

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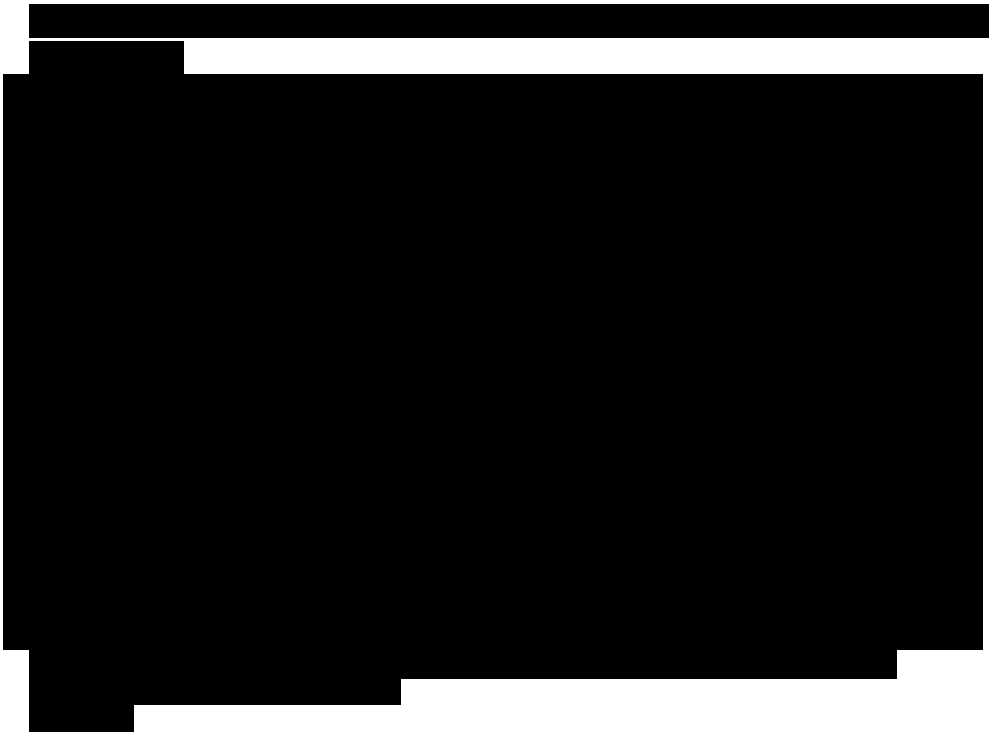
[redacted]



[redacted]

7.1.5.2 Secondary endpoint: Overall survival , tumour cell PD-L1 expression <1%

[redacted]

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[redacted]

7.1.5.3 Secondary endpoint: Objective response rate, tumour cell PD-L1 expression <1%

[redacted]

Table 8: Overview of patients response to treatment in RELATIVITY-047, tumour cell PD-L1 expression <1%

	Nivo+rela (n=209)	Nivolumab monotherapy (n=212)
Objective response rate, % (95 % CI)	[redacted]	[redacted]
Complete response, %	[redacted]	[redacted]
Partial response, %	[redacted]	[redacted]
Stable disease, %	[redacted]	[redacted]
Non complete response/non partial response, %	[redacted]	[redacted]
Progressive disease, %	[redacted]	[redacted]
Unable to determine, %	[redacted]	[redacted]

Abbreviations: CI, confidence intervals.

7.1.6 Results for overall population, ITT population

[redacted]

7.1.6.1 Quality of life data reported, ITT population

Overall, no substantial differences in HRQoL were noted between nivo+rela and nivolumab monotherapy treatment groups in the RELATIVITY-047 trial, as assessed both using the Functional Assessment of Cancer Therapy-Melanoma (FACT-M), and the EuroQol 5 dimensions (EQ-5D) visual analogue scale (VAS). For additional information please see Appendix D Efficacy and safety results per study.

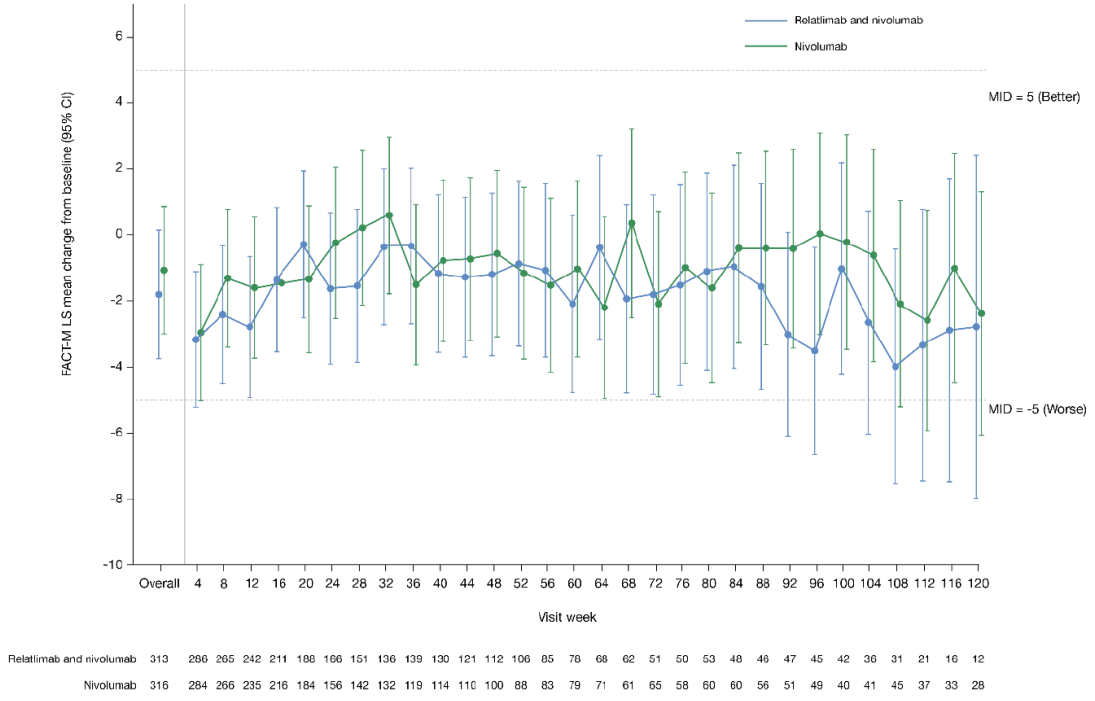
FACT-M stands for Functional Assessment of Cancer Therapy - Melanoma, which is a standardized questionnaire used to assess the health-related quality of life of patients with melanoma. It is a self-reported measure that assesses various aspects of health-related quality of life, including physical, emotional, social, and functional well-being.

The FACT-M questionnaire consists of 43 items that are divided into five subscales: physical well-being, social/family well-being, emotional well-being, functional well-being, and melanoma-specific concerns. The physical well-being subscale assesses symptoms such as fatigue, pain, and nausea, while the social/family well-being subscale assesses the impact of the disease on the patient's relationships and social activities. The emotional well-being subscale assesses anxiety, depression, and other emotional symptoms, while the functional well-being subscale assesses the patient's ability to perform daily activities. The melanoma-specific concerns subscale assesses the impact of the disease on the patient's body image, fear of recurrence, and other disease-specific concerns.

The FACT-M questionnaire is a reliable and valid tool that has been widely used in clinical trials and other research studies to assess the impact of interventions on health-related quality of life in patients with melanoma. It is a useful tool for clinicians and researchers to better understand the patient's experience of the disease and to tailor interventions to meet their specific needs.

Over the course of treatment, the FACT-M subscales results remained stable, as the changes from baseline did not reach clinically meaningful thresholds (see Figure 9). The perceived treatment tolerance of nivo+rela was similar to nivolumab monotherapy, with a low proportion of patients reporting to be “very much bothered by side effects of treatments,” as measured by item GP-5 of the FACT-M questionnaire [31, 36].

Figure 9: Longitudinal analysis of FACT-M total score change from baseline, ITT population



Abbreviations: CI, confidence Interval; FACT-M, Functional Assessment of Cancer Therapy-Melanoma; ITT, intent-to-treat; MID, minimum important difference. MID of 5 is based on study by Askew et al. [37].
Source: [36]

The response rates of the FACT-M questionnaire are reported in Table 9.

Visit	FACT-M	
	Nivo+rela	Nivolumab monotherapy
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
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[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]

EQ-VAS stands for EuroQol Visual Analog Scale, which is a standardized tool used to measure health-related quality of life. It is a self-reported measure that asks individuals to rate their current health status on a scale from 0 to 100, where 0 represents the worst possible health status and 100 represents the best possible health status.

The EQ-VAS is often used in conjunction with the EQ-5D questionnaire, which assesses health-related quality of life across five dimensions: mobility, self-care, usual activities, pain/discomfort, and anxiety/depression. The EQ-VAS provides a single summary score that can be used to compare health status across different conditions or populations.

The EQ-VAS is a simple and easy-to-use tool that can be completed by patients in a matter of minutes. It has been widely used in clinical trials and health economic evaluations to assess the impact of interventions on health-related quality of life.

[redacted]

The follow-up phase begins when the decision to discontinue a participant from study therapy is made (no further treatment with study therapy) and ends when survival data have been collected for all participants. The main aim with the follow-up phase is to collect survival and safety data.

[redacted]

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[redacted].

Visit	EQ-VAS descriptive system	
	Nivo+rela	Nivolumab monotherapy
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
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[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]

Visit	EQ-VAS descriptive system	
	Nivo+rela	Nivolumab monotherapy
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]

7.1.7 Safety

7.1.7.1 Treatment-related adverse events, ITT population

Treatment-related adverse events (TRAEs) were similar in both the nivo+rela and nivolumab monotherapy arms of the clinical trial. The most frequent TRAEs were pruritus, fatigue, and rash in both arms of the clinical trial. There were no consistent differences observed in the frequencies of drug-related AEs between the PD-L1 and LAG-3 expression subpopulations [7]. As shown in Table 11, nivo+rela was associated with a safety profile that is generally manageable with standard protocols.

Table 11: Current safety profile of RELATIVITY-047, ITT population

	Nivo+rela (n=355)		Nivolumab monotherapy (n=359)	
	Any grade, n (%)	Grade 3/4, n (%)	Any grade, n (%)	Grade 3/4, n (%)
Any AE	352 (99.2)	161 (45.4)	344 (95.8)	139 (38.7)
TRAE	301 (84.8)	78 (22.0)	262 (73.0)	43 (12.0)
Leading to discontinuation	61 (17.2)	34 (9.6)	31 (8.6)	14 (3.9)
TRAEs >5%				
[redacted]				

Abbreviation: AE, adverse event; ITT, intent-to-treat; nivo+rela, nivolumab plus relatlimab; TRAE, treatment-related adverse event.

[redacted]

[redacted]

Table 12: Patient disposition at 48 months of the RELATIVITY-047 trial

	Nivo+rela (n=355)	Nivolumab monotherapy (n=359)
[redacted]		
[redacted]		
Reason for treatment discontinuation		
[redacted]		
[redacted]		
[redacted]		
[redacted]		
[redacted]		
[redacted]		
[redacted]		
[redacted]		

7.1.7.2 Subsequent treatment

A proportion of patients received subsequent systemic therapy during the ongoing trial. As for October 2022, 36.9% of subjects in the nivo+rela arm received subsequent systemic therapy, compared to 37.9% for the nivolumab monotherapy. Main subsequent systemic therapies included PD-1 plus CTLA-4 inhibitors and BRAF/MEK inhibitors (see Table 13).

Table 13: Summary of subsequent systemic therapies, ITT population

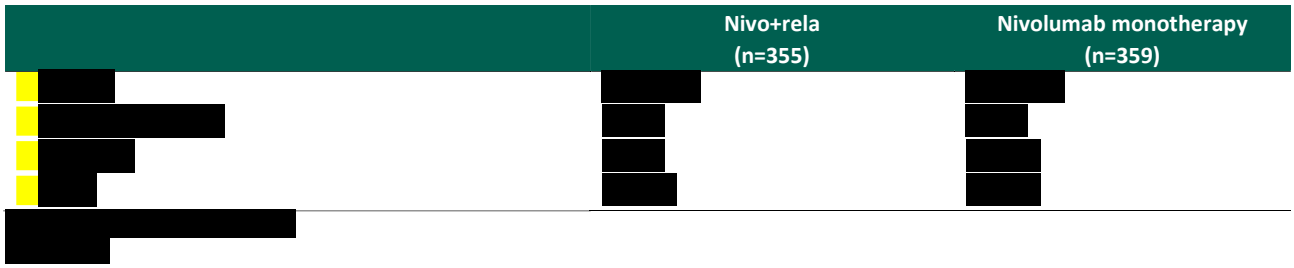
	Nivo+rela (n=355)	Nivolumab monotherapy (n=359)
Number of subjects who received subsequent systemic therapy, n (%)	131 (36.9)	136 (37.9)
Type of subsequent systemic therapy, n (%)		
PD-1/CTLA-4 inhibitors	53 (14.9)	66 (18.4)
BRAF/MEK inhibitors	49 (13.8)	57 (15.9)

Abbreviation: AE, adverse event; CTLA-4, cytotoxic T-lymphocyte-associated protein 4; ITT, intent-to-treat; MEK, mitogen-activated protein kinase; nivo+rela, nivolumab plus relatlimab; PD-L1, programmed death-ligand 1; TRAE, treatment-related adverse event.
Source: [59]

7.1.7.3 Deaths

[redacted]

	Nivo+rela (n=355)	Nivolumab monotherapy (n=359)
[redacted]		
[redacted]		



7.2 Comparative analyses of efficacy and safety

The direct, in-trial comparison available through the RELATIVITY-047 (see Section 7.1) study has been presented to compare nivo+rela against nivolumab monotherapy. As such, no additional studies on comparative efficacy and safety are presented.

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8. Health economic analysis

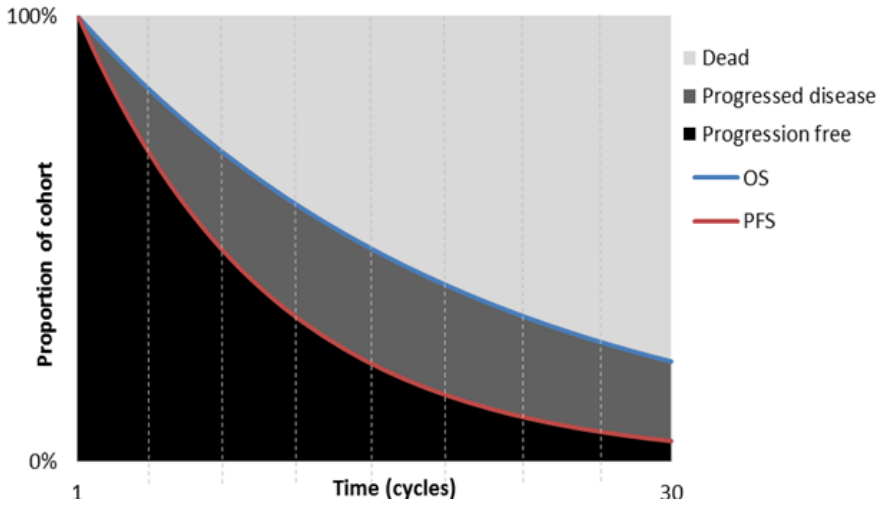
A cost-effectiveness model was developed to estimate the cost-effectiveness of nivo+rela as a 1L treatment of adults and adolescents 12 years of age and older with advanced (unresectable or metastatic) melanoma with PD-L1<1%. The model compares costs and health outcomes associated with nivo+rela treatment to outcomes associated with nivolumab monotherapy (the comparator) treatment. The cost-effectiveness model was built for the purpose of supporting the technology assessment (HTA) processes. The analysis utilises a direct trial comparison using outcomes from the RELATIVITY-047 clinical trial.

8.1 Model

The structure of the model comprises of three health states: progression-free (PF), progressed disease (PD), and death. These health states correspond to the primary and secondary endpoints of the RELATIVITY-047 trial (PFS and OS, respectively). A partitioned survival model (PSM) modelling technique was used, as this is common in oncology indications and consistent with previous immunotherapy health technology assessment (HTA) submissions. This means that health state occupancy was calculated directly from the areas under the PFS curve for progression free (PF), between the PFS and OS curves for progressed disease (PD), and above the OS curve for death, as observed in RELATIVITY-047. Figure 11 presents a visual description of the PSM for illustrational purposes. In the PF health state, RELATIVITY-047 time to treatment discontinuation (TTD) data was used to inform duration (and hence cost) of treatment. [redacted]

The model was developed in Microsoft Excel (Office 365) 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, and for navigation purposes. All model references and assumptions are clearly described within the Excel file.

Figure 11: Overview of the partitioned survival method (illustrational)



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

A one-week cycle length was used for the first 28 weeks of the time horizon in the model, followed by 4-week cycles to the end of the time horizon. Adjustments in treatment administrations were made to accommodate the administration cycles of the included therapies.

The quality of life aspect of treatment was modelled using data derived from the RELATIVITY-047 clinical trial and mapped to Danish specific EQ-5D-5L; see Section 8.4 for further details.

A summary of the core elements of the economic model is shown in Table 15.

Table 15: Technical description of the economic model

Aspect	Details	Comment
Analytical method	Cohort-based partitioned survival model	Analytical technique that is applied very commonly in oncology and has been used in various technology appraisals for anti-cancer treatments
Time horizon	Lifetime (40 years)	To capture the costs and outcomes over the patient's lifetime The model shows less than 1% of patients survive at year 40 in the nivo+rela and the nivolumab monotherapy arm, therefore the time horizon selected was 40 years
Cycle length	Weekly for 0-28 weeks, per 4-week cycles afterwards	Weekly cycles to accommodate differing administration cycles for immunotherapy and non-immunotherapies followed by 4-weekly cycles for rest of time period
Half-cycle correction	Yes	The model calculated mid-cycle estimates in each health state by taking the average of patients present at the beginning and at the end of each cycle
Discounting options	Costs and health outcomes discounted with 3.5% yearly for the first 35 years and 2.5% for the remainder of the time horizon	Both costs and outcomes are subject to annual discounting in the evaluation
Treatment arms	Nivo+rela Nivolumab monotherapy	In line with RELATIVITY-047, nivo+rela and nivolumab monotherapy are considered to be relevant comparators for the main analysis
Software used	Microsoft Excel (Office 365)	Excel is an accessible and widely available platform
Input		
Clinical efficacy and safety	RELATIVITY-047 trial – based on the October 2022 DBL	The RELATIVITY-047 trial is the key registrational trial for nivo+rela regimen in the 1L treatment of untreated, unresectable or metastatic melanoma
Treatment duration	Nivo+rela: RELATIVITY-047 TTD KM Nivolumab monotherapy: RELATIVITY-047 TTD KM	[redacted]
Costs	Danish official price lists using the DRG Grouper from 2023	-
Utilities	RELATIVITY-047 EQ-5D-3L data (time to death (TD) utilities)	Mapped to EQ-5D-5L and utility values derived with Danish-specific weights
Output		
Cost-effectiveness ratios	Incremental cost effectiveness ratio (ICER)	ICER: Incremental cost per effect (e.g. quality-adjusted life year gained)
Costs	Disaggregated, total and incremental	-

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Aspect	Details	Comment
QALYs	Disaggregated, total and incremental	-
Life years (LY)	Disaggregated, total and incremental	-
Incremental cost-effectiveness plane	Yes	-
Cost-effectiveness acceptability curve and frontiers	Yes	-
Automated PSA and DSA	Yes	-

Abbreviations: 1L, First-line; AE, Adverse events; DBL, Database lock; DSA, Deterministic sensitivity analysis; EQ-5D, EuroQol-5 dimensions; FPNMA; Fractional Polynomial Network Meta-Analysis; HTA, Health technology assessment; ICER, Incremental cost-effectiveness ratio; KM, Kaplan-Meier; nivo+rela, nivolumab plus relatlimab; OS, Overall survival; PD, Progressed disease; PF, Progression-free; PFS, Progression-free survival; PSA, Probabilistic sensitivity analysis; QALY, Quality adjusted life year; TTD, Time to discontinuation

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

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

The input data used to inform clinical effect, adverse reactions, and health state utility values (HSUV) in the model have been sourced from the RELATIVITY-047 trial (see Table 16 below). The aim of the cost-effectiveness analysis is to capture the likely outcomes in Danish clinical practice as accurately as possible. Danish treatment guidelines and the DMC Scientific Committee were consulted.

Table 16: Input data used in the model

Variable	Value at source	Input value used in the model	How the input value was obtained/ estimated	How the input value was obtained/ estimated
Patient inputs	% Female among patients	41.74%	41.74%	RELATIVITY-047, ITT population. See Table 48.
	Patients' starting age	62 years	62 years	
	Body surface area	1.82 m^2	1.82 m^2	
	Average weight	79.7 kg	79.7 kg	
Posology	Nivo+rela	Nivolumab: 480 mg Relatlimab: 160 mg Fixed dose per 4-weeks	Nivolumab: 480 mg Relatlimab: 160 mg Fixed dose per 4-weeks	SmPC Opdualag [7]
	Nivolumab monotherapy	Fixed dose: 480 mg per 4 weeks	Weight based dose: 6 mg/kg per 4-weeks	SmPC nivolumab [29] Danish clinical practice
Utility inputs	>52 weeks to death	[redacted]	[redacted]	RELATIVITY-047 ITT population time to death utilities (TD) DK weights. See Section 8.4.1
	27-52 weeks to death	[redacted]	[redacted]	
	5-26 weeks to death	[redacted]	[redacted]	
	≤4 weeks to death	[redacted]	[redacted]	
	AE disutilities	See Table 25		

Variable	Value at source	Input value used in the model	How the input value was obtained/ estimated	How the input value was obtained/ estimated
TRAEs	Probability of grade 3/4 TRAEs	Based on TRAEs that were experienced in at least 5% of patients in the RELATIVITY-047 trial, of which grade 3 and 4 were included.	RELATIVITY-047, ITT population. See Table 11	

Abbreviations: EQ VAS EuroQol 5-dimension visual analogue scale, EQ-5D visual analogue scale; FACT-M, Functional Assessment of Cancer Therapy – Melanoma; ITT, intention to treat, ORR, objective response rate; OS, overall survival; PD-1, programmed death -1; PFS, progression-free survival; TRAE, treatment-related adverse events. Relationship between the clinical documentation, data used in the model and Danish clinical practice

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

8.2.2.1 Patient population

The characteristics of the patient population considered in the evaluation are based on patients enrolled in the RELATIVITY-047 clinical trial.

8.2.2.1.1 Danish clinical practice

The relevant population in Denmark are patients who are considered by clinicians as unsuitable candidates for nivolumab in combination with ipilimumab (due to tolerability) and therefore treated with an anti-PD1 monotherapy. The eligible population is expected to be [redacted]

8.2.2.1.2 Clinical documentation and model submitted (in relation to Danish clinical practice)

The model population is treatment-naïve adults and adolescents12 years of age and older with unresectable or metastatic melanoma, with tumor cell PD-L1 expression <1%, regardless of BRAF status, and who are clinically assessed not to have aggressive disease. The characteristics of the patient population considered in the evaluation are based on patients enrolled in the RELATIVITY-047 clinical trial (see Table 48). The characteristics of the patient population considered in the evaluation are based on patients enrolled in the RELATIVITY-047 clinical trial (see Table 48).

8.2.2.2 Intervention

The intervention is nivo+rela, which is further described in Section 5.3.

8.2.2.3 Comparators

8.2.2.3.1 Danish clinical practice

As mentioned in Section 5.2.2, the relevant comparator for nivo+rela is an anti-PD1 monotherapy (nivolumab monotherapy). In this submission, nivolumab monotherapy was used as the comparator to utilize the trial data from the RELATIVITY-047 trial. It was deemed as an appropriate approach by the DMC expert committee to use nivolumab monotherapy as a proxy for other anti-PD1 monotherapies.

In accordance with Danish clinical practice, a weight based dosing regimen (6 mg/kg per 4 weeks) was used in the model.

8.2.2.3.2 Clinical documentation and model submitted (in relation to Danish clinical practice)

The model submitted includes data available through the RELATIVITY-047 study (see Section 7.1), comparing nivo+rela against nivolumab monotherapy.

8.2.2.4 Adverse reaction outcomes

The model considered TRAEs that were experienced in at least 5% of patients in the RELATIVITY-047 trial, of which grade 3 and 4 were included in the model. TRAEs in the clinical documentation and used in the model is presented in Section 7.1.7.

8.3 Extrapolation of relative efficacy (survival extrapolation)

8.3.1 Data sources

PFS and OS data were projected using parametric survival models and spline models, as well as the piecewise approach modelling for PFS based on the October 2022 DBL of RELATIVITY-047.

All survival modelling was conducted using the FlexSurv package in R and modelled using the FlexSurvReg function. Standard parametric and spline-based survival models were fitted to individual patient level data from the RELATIVITY-047 trial.

The plausibility of the extrapolated portions of the survival curves were validated using external data from the CheckMate-067 trial, as both the CheckMate-067 trial and the RELATIVITY-047 trial were conducted in patient populations with previously untreated, unresectable, or metastatic melanoma. CheckMate-067 is a phase 3 trial for patients with previously untreated unresectable stage III or IV melanoma. Patients received: nivolumab 1mg/kg + ipilimumab 3mg/kg for 4 doses every 3 weeks followed by nivolumab 3mg/kg every 2 weeks; nivolumab 3 mg/kg every 2 weeks + placebo; or ipilimumab 3mg/kg every 3 weeks for 4 doses + placebo.

8.3.2 Progression-free survival – 3 month cut-point

All models fitted the initial 3 months of the KM curve poorly for PFS, as the treatment arms sharply drop in line with each other before diverging. This is influenced by the trial protocol, as the first assessment occurred 12 weeks after randomisation. Due to this, the preferred approach to model PFS is a piecewise model with a 3 month cut-point. This uses KM data for the first 3 months, with standard parametric models fitted from 3 months onwards. The following sections below describes the piecewise approach from the three month cut-point and onwards. For completeness a description of the extrapolations of the PFS curves from baseline is presented in Appendix F Extrapolation.

8.3.2.1 Proportional hazards assumptions

The proportional hazards assumption was tested for the RELATIVITY-047 PFS for PD-L1 expression <1% using log-cumulative hazard plots (Figure 12), the Schoenfield residuals plot (Figure 13) and the Grambsch-Therneau test. Visual inspection of the log-cumulative hazards and Schoenfeld residuals plots was undertaken to assess proportionality of treatment effects over time. These mostly demonstrate that proportional hazard hold; however, the log-cumulative hazards do initially cross, suggesting proportional hazards do not hold at the beginning. The Grambsch-Therneau test does not reject the proportional hazards assumption (p = 0.86). The Quantile-Quantile plot indicates some deviation from the AFT assumption (Figure 14).

For these reasons, both independent and dependent models are available as options in the model. However, the submission focuses on the dependent models to best reflect the similarity between the two treatment arms—both

being immunotherapies with similar mechanisms of action—and because it cannot be rejected that proportional hazard holds.

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[redacted]

8.3.2.2 Goodness of fit statistics

As mentioned in Sections 8.3.2 and 8.3.2.1, the preferred approach to model PFS is a piecewise dependent model with a 3 month cut-point. This uses KM data for the first 3 months, with standard parametric models fitted from 3 months onwards. As this is for a piecewise model, splines were not considered to avoid overfitting.

The goodness of fit statistics (from 3 months) are presented in Table 17. In terms of AIC, the best-fitting models are log-logistic, log-normal and generalised gamma and in terms of BIC, the best-fitting models are log-logistic, log-normal and Weibull.

Table 17: Statistical goodness-of-fit indicators values for dependent parametric models fitted to PFS data for nivo+rela and nivolumab monotherapy from RELATIVITY-047, PD-L1 expression <1% (data cut at 3 months)

Dependent distributions	AIC	BIC
Log-logistic	1042.42	1052.61
Log-normal	1044.90	1055.08
Generalised Gamma	1045.21	1058.78
Weibull	1047.03	1057.21
Gamma	1051.00	1061.18
Gompertz	1053.48	1063.66
Exponential	1093.23	1100.02

Abbreviations: AIC, Akaike information criterion; BIC Bayesian information criterion; nivo+rela, nivolumab + relatlimab; PD-L1, Programmed death-ligand 1; PFS, Progression-free survival.
Note: This table presents goodness of fit statistics for the period after three months.

The standard parametric model fits compared to the Kaplan-Meier data are shown in and the corresponding hazards are shown in [redacted] and [redacted], respectively. The long-term extrapolated survival and hazards, over 20 years, are shown in [redacted] and [redacted] respectively. The landmark survival probabilities for each fitted model compared to the RELATIVITY-047 and CheckMate-067 KM data are shown [redacted] and [redacted] for nivo+rela and nivolumab monotherapy, respectively.

[redacted] and Gompertz provides the best fit to the smoothed hazards ([redacted]. The Gompertz, however, estimates a plateau with hazards reaching general [redacted]

It is not unrealistic for a plateau to be reached from 5 years in immunotherapies, as this has been demonstrated in CheckMate-067 data with longer follow-up **[39]**. However, the Gompertz does slightly overestimate the tail of the KM curve for nivo+rela.

The log-normal, log-logistic and generalised gamma all demonstrate good statistical fit in terms of AIC, but the log-normal provides a better visual fit. The log-normal also demonstrates plausible survival estimates when compared to the CheckMate-067 data. The Gompertz provides plausible long-term estimates, but with a stronger plateau. Overall, the piecewise model with a 3-month cut-point using the dependent log-normal is preferred as the base case, and Gompertz is used as a scenario.

[redacted]

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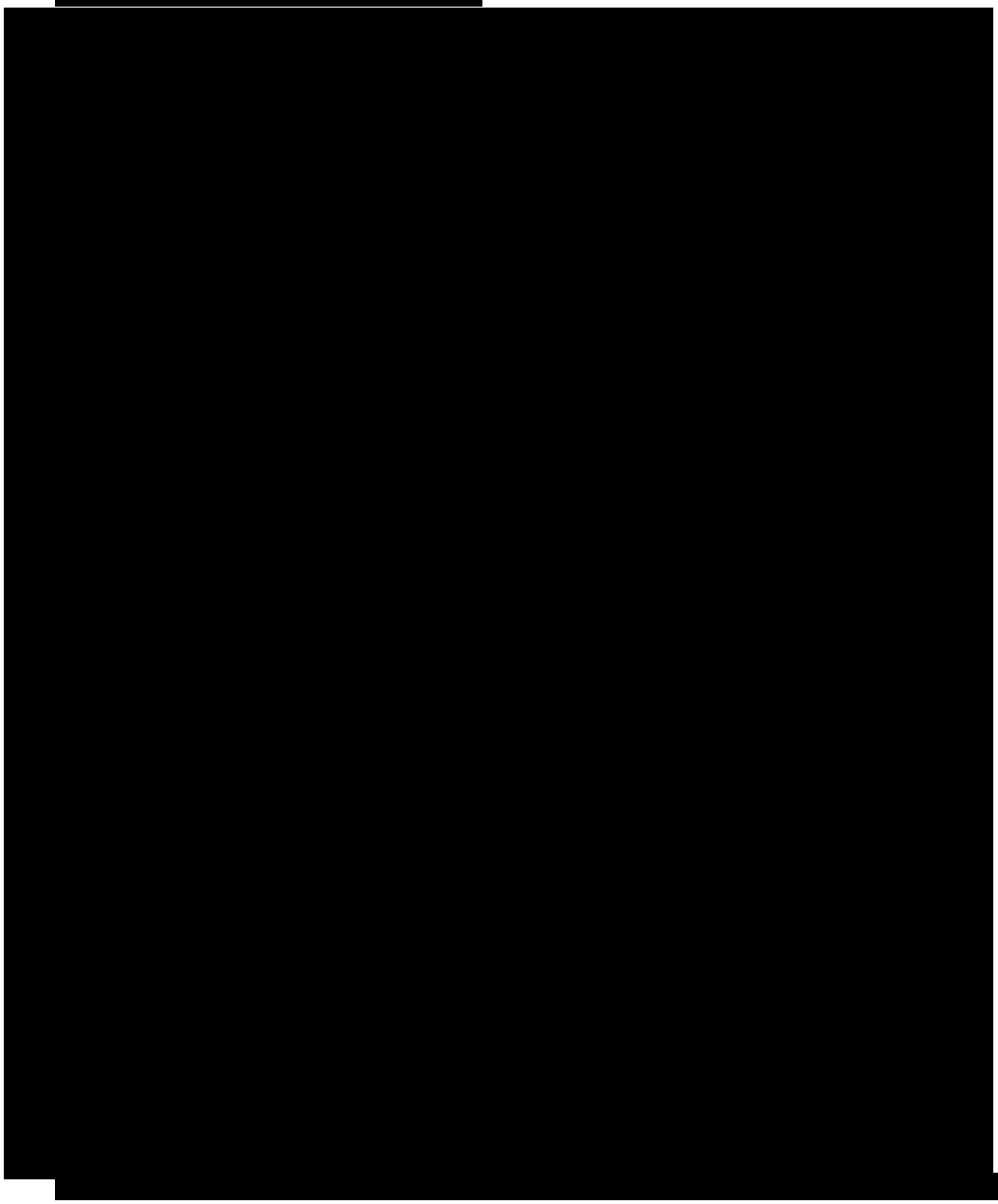

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[redacted]

Model	Progression-free survival								
	6mo	1yr	2yr	3yr	4yr	5yr	10yr	15yr	20yr
[redacted]									
[redacted]									
[redacted]									
[redacted]									
[redacted]									
[redacted]									
[redacted]									
[redacted]									
[redacted]									

[redacted]

Model	Progression-free survival								
	6mo	1yr	2yr	3yr	4yr	5yr	10yr	15yr	20yr
[redacted]									
[redacted]									
[redacted]									
[redacted]									
[redacted]									
[redacted]									
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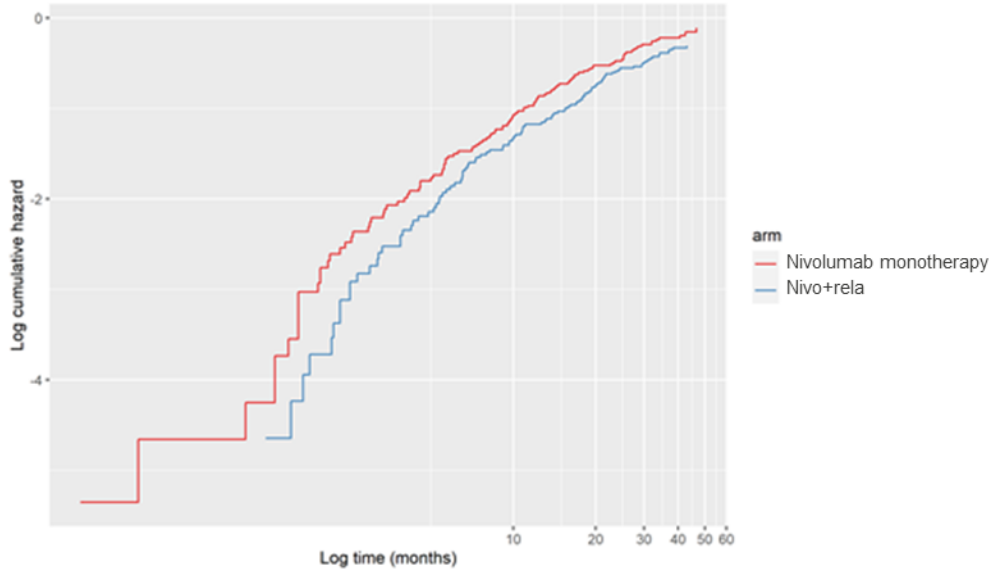
8.3.3 Overall Survival

8.3.3.1 Proportional hazards assumptions

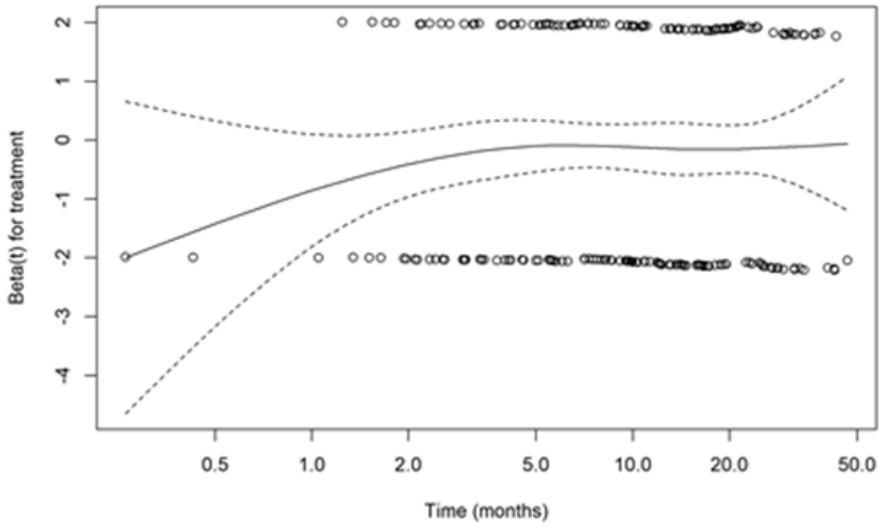
The proportional hazards assumption was tested for the RELATIVITY-047 PD-L1 expression <1% OS using log-cumulative hazard plots (Figure 19), the Grambsch-Therneau test and Schoenfield residuals plot (Figure 20). The Grambsch-Therneau test clearly does not reject the proportional hazards assumption (p = 0.34). Visual inspection of the log-cumulative hazards and Schoenfeld residuals plots was undertaken to assess proportionality of treatment effects over time. These also demonstrate that proportional hazards hold. Additionally, the Quantile-Quantile plot indicates the Accelerated Failure Time (AFT) assumption holds (Figure 21).

Figure 19: Log-cumulative hazards plot RELATIVITY-047 OS nivo+rela vs. nivolumab monotherapy, PD-L1 expression <1%



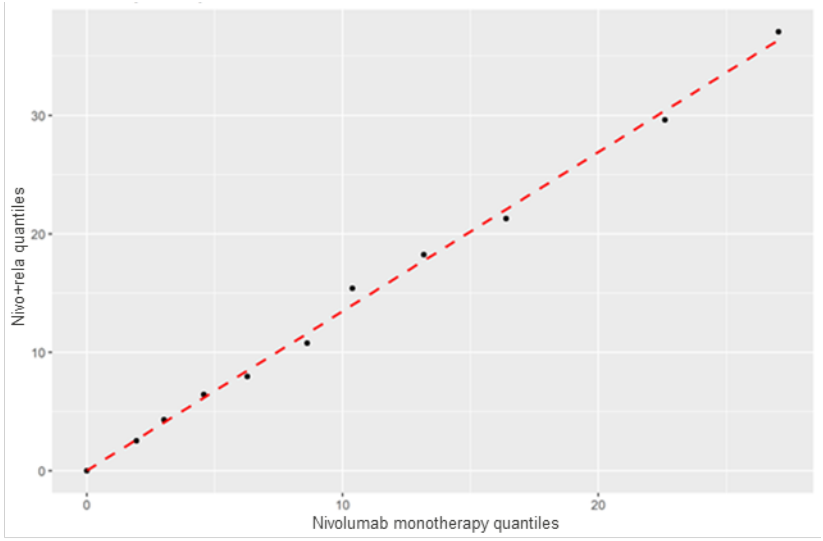
Abbreviations: NIVO, nivolumab; OS, overall survival; nivo+rela, nivolumab plus relatlimab; PD-L1, programmed death-ligand 1.

Figure 20: Schoenfeld residuals plot RELATIVITY-047 OS nivo+rela vs. nivolumab monotherapy, PD-L1 expression <1%



Abbreviations: Nivo+rela, nivolumab plus relatlimab; OS, overall survival; PD-L1, Programmed death-ligand 1.

Figure 21: Quantile-Quantile plot for RELATIVITY-047 OS nivo+rela vs. nivolumab monotherapy, PD-L1 expression <1%



Abbreviations: Nivo+rela, nivolumab plus relatlimab; OS, overall survival; PD-L1, Programmed death-ligand 1.

Both independent and dependent models were fitted to OS for the PD-L1 expression <1% population and are available in the model. However, dependent models are considered more appropriate due to the fact that proportional hazards appear to hold and due to the similarity between the two treatment arms, both being immunotherapies with similar mechanisms of action.

Therefore, only dependent analysis results are presented and described in this submission. Both standard parametric models and spline models are fitted to the data.

8.3.3.2 Goodness-of-fit statistics

The goodness-of-fit statistics are presented in Table 20. In terms of AIC and BIC, the best-fitting models are Generalised Gamma, spline normal 1 knot and spline odds 1 knot.

Since it is a dependent survival model, one curve was fitted to both arms of the trial data. Therefore, Table 20 refers to the AIC and BIC goodness-of-fit data for the single model that represents both nivo+rela and nivolumab monotherapy goodness-of-fit.

Table 20: Statistical goodness-of-fit indicators values for dependent parametric models fitted to OS data for nivo+rela and nivolumab monotherapy from RELATIVITY-047, PD-L1 expression <1%

Dependent distributions	AIC	BIC
Generalised Gamma	2084.91	2101.08
Spline normal 1 knot	2085.40	2101.57
Spline odds 1 knot	2085.90	2102.07
Spline hazard 1 knot	2086.60	2102.77
Spline normal 2 knots	2086.65	2106.86
Spline odds 2 knots	2087.58	2107.80
Spline hazard 2 knots	2088.15	2108.36
Log-normal	2092.27	2104.40
Gompertz	2096.21	2108.34
Log-logistic	2104.37	2116.50

Dependent distributions	AIC	BIC
Weibull	2121.75	2133.87
Gamma	2126.00	2138.13
Exponential	2131.92	2140.01

Abbreviations: AIC, Akaike information criterion; BIC, Bayesian information criterion; OS, Overall survival; nivo, nivolumab; PD-L1, Programmed death-ligand 1.

The extrapolated survival and hazard compared to the KM curves for the standard parametric models are shown in Figure 22 and Figure 23, respectively. The long-term extrapolated survival and hazards for standard parametric model fits, over 20 years, are shown in Figure 26 and Figure 27, respectively. The extrapolated survival and hazard compared to the KM curves for the spline models are shown in Figure 24 and Figure 25 and the long-term extrapolated survival and hazards for the spline models are shown in Figure 28 and Figure 29, respectively.

Upon visual inspection, generalised gamma and Gompertz both demonstrate a reasonable fit to the KM data and smoothed hazards. The other standard parametric models do not capture the smoothed hazards well; while the log-normal model ranked second highest on AIC/BIC, according to the figures (Figure 26 and Figure 27) it does not fit the tail of the KM curves well.

All spline models demonstrate a reasonable fit to the KM plots and the smoothed hazards. However, according to the landmark analysis in Table 21 and Table 22, they do not demonstrate any improvement over generalised gamma and Gompertz, but with added complexity. Therefore, it was decided not to consider spline models further.

A landmark validation analysis was conducted using the nivolumab monotherapy data from Checkmate-067, see Table 21 and Table 22. Here it is evident that the nivolumab monotherapy OS curve is forming a plateau and drops less towards the end of the curve. When looking at the landmarks OS for the extrapolated nivo+rela curves, the Gompertz model is the only curve that captures a similar pattern.

Dependent generalised gamma is used as the base case extrapolation for OS. As mentioned above, the generalised gamma model may not capture the expected plateau fully and the Gompertz model is therefore included as a scenario analysis.

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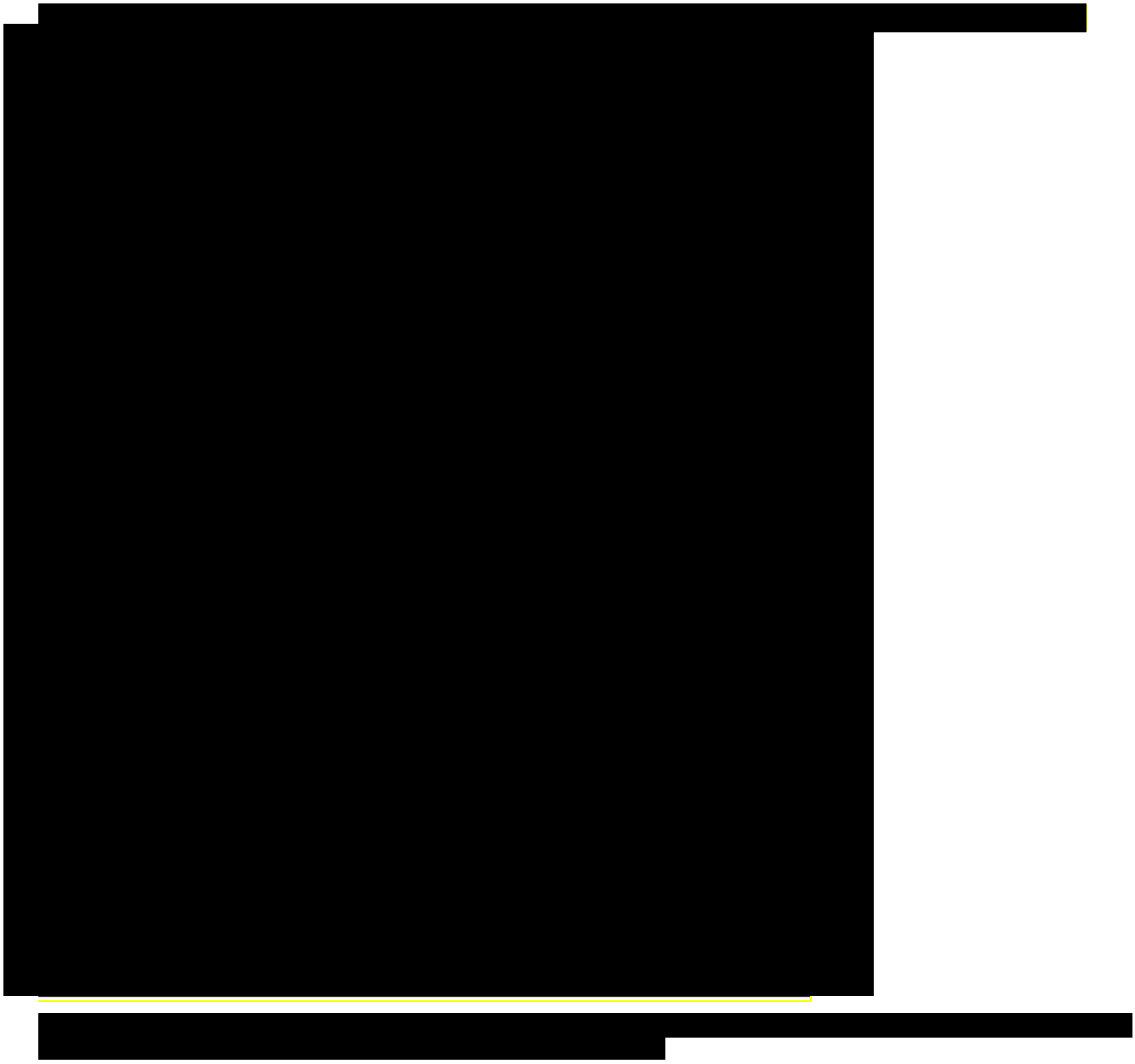

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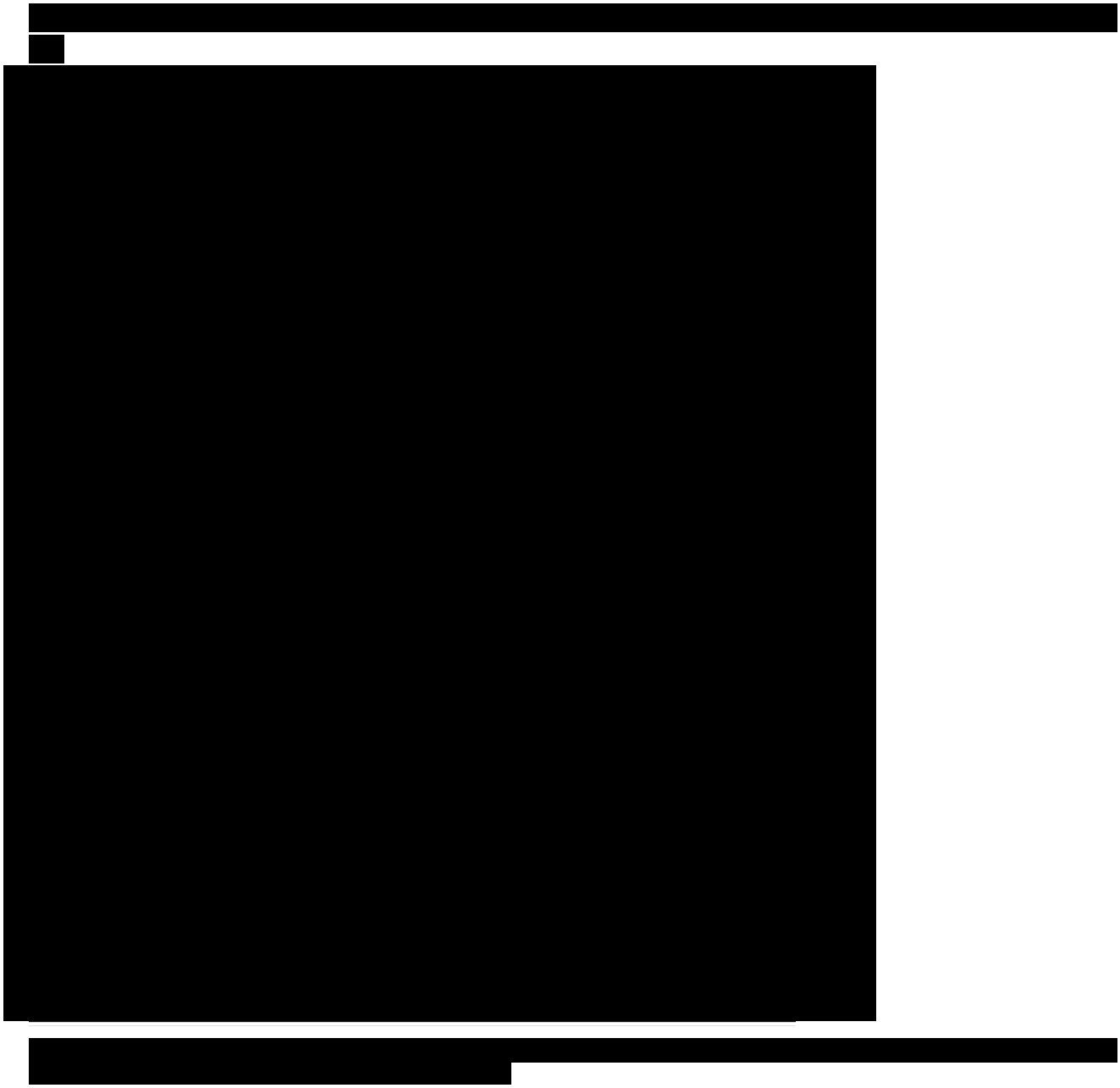

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[redacted]

Model	Overall survival								
	6mo	1yr	2yr	3yr	4yr	5yr	10yr	15yr	20yr
[redacted]									
[redacted]									
[redacted]									
[redacted]									
[redacted]									
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[redacted]									

[redacted]

Model	Overall survival								
	6mo	1yr	2yr	3yr	4yr	5yr	10yr	15yr	20yr
[redacted]									
[redacted]									
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8.4 Documentation of health-related quality of life (HRQoL)

8.4.1 Overview of health state utility values (HSUV)

8.4.1.1 Health state utility values identified from systematic literature search

Health related quality of life data was collected in the RELATIVITY-047—including EQ-5D-3L—and were used to support this submission. As such, an SLR is redundant for this application.

8.4.1.2 Health state utility values reported in trial data

Utility estimates used in the economic model are based on an analysis of EQ-5D utility scores for the ITT population reported in the RELATIVITY-047 trial (October 2022 data-cut). The reported EQ-5D-3L values were mapped to the EQ-5D-5L values using the van Hout and Shaw [40] and Danish utility weights [41]. The effect of disease progression and treatment status on HSUV was formally assessed using linear mixed effects models fitted to the full analysis set. Analyses were conducted for both time to death (TD) utilities (>52 weeks to death, 27-52 weeks to death, 5-26 weeks to death and ≤4 weeks to death) and for overall health state utilities (progression free and progressed disease). The least squares means from the mixed effects models including only TD or progression status and treatment status were found to have the best fit. These models improved the simple arithmetic means by factoring in individual variance, but without the additional difficulties involved in interpreting results including baseline characteristics. The lack of significance of treatment arm means it is not necessary to include treatment arm as a fixed effect.

A detailed description of the utility analysis including EQ-5D completion rates and handling of missing data is provided in Appendix H Mapping of HRQoL data.

8.4.2 Health state utility values used in the health economic model

The base case uses TD utilities, where the utility is estimated from RELATIVITY-047 and is consistent across treatments. Utilities are adjusted to age using the multiplicative method, as recommended by the DMC [42]. The values used in the health economic analysis are presented in Table 23.

The TD approach for estimating utilities is preferred over the utility by progression status approach because it captures the decline in HRQoL over time more granularly relative to the use of utilities by progression status. The deterioration in HRQoL over time for patients typically occurs as a patients approaches death, and these declines are more accurately reflected in the TD approach. Further, the relatively small difference observed between utilities for progression-free and progressed patients (see Table 24) indicates that the actual impact of disease progression is not captured fully with this simplified modelling approach. The high number of patient reported EQ-5D in RELATIVITY-047 enables TD utilities as a more realistic approach to model the patients HRQoL.

Table 23: TD utilities used in the health economic analysis (Danish EQ-5D-5L), ITT

	>52 weeks to death		27-52 weeks to death		5-26 weeks to death		≤4 weeks to death	
	Mean (SE)	95% CI	Mean (SE)	95% CI	Mean (SE)	95% CI	Mean (SE)	95% CI
Utility value	[redacted]							

Abbreviations: CI, confidence interval, TD, time to death; EQ-5D-5L. Euroqol 5-dimension 5-level; ITT, Intention to treat: SE, standard error
Source: [43]

Table 24 presents overall utilities by health state, these utility values are used in a scenario analysis.

Table 24: Overall utilities by health state (mixed effects model least squares mean), Danish weights, ITT

Health state	Mean utility (SE)	95% CI	Reference
PF	[redacted]	[redacted]	RELATIVITY-047, utility analysis [43]
PD	[redacted]	[redacted]	
Death	[redacted]	[redacted]	Assumption

Abbreviations: CI, confidence interval; DBL, database lock; PD, progressed disease; ITT, Intention to treat ; PF, progression-free; SE, standard error.
Source: [43]

8.4.3 AE disutilities

The model considered TRAEs that were experienced in at least 5% of patients in the RELATIVITY-047 trial, of which grade 3 and 4 were considered in the analysis (Table 25).

The cost and disutility of AEs are applied one-off in the first model cycle. That is, the total treatment cost and disutility per episode of each AE is multiplied by the proportion of each AE outlined in Table 25 and included in week one. It is assumed that both the treatment cost per episode and disutility per episode accounts for the duration of the AE. The application of AE costs and disutility in week one is potentially a conservative assumption for two reasons:

- AEs which are incurred after one year on treatment would be discounted in terms of costs and QALYs; 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 and disutility of AEs in week one will overestimate the impact of AE

Nevertheless, it should be noted that the total impact of AEs on the ICER is marginal; it is estimated that on average AEs have an impact lower than 1% on the total costs for nivo+rela and nivolumab monotherapy. The disutilities values were sourced mainly from the Nafees 2017 study and are presented below in Table 25.

Table 25: Adverse events disutilities

Adverse Event	Disutility value	Source
Pruritus	-0.146	Assumed same as rash
Fatigue	-0.288	Nafees 2017 [44]
Rash	-0.146	
Diarrhoea	-0.216	
Arthralgia	-0.288	Assumed same as fatigue
Asthenia	-0.288	
Alanine aminotransferase increased	0.000	Attard 2014 [45]
Aspartate aminotransferase increased	0.000	Assumed same as alanine aminotransferase increased
Myalgia	-0.288	Assumed same as fatigue
Infusion related reaction	-0.146	Assumed same as rash

8.4.4 Strengths and weaknesses of HRQoL data

Strengths of the HRQoL data used in this analysis included the relatively large sample size at baseline. In addition, the results have been presented using Denmark-specific weights. While completion rates for the EQ-5D-3L were high, the sample size waned over time which made it difficult to interpret data and compare treatment arms at later time points.

8.5 Resource use and costs

Cost input values and frequencies for the analysis was obtained from the Danish treatment guidelines [46-48]. Different sources were used to obtain the unit cost for all resource types. All costs are presented in 2023 prices if available, while those that were not available were inflated to 2023 using the Danish consumer price index [49].

8.5.1 Drug acquisition and administration costs

Drug acquisition costs for nivo+rela and nivolumab monotherapy are presented in Table 26. Subsequent treatment costs are presented in Table 28. Unit costs (pharmacy purchase price [AIP]) were sourced from the Medicinpriser.dk (March 2023). In accordance with Danish clinical practice, costs for nivolumab monotherapy are calculated using weight based dosing (6 mg/kg). The same administration cost was used for both treatment regimens (see Table 27). Dose intensity is also assumed to be 100% for both drugs in first and subsequent treatment lines.

Table 26: Drug acquisition costs for nivo+rela and nivolumab monotherapy

Treatment	Dose per tablet	Units per package	Cost per package (DKK)	Reference/source for costs
Nivo+rela	240 mg / 80 mg	1	56 250.00	[50]
Nivolumab	40 mg	1	3508.46	[50]
	100 mg	1	8715.54	
	120 mg	1	10 458.66	
	240 mg	1	20 917.31	

Abbreviations: DKK, Danish Kroner; mg, milligrams; nivo+rela, nivolumab + relatlimab; IV, intravenous.

Table 27: Administration cost

Name of resource	Cost (DKK)	Comment	Reference DK (2023)
Administration	1 634	Same cost considered for all administrations by intravenous infusion	DRG 09MA98. (DC439M) Malignant melanoma of the skin with metastases + (BWAA62) Medication administration by intravenous infusion [51]

Abbreviations: DKK, Danish Kroner; DRG, Diagnose related groups.

[redacted]

Time to treatment discontinuation (TTD) was measured directly and KM curves are available (see figure [redacted]. As TTD is measured in the trial, for both nivo+rela and nivolumab monotherapy, TTD KM data is directly used to inform treatment duration in the model. [redacted] As seen in [redacted]

[redacted]

8.5.3 Subsequent / second-line treatments

A user-modifiable distribution of multiple subsequent treatments is included in the model.

When patients progress on 1L treatment, a proportion of the initial randomised cohort will go on to a subsequent treatment. It was assumed that out of the patients progressing, all received subsequent systematic anti-cancer treatment in 2L in both treatment arms.

Table 28 presents the distribution of patients who received one or more of the top 14 most common subsequent treatments by initial treatment.

Table 28: Distribution of subsequent treatments applied in the base case model

Drug	Dosing	Nivo+rela	Nivo
Nivolumab monotherapy	[redacted]	[redacted]	[redacted]
Nivo+rela	[redacted]	[redacted]	[redacted]
Nivolumab + ipilimumab	[redacted]	[redacted]	[redacted]
Ipilimumab	[redacted]	[redacted]	[redacted]
Pembrolizumab	[redacted]	[redacted]	[redacted]
Dabrafenib	[redacted]	[redacted]	[redacted]
Vemurafenib	[redacted]	[redacted]	[redacted]

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Drug	Dosing	Nivo+rela	Nivo
Dabrafenib + Trametinib	[redacted]	[redacted]	[redacted]
Encorafenib + Binimetinib	[redacted]	[redacted]	[redacted]
Vemurafenib + Cobimetinib	[redacted]	[redacted]	[redacted]

Source: Relativity-047, [redacted]
Abbreviations: nivo+rela, Nivolumab + relatimab

Table 29 presents the average time on subsequent treatment dependent on the subsequent treatment received. Average duration of subsequent treatment was based on the median PFS reported for 2L therapy post anti-PD1 treatment reported in the study by Zimmer et al. [52]. The study only reported the median PFS, thus the mean PFS was estimated using an exponential distribution. This resulted [redacted] which is used as the estimated treatment duration for subsequent treatments in the model.

Table 29: Duration of subsequent treatments applied in the base case model

Drug	Average duration, months	Source
Nivolumab monotherapy	[redacted]	[redacted]
Nivo+rela	[redacted]	
Nivolumab + ipilimumab	[redacted]	
Ipilimumab	[redacted]	[redacted]
Pembro	[redacted]	[redacted]
Dabrafenib	[redacted]	
Vemurafenib	[redacted]	
Dabrafenib + Trametinib	[redacted]	
Encorafenib + Binimetinib	[redacted]	
Vemurafenib + Cobimetinib	[redacted]	
Atezolizumab + Vemurafenib + Cobimetinib	[redacted]	

Abbreviations: nivo+rela, Nivolumab + relatimab; PD-1, programmed death -1; PFS, progression-free survival.

Table 30 presents the included acquisition cost of each subsequent treatment.

Table 30: Drug acquisition costs for subsequent treatment (progressed disease)

Treatment	Dose per tablet	Units per package	Cost per package (DKK)	Reference/source for costs
Nivolumab	40 mg	1	3 508.46	[50]
	100 mg	1	8 715.54	
	240 mg	1	20 917.31	
Ipilimumab	50 mg	1	24 386.89	
Pembrolizumab	100 mg	1	22 058.88	
Dabrafenib	9000 mg	1	44 032.48	
Vemurafenib	13 440 mg	1	12 397.31	
Trametinib	60 mg	1	45 926.34	

Treatment	Dose per tablet	Units per package	Cost per package (DKK)	Reference/source for costs
Encorafenib	3 150 mg	1	11 960.00	
Binimetinib	1 260 mg	1	21 471.00	
Cobimetinib	1 260 mg	1	36 228.72	
Atezolizumab	840 mg	1	20 722.76	

Abbreviations: DKK, Danish Kroner; IV, intravenous; mg, milligrams.

The same administration cost was used for the subsequent treatment regimens as were for the 1L therapies (see Table 27). Vial sharing is applied where applicable to limit drug wastage for both 1L and 2L treatments. Please note that subsequent treatment costs are reported including administration costs in the results (Table 38).

8.5.4 Disease management costs

Table 31 presents the disease management costs per every 4 weeks for patients in the PFS and PD health states.

Table 31: Disease management costs in the event-free and progressed disease health states

Resource name	Resource use in Health state PF, per 4 weeks	Resource use in Health state PD, per 4 weeks	Unit cost (DKK)	Reference for unit costs
Medical oncologist consultation	1	1	1 634	According to guidelines, frequency assumption as per knowledge from Nordic setting. DRG Grouper 2023, DRG 09MA98. (DC439M) Malignant melanoma of the skin with metastases + (ZZ0202) Observation of patient after examination/treatment
PET-CT scan	0.2	0.2	2 440	According to guidelines, frequency assumption as per knowledge from Nordic setting. Assumed 1 time at diagnosis, divided over 5 years. DRG Grouper 2023, DRG 30PR06: CT-scanning, kompliceret.

Abbreviation: DKK, Danish Kroner; DRG, Diagnose related groups; PFS, Progression free survival; PD, progressive disease; PET-CT, positron emission tomography computerised tomography.

Treatment monitoring costs including a complete blood count test were applied when patients were on treatment and receiving monitoring tests: these costs are expected to be consistent for both nivo+rela and nivolumab monotherapy. Table 32 presents the frequency of patients receiving monitoring tests during treatment, along with the unit costs of the tests.

Table 32: Treatment monitoring costs

	Nivo+rela monitoring, per 4 weeks	Nivolumab monotherapy monitoring, per 4 weeks	Unit cost of tests (DKK)	Frequency source	Source
Full blood count	1	1	116	Assumption	Rigshospitalets Labportal (2023). Test code for complete blood count 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). https://labportal.rh.dk/Labportal.asp

Abbreviations: DKK, Danish Kroner; PFS, Progression free survival; PD, Progressive disease.

8.5.5 Patient costs for time spent on treatment and transportation

Costs for patients' time and transportation were included in the base case in line with Danish guidelines [42]. These items aimed to cover the cost paid by patients in regards to each treatment administration (Table 33).

Table 33: Patient costs included in the model for time spent on treatment and transportation

Resource	Cost per treatment administration (DKK)	Source/Comment
Unit cost for transportation	140	Cost unit (140 DKK per visit of transportation) is sourced from Medicinrådet (2022), Værdisætning af enhedsomkostninger. Unit cost is expressed in 2022 values as 2023 values were not available.
Patient time cost per visit	362	Assumption of 2 hours for travel and infusion. Cost unit (181 DKK per hour of patient/caregiver time) is sourced from Medicinrådet (2022), Værdisætning af enhedsomkostninger. Unit cost is expressed in 2022 values as 2023 values were not available.
Caregiver time costs	362	
Patient costs for time spent on treatment and transportation, total	864	-

Abbreviations: DKK, Danish Kroner.
Reference: [54]

8.5.6 Treatment-related adverse event costs

Costs for TRAEs were captured as inpatient and outpatient events. The model considered TRAEs that were experienced in at least 5% of patients in the RELATIVITY-047 trial, of which grade 3 and 4 were included in the model and considered to have an effect on costs (Table 11). Table 34 below displays the frequencies, resource use, and costs considered for the TRAE.

Table 34: Grade 3 or 4 treatment-related adverse event cost and frequencies

TRAE	Nivo+rela, grade 3 or 4	Nivolumab monotherapy, grade 3 or 4	Cost (DKK)	Source
Pruritus	[redacted]	[redacted]	1634	Assumption: Grade 3 and 4 TRAE would be treated with
Fatigue	[redacted]	[redacted]		

TRAE	Nivo+rela, grade 3 or 4	Nivolumab monotherapy, grade 3 or 4	Cost (DKK)	Source
Rash	[redacted]	[redacted]		an outpatient visit; Grade 1 and 2 TRAE would not be treated. Costs from DRG Grouper 2023, DRG 09MA98. (DC439M) Malignant melanoma of the skin with metastases + (ZZ0202) Observation of patient after examination or treatment
Diarrhoea	[redacted]	[redacted]		
Arthralgia	[redacted]	[redacted]		
Asthenia	[redacted]	[redacted]		
Alanine aminotransferase increased	[redacted]	[redacted]		
Aspartate aminotransferase increased	[redacted]	[redacted]		
Myalgia	[redacted]	[redacted]		
Infusion related reaction	[redacted]	[redacted]		

Abbreviations: DRG, Diagnose related groups; DKK, Danish Kroner; Nivo+rela, nivolumab plus relatlimab; TRAE, treatment-related adverse event.

8.6 Scenario analyses

The results were tested in several different scenarios to explore the impact of alternating individual inputs. Table 35 describes the scenarios explored.

Table 35: Scenario analyses - Description

Scenario	Base case value	Scenario value	Detailed description
Scenario 1	OS extrapolations - Generalized gamma	OS extrapolations - Gompertz for nivo+rela and nivolumab monotherapy	Explores a scenario with an alternative extrapolation for OS
Scenario 2	PFS extrapolations - Lognormal	PFS extrapolations - Gompertz for nivo+rela and nivolumab monotherapy	Explores a scenario with an alternative extrapolation for PFS
Scenario 3	Comparator cost based on nivolumab monotherapy cost and administration regimen	Comparator cost based on pembrolizumab cost and administration regimen	Explores alternative costs for the comparator
Scenario 4	TD utilities	Health state specific overall utility; see section 8.4.1 for more details	Scenario explores an alternative approach to estimating utilities

Abbreviations: nivo+rela, nivolumab plus relatlimab; OS, Overall survival; TD, Time to death; PFS, progression free survival

8.7 Results

8.7.1 Base case overview

Table 36 provides a summary of base case settings applied in the analysis. Table 37 outlines the key assumptions that are applied.

Table 36: Base case settings summary

Parameters groups	Base case inputs
General settings	Time horizon: 40 years
	Country: Denmark
	Perspective: Limited societal perspective
	Discount rates: Years 1 – 35, 3.5% for costs and QALYs; for years 35+, 2.5%
Intervention	Nivo+rela

Parameters groups	Base case inputs
Comparator	Nivolumab monotherapy
Parametric function for OS	Generalized gamma (same in both arms)
Parametric function for PFS	Lognormal (same in both arms)
Parametric function for TTD	Treatment duration follows the TTD KM for each treatment, no extrapolation [redacted]
Utilities	TD utilities: Please refer to section 8.4.2
Disutilities	
Costs	Disease management costs: Table 31 Drug acquisition costs: Table 26 Drug administration costs: Table 27 Drug monitoring costs: Table 32 Adverse Events costs: Table 34 Transportation costs: Table 33 Subsequent treatment costs: Table 28

Abbreviations: KM, Kaplan-Meier; Nivo+rela; nivolumab + relatimab, OS, Overall Survival; PFS, progression-free survival; TTD, Time to discontinuation; QALYs, quality adjusted life years.

Table 37: Key assumptions in the economic model

Model inputs	Rationale	Source
Time to discontinuation and stopping rules	[redacted] For nivo+rela and nivolumab monotherapy, KM data from RELATIVITY-047 is used to model treatment costs.	RELATIVITY-047, Danish clinical practice
Subsequent treatment	Durations of subsequent immunotherapy treatments are based on the estimated mean PFS reported for 2L therapy post anti-PD1 treatment.	RELATIVITY-047
Disease management costs	It is assumed PF and PD costs are applied as a constant cost.	DRG Grouper 2023
Compliance	The model assumes that compliance to treatment in RELATIVITY-047 is reflective of the real world setting.	RELATIVITY-047
AEs	AE rates from RELATIVITY-047 are used	RELATIVITY-047
QoL	TD utilities are included in the base case analysis.	RELATIVITY-047

Abbreviations: 1L, First-line; AE, adverse event; EQ-5D-3L, EuroQol 5 dimensions 3 levels; EQ-5D-5L, EuroQol 5 dimensions 5 levels; ICER, incremental cost effectiveness ratio; nivo+rela, nivolumab + relatlimab; KM, Kaplan-Meier; OS, Overall Survival; PD, Progressed disease; PD-L1, Programmed death ligand 1; PF, progression-free; PFS, progression-free survival; QALY, Quality adjusted life years; QoL, quality of life, TD, Time to death

8.7.2 Base case results

The incremental costs, LYs, and QALYs are presented in Table 38. Nivo+rela was associated with higher LYs and QALYs than nivolumab monotherapy over the modelled time horizon, accruing an additional [redacted] LYs and [redacted] QALYs vs. nivolumab monotherapy. The use of nivo+rela resulted incremental costs of [redacted] compared to nivolumab monotherapy.

The cost per QALY gained associated with treatment with nivo+rela vs nivolumab monotherapy was [redacted]

[redacted]

Per patient	Nivo+rela	Nivolumab monotherapy	Difference
Life years gained			
Total life years gained	[redacted]	[redacted]	[redacted]
QALYs			
Total QALYs	[redacted]	[redacted]	[redacted]
QALYs (adverse reaction decrements)	[redacted]	[redacted]	[redacted]
Costs			
Total costs (DKK)	[redacted]	[redacted]	[redacted]
Disease management (DKK)	[redacted]	[redacted]	[redacted]
Acquisition (DKK)	[redacted]	[redacted]	[redacted]
Administration (DKK)	[redacted]	[redacted]	[redacted]
Monitoring (DKK)	[redacted]	[redacted]	[redacted]
Adverse events (DKK)	[redacted]	[redacted]	[redacted]
Subsequent treatment (DKK)	[redacted]	[redacted]	[redacted]
Patient time and transportation (DKK)	[redacted]	[redacted]	[redacted]
Incremental results	Nivo+rela vs. nivolumab monotherapy		
ICER (DKK per QALY)	[redacted]		

Abbreviations: DKK, Danish Kroner; ICER, incremental cost-effectiveness ratio; nivo+rela, nivolumab + relatlimab; QALYs, Quality adjusted life years.
Note: The category subsequent treatment includes acquisition, administration, monitoring, adverse event, patient time and transportation costs in the 2L setting

8.8 Scenario analyses

The results of the scenario analyses are presented in Table 39.

Table 39: Scenario analyses - Results

Scenario	Scenario description	Incremental costs, nivo+rela vs nivolumab monotherapy (DKK)	Incremental QALYs, nivo+rela vs nivolumab monotherapy	ICER vs nivolumab monotherapy (DKK/QALY)
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Scenario	Scenario description	Incremental costs, nivo+rela vs nivolumab monotherapy (DKK)	Incremental QALYs, nivo+rela vs nivolumab monotherapy	ICER vs nivolumab monotherapy (DKK/QALY)
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: DKK, Danish Kroner; ICER, incremental cost-effectiveness ratio; nivo+rela, nivolumab + relatlimab; QALYs, Quality adjusted life years; OS, Overall survival; PFS, Progression free survival

8.9 Sensitivity analyses

8.9.1 Deterministic sensitivity analyses

[redacted]

[redacted]

Variable		Incremental Costs (DKK)	Incremental QALY	ICER (DKK)	Incremental ICER from base case
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

8.9.2 Probabilistic sensitivity analyses

[redacted]

[redacted]

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[redacted]

Incremental outcomes	Nivo+rela vs. nivolumab monotherapy
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	
[redacted]	[redacted]
[redacted]	

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9. Budget impact analysis

9.1 Number of patients

A budget impact analysis was performed for the expected additional cost of introducing nivo+rela to the Danish clinical setting. In line with DMC guidelines, a time horizon of 5 years was used for this analysis and costs are not discounted. The number of patients eligible for treatment with nivo+rela in Denmark was estimated to be [redacted]

Table 42 describes the number of patients expected to be treated with nivo+rela and nivolumab monotherapy if nivo+rela receives approved reimbursement. If approval is not granted, the number of patients expected to be treated with nivolumab monotherapy is presented in Table 43.

Table 42: Number of patients that are expected to be treated over the next 5-year period – if nivo+rela is approved for reimbursement

	Year 1	Year 2	Year 3	Year 4	Year 5
Number of patients per year – nivo+rela	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Number of patients per year – nivolumab monotherapy	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Total	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: nivo+rela, nivolumab plus relatlimab.

Table 43: Number of patients expected to be treated during the next 5-year period – if nivo+rela is NOT approved for reimbursement

	Year 1	Year 2	Year 3	Year 4	Year 5
Number of patients per year- nivo+rela	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Number of patients per year – nivolumab monotherapy	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Total	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: nivo+rela, nivolumab plus relatlimab.

9.2 Budget impact results

The budget impact is estimated directly in the health economic model and, thus, takes into consideration patients survival over time. This means that patients that are initiated on treatment year 1 are expected to incur costs in the budget impact analysis overt time, due to treatment length and progression related costs. Patient time and transport is not included in the budget impact.

[redacted] The remaining costs in year 4 and 5 in Table 44 are due to patients still being alive and incurring costs as a result of progression.

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Table 44: Total expenditure per year - if nivo+rela is approved for reimbursement

	Year 1	Year 2	Year 3	Year 4	Year 5
Nivo+rela (DKK)	0	40 768 659	69 585 169	75 348 069	76 496 505
Nivolumab monotherapy (DKK)	28 728 597	15 631 026	3 193 364	1 138 055	891 516
Total (DKK)	28 728 597	56 399 685	72 778 533	76 486 124	77 388 021

Abbreviations: DKK, Danish Kroner, nivo+rela, nivolumab plus relatlimab.

Table 45: Total expenditure per year - if nivo+rela is not approved for reimbursement

	Year 1	Year 2	Year 3	Year 4	Year 5
Nivo+rela (DKK)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Nivolumab monotherapy (DKK)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Total (DKK)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: DKK, Danish Kroner; nivo+rela, nivolumab plus relatlimab.

Table 46: Budget impact

	Year 1	Year 2	Year 3	Year 4	Year 5
Total expenditure per year if nivo+rela is approved	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Total expenditure per year if nivo+rela is not approved	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Difference (impact) (DKK)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: DKK, Danish Kroner; nivo+rela, nivolumab plus relatlimab.

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10. Discussion on the submitted documentation

Melanoma accounts for the vast majority of deaths caused by cutaneous cancers. While survival rates are high for localized melanoma, 2-year survival rates drop to 18-40% for metastatic disease (estimated survival rates for stage IV). Immunotherapies and especially dual immunotherapy have improved survival rates in advanced melanoma but novel therapies that demonstrate durable response with improved benefit-risk profiles are still needed. In particular, patients who are ineligible for the currently recommended dual immunotherapies (in Danish Treatment Guidelines) lack alternative treatment options.

With nivo+rela, more patients will have the opportunity to benefit from dual immunotherapy. Data from RELATIVITY-047 showed similar rates of treatment-related adverse events (TRAEs) between nivo+rela and nivolumab monotherapy, with nivo+rela demonstrating a statistically significant and clinically meaningful PFS benefit compared with nivolumab monotherapy for patients with tumour cell PD-L1 expression <1% [redacted], which was maintained at longer follow-up (median 25.31 months). The median OS for nivo+rela vs. nivolumab monotherapy was [redacted]. In addition, health state utility weights collected in RELATIVITY-047 were used in the model and are representative of the target population. The economic model described in this report has several strengths. Based on the current understanding of the natural history and possible outcomes of melanoma, the model utilises a simple 3 health state partitioned survival approach to track clinical outcomes, which have been validated and previously used in submission to the DMC [55]. As the model utilises a direct, in-trial comparison between nivo+rela and nivolumab monotherapy, the clinical evidence is not compromised by indirect adjustments.

The economic analysis is however not without limitations. [redacted]

11. List of experts

Clinical experts have not been consulted for this indication.

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

The direct, in-trial comparison available through the RELATIVITY-047 study is presented (see Section 7.1) to compare nivo+rela against nivolumab monotherapy. As such, an SLR is not required for this application.

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14. Appendix B Main characteristics of included studies

An overview of the RELATIVITY-047 trial is presented in Table 47.

Table 47: Overview of RELATIVITY-047

RELATIVITY-047	NCT03470922
Objective	• The primary objective of the study was to compare PFS of nivo+rela with nivolumab monotherapy in subjects with previously untreated, unresectable, or metastatic melanoma • The secondary objectives included to compare OS and ORR in the same population
Publications – title, author, journal, year	Tawbi HA, Schadendorf D, Lipson EJ, Ascierto PA, Matamala L, Castillo Gutiérrez E, Rutkowski P, Gogas HJ, Lao CD, De Menezes JJ, Dalle S, Arance A, Grob JJ, Srivastava S, Abaskharoun M, Hamilton M, Keidel S, Simonsen KL, Sobiesk AM, Li B, Hodi FS, Long GV; RELATIVITY-047 Investigators. Relatlimab and Nivolumab versus Nivolumab in Untreated Advanced Melanoma. N Engl J Med. 2022 Jan 6;386(1):24-34. doi: 10.1056/NEJMoa2109970.
Study type and design	Randomised, double-blind, phase 2/3 study. Subjects were randomised 1:1 to treatment with nivo+rela or nivolumab monotherapy. Randomisation was stratified by tumour LAG-3 expression (≥ 1% vs < 1%), BRAF mutation (V600 mutation positive vs V600 wild-type), AJCCv8 stage and by tumour PD-L1 expression (≥ 1% vs < 1%).
Sample size (n)	• Intervention: n=355 • Comparator: n=359
Main inclusion and exclusion criteria	Inclusion criteria: • Histologically confirmed stage III (unresectable) or stage IV melanoma, per the 8th edition of the AJCC staging system • No prior systemic anticancer therapy for unresectable or metastatic melanoma, but prior adjuvant or neoadjuvant melanoma therapy with a specified regimen was allowed (anti-PD-1, anti-CTLA-4, or BRAF-MEK containing regimen if ≥ 6 months between last dose and date of recurrence; interferon with last dose ≥ 6 weeks before randomization) • ECOG performance status of 0 or 1, or a Lansky performance score ≥ 80% for minors • Known BRAF V600 mutation status or consent to BRAF V600 mutation testing per local institutional standards during the screening period Exclusion criteria: • Active or untreated brain or leptomeningeal metastases • Uveal melanoma • Active autoimmune disease or condition requiring systemic treatment with either corticosteroids (> 10 mg daily prednisone equivalent) or other immunosuppressive medications within 14 days of start of study treatment • History of myocarditis
Intervention	Nivo+rela, of which n=237 completed treatment Participants received IV fixed-dose combination nivo+rela at a 1:3 ratio every 4 weeks (Q4W). For adults, dosing is relatlimab 160 mg plus nivolumab 480 mg. Adolescents ≥ 40 kg will receive adult dosing; for adolescents < 40 kg, dosing is relatlimab 2 mg/kg plus nivolumab 6 mg/kg. Treatment was continued until disease progression, treatment discontinuation, unacceptable toxicity, withdrawal of consent, or end of study
Comparator	Nivolumab monotherapy, of which n=227 completed treatment Participants receive nivolumab monotherapy IV Q4W. Dosing for adults is 480 mg. Adolescents ≥ 40 kg will receive adult dosing; for adolescents < 40 kg, dosing is 6 mg/kg.

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RELATIVITY-047	NCT03470922
	Treatment was continued until disease progression, treatment discontinuation, unacceptable toxicity, withdrawal of consent, or end of study
Follow-up time	[redacted]
Is the study used in the health economic model?	Yes
Primary, secondary and exploratory endpoints	Primary Outcome Measures: • PFS Secondary Outcome Measures: • OS • ORR Other Pre-specified Outcome Measures: • AEs • SAEs • AEs Leading to Discontinuation • Participant Deaths in the Study • Participants Experiencing Laboratory Abnormalities in Specific Liver and Thyroid Tests
Method of analysis	[redacted]
Subgroup analyses	The pre-defined subgroup for PD-L1 expression (≥1% or <1%) is relevant for this submission, as the focus of the EMA label is patients who are PD-L1 negative (<1%). Other stratifications include by gender, race, ethnicity, LAG-3 expression (≥1% or <1%), BRAF V600 mutation status, metastasis stage, melanoma subtype, ECOG PS, and tumour burden [56, 57].

Abbreviations: AE, adverse events; AJCC, American Joint Committee on Cancer; ECOG PS, Eastern Cooperative Oncology Group Performance Status Scale; EMA, European Medicines Agency; LAG-3, lymphocyte activation gene-3; LDH, lactate dehydrogenase; M, presence of metastases; NCT, National Clinical Trial; ORR, objective response rate; OS, overall survival; PD-L1, programmed death-ligand 1; PFS, progression free survival; Q4W, every 4 weeks; SAE, serious adverse events.
Source: [7, 34, 36]

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

Baseline demographics and disease characteristics for all randomised patients with PD-L1 < 1% in the RELATIVITY-047 are presented in Table 48.

Table 48: Patient baseline characteristics in RELATIVITY-047 for all randomised patients with PD-L1 < 1%

	Nivo+rela (n=209)	Nivolumab monotherapy (n=212)
Median age, years (range)	62.0 (20–94)	63.0 (26-90)
Mean age, years	60.7	61.0
Age category (%)		
>=18 and <65	113 (54.1)	113 (53.3)
>=65 and <75	53 (25.4)	65 (30.7)
>=75 and <85	37 (17.7)	30 (14.2)
>=85	6 (2.9)	4 (1.9)
Female, n (%)	91 (43.5)	90 (42.5)
Stage at study entry (%)		
Unresectable stage III	22 (10.5)	11 (5.2)
Metastatic stage IV	187 (89.5)	200 (94.3)
Unknown or not reported	0	1 (0.5)
Previous systemic therapy, n (%)		
Adjuvant	19 (9.1)	12 (5.7)
Neoadjuvant	1 (0.5)	1 (0.5)
Unknown or other	0	1 (0.5)
Metastasis stage, n (%) [a]		
M0	22 (10.5)	11 (5.2)
M1a or b	94 (45.0)	108 (50.9)
M1c	90 (43.1)	84 (39.6)
M1d	2 (1.0)	6 (2.8)
M1	1 (0.5)	3 (1.4)
Not reported	0	0
Melanoma subtype classification, n (%)		
Cutaneous acral	28 (13.4)	29 (13.7)
Cutaneous non-acral	136 (65.1)	146 (68.9)
Mucosal	18 (8.6)	20 (9.4)
Other	27 (12.9)	17 (8.0)
ECOG performance status, n (%) [b]		
0	137 (65.6)	142 (67.0)
1	72 (34.4)	70 (33.0)
Tumour LAG-3 expression, n %		
≥1%	134 (64.1)	129 (60.8)
<1%	75 (35.9)	83 (39.2)
BRAF mutation status, n %		
Patients with BRAF mutations	81 (38.8)	79 (37.3)
Patients without BRAF mutations	128 (61.2)	133 (62.7)

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	Nivo+rela (n=209)	Nivolumab monotherapy (n=212)
Baseline LDH level (%)		
≤ ULN	131 (62.7)	128 (60.4)
> ULN	77 (36.8)	84 (39.6)
Not reported	1 (0.5)	0

Abbreviation: ECOG PS, Eastern Cooperative Oncology Group Performance Status Scale.
Notes: [a] Metastasis stages are defined according to the AJCC Cancer Staging Manual, 8th edition
[b] The ECOG PS is assessed on a 5-point scale, with 0 indicating no performance restrictions and higher scores indicating greater disability
Source: [7, 34, 36]

15.1 Comparability of patients across studies

The treatment (nivo+rela) is compared with the comparator (nivolumab monotherapy) directly in the RELATIVITY-047 trial, 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

Definition, validity and clinical relevance of included outcome measures

Table 49: Definitions of endpoints used in RELATIVITY-047

Outcome	Definition	Validity and clinical relevance
Progression free survival	Time between the date of randomization and the first date of documented progression, or death due to any cause, whichever occurred first.	PFS is commonly used in oncology research as a direct or surrogate measure of clinical benefit for drug approvals.
Overall survival	Time between the date of randomization and the date of death due to any cause. For subjects that were alive, their survival time was censored at the date of last contact.	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.
Objective response rate	Percentage of randomized participants who, at a given time point, achieve a complete or partial response as assessed by a Blinded Independent Central Review (BICR).	ORR is commonly used as an end point to assess the clinical benefit for drug approvals.

Source: [35]

16.1 Results per study

Table 50: Results of RELATIVITY-047 (NCT03470922)

Outcome	Study arm	N	Result (CI)	Estimated absolute difference in effect			Estimated relative difference in effect			Description of methods used for estimation	References
				Difference	95% CI	P value	Difference	95% CI	P value		
Median PFS (PD-L1 expression <1%), months	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]		A comparison of PFS between treatment groups was performed with a two-sided log-rank test stratified according to LAG-3 status, AJCC metastasis stage, and BRAF status. A Cox proportional-hazards model was used to estimate hazard ratios and two-sided 95% CI. KM methods were used to estimate additional end points. The confidence intervals for the	[7, 34, 36].
Median OS (PD-L1 expression <1%), months	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]			
OS at 12 months (PD-L1 expression <1%), %	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]		
OS at 24 months (PD-L1 expression <1%), %	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]		
OS at 36 months (PD-L1 expression <1%), %	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]		
OS at 48 months (PD-L1 expression <1%), %	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]		
ORR (PD-L1 expression <1%), %	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]		

Outcome	Study arm	N	Result (CI)	Estimated absolute difference in effect			Estimated relative difference in effect			Description of methods used for estimation	References
				Difference	95% CI	P value	Difference	95% CI	P value		
	[redacted]	[redacted]	[redacted]							reported end points have not been adjusted for multiplicity. The proportional-hazards assumption was tested by the addition of a time-dependent covariate, defined by treatment by-time interaction, to the stratified Cox regression model. A two-sided Wald chi-square P value of less than 0.1 may indicate a potential nonconstant treatment effect. The P value in this analysis was 0.1497, indicating no evidence of a nonconstant hazard.	
EQ-VAS (ITT population), mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]						
	[redacted]	[redacted]	[redacted]								
FACT-M (ITT population), mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]						
	[redacted]	[redacted]	[redacted]								

Abbreviations: CI, confidence intervals; FACT-M, functional assessment of cancer therapy – melanoma; HR, hazard ratio; NA, not available; ORR, objective response rate; OS, overall survival; PFS, progression-free survival; RR, relative risk; SD, standard deviation; VAS, visual analogue scale.

17. Appendix E Comparative analysis of efficacy and safety

The direct, in-trial comparison available through the RELATIVITY-047 (see Section 7.1) study is presented to compare nivo+rela against nivolumab monotherapy. As such, no additional comparative analysis is presented for this application.

18. Appendix F Extrapolation

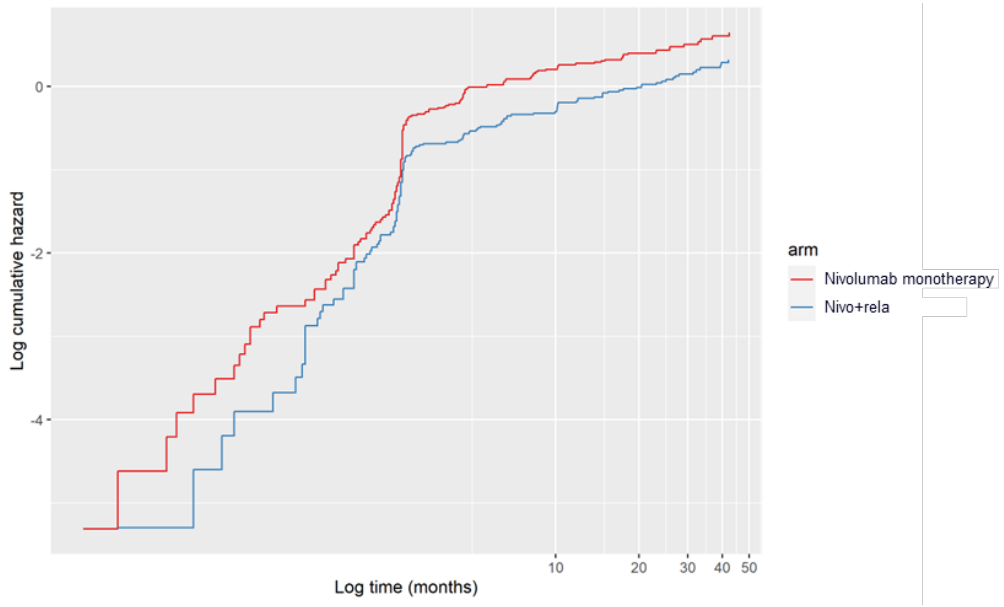
[redacted]

18.1.2 Assessment of proportional hazards

Visual inspection of the log-cumulative hazards and Schoenfeld residuals plots was undertaken to assess proportionality of treatment effects over time (Figure 36 and Figure 37). These mostly demonstrate that the proportional hazard holds, except for a change in the shape of the log-cumulative hazards plot at around 3 months. The Grambsch-Therneau correlation test between Schoenfeld residuals and log of time failed to reject the proportional hazards assumption (p=0.42). The Quantile-Quantile plot indicates some deviation from the Accelerated Failure Time (AFT) assumption at around 3 months.

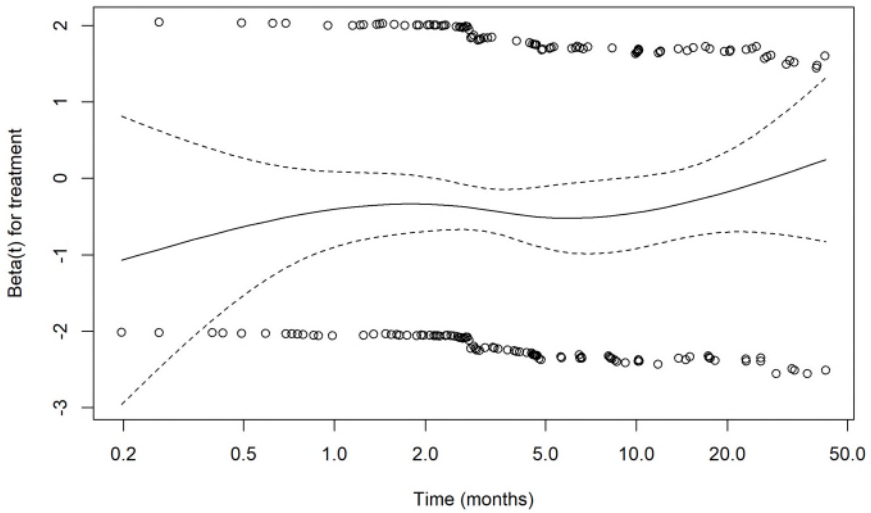
Both independent and dependent models were fitted to PFS for the PD-L1 expression <1% population, as both could appropriately capture survival they should also be considered.

Figure 36: Log-cumulative hazard plot for nivo+rela vs nivolumab monotherapy PFS, PD-L1 expression <1%



Abbreviations: Nivo+rela, nivolumab plus relatlimab; PD-L1, Programmed death-ligand 1; PFS, Progression-free survival.

Figure 37: Schoenfeld residuals plot for nivo+rela vs nivolumab monotherapy PFS, PD-L1 expression <1%



Abbreviations: Nivo+rela, nivolumab + relatlimab; PD-L1, Programmed death-ligand 1; PFS, Progression-free survival.

[redacted]

18.1.2.1 Dependent extrapolation models

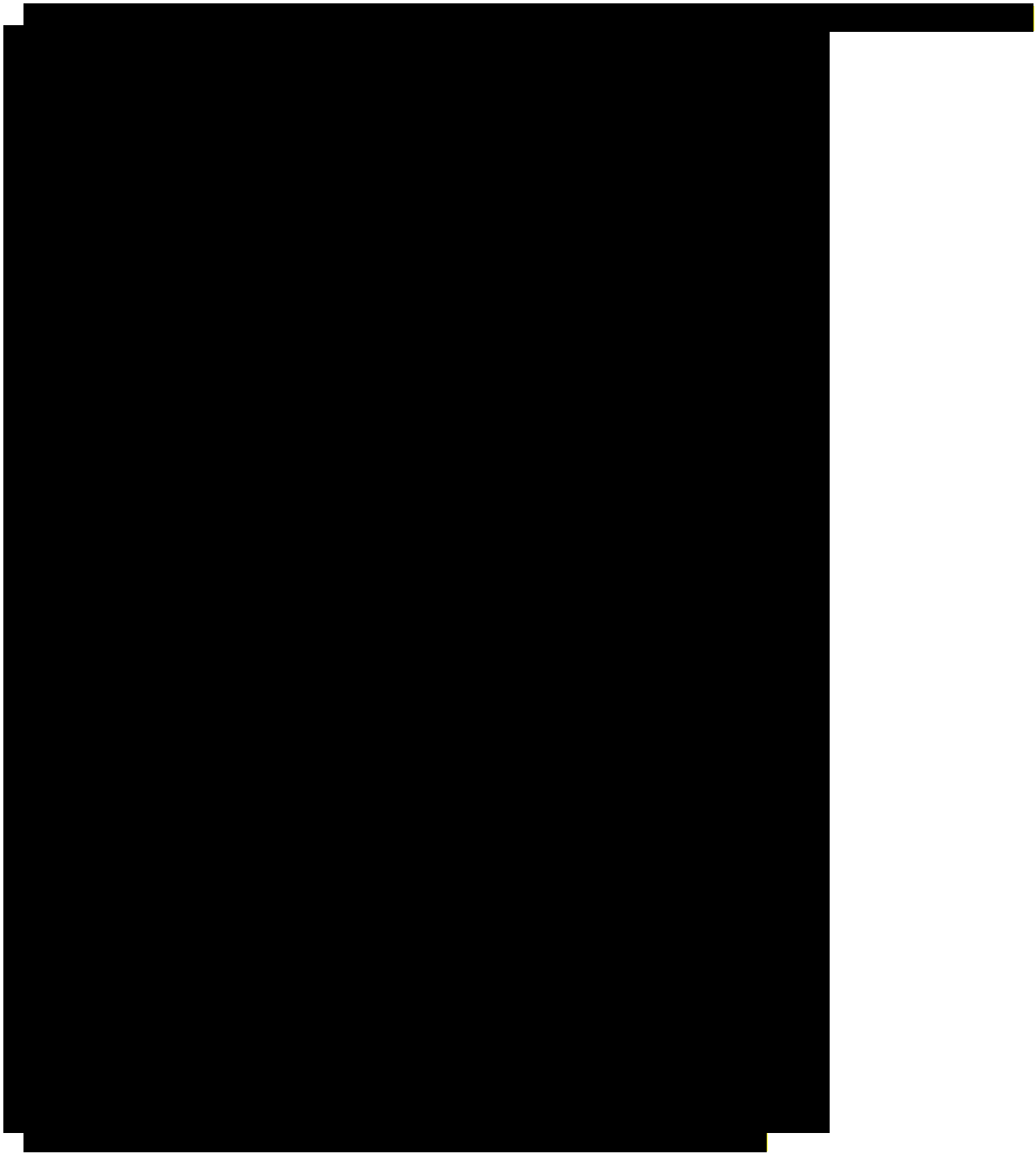
Table 51 shows the goodness-of-fit statistics for the dependent curves fitted to nivo+rela and nivolumab monotherapy for PFS. In terms of both AIC and BIC, the best-fitting models are spline odds 1 knot, spline odds 2 knots, and spline hazard 2 knots. The spline models all outperform the standard parametric models, with a very large difference (+49.14) between the best-performing spline model and the best-performing standard parametric model, suggesting that standard parametric models are a poor fit to the observed data and therefore may be inappropriate to model PFS from baseline. However, from visual inspection of the spline models it is also evident that these does not fit especially the nivo+rela KM curve well.

Table 51: Statistical goodness-of-fit indicators (AIC/BIC) values for dependent parametric models fitted to PFS data for nivo+rela and for nivolumab monotherapy (PFS data from baseline)

Dependent model	AIC	BIC
Spline odds 1 knot	1970.25	1986.42
Spline odds 2 knots	1972.33	1992.55
Spline hazard 2 knots	1973.01	1993.23
Spline hazard 1 knot	1980.11	1996.28
Spline normal 2 knots	1980.14	2000.35
Spline normal 1 knot	1987.48	2003.65
Generalized Gamma	2019.39	2035.56
Gompertz	2069.07	2081.20
Log-normal	2072.62	2084.74
Log-logistic	2082.13	2094.26
Weibull	2163.59	2175.72
Gamma	2190.36	2202.49
Exponential	2230.12	2238.20

Abbreviation: AIC, Akaike information criterion; BIC, Bayesian information criterion; nivo+rela, nivolumab plus relatlimab; Progression-free survival

The standard parametric model fits compared to the Kaplan-Meier data for both treatment arms are shown in Figure 39 and Figure 34, corresponding smoothed hazards are shown in Figure 40 and Figure 42.



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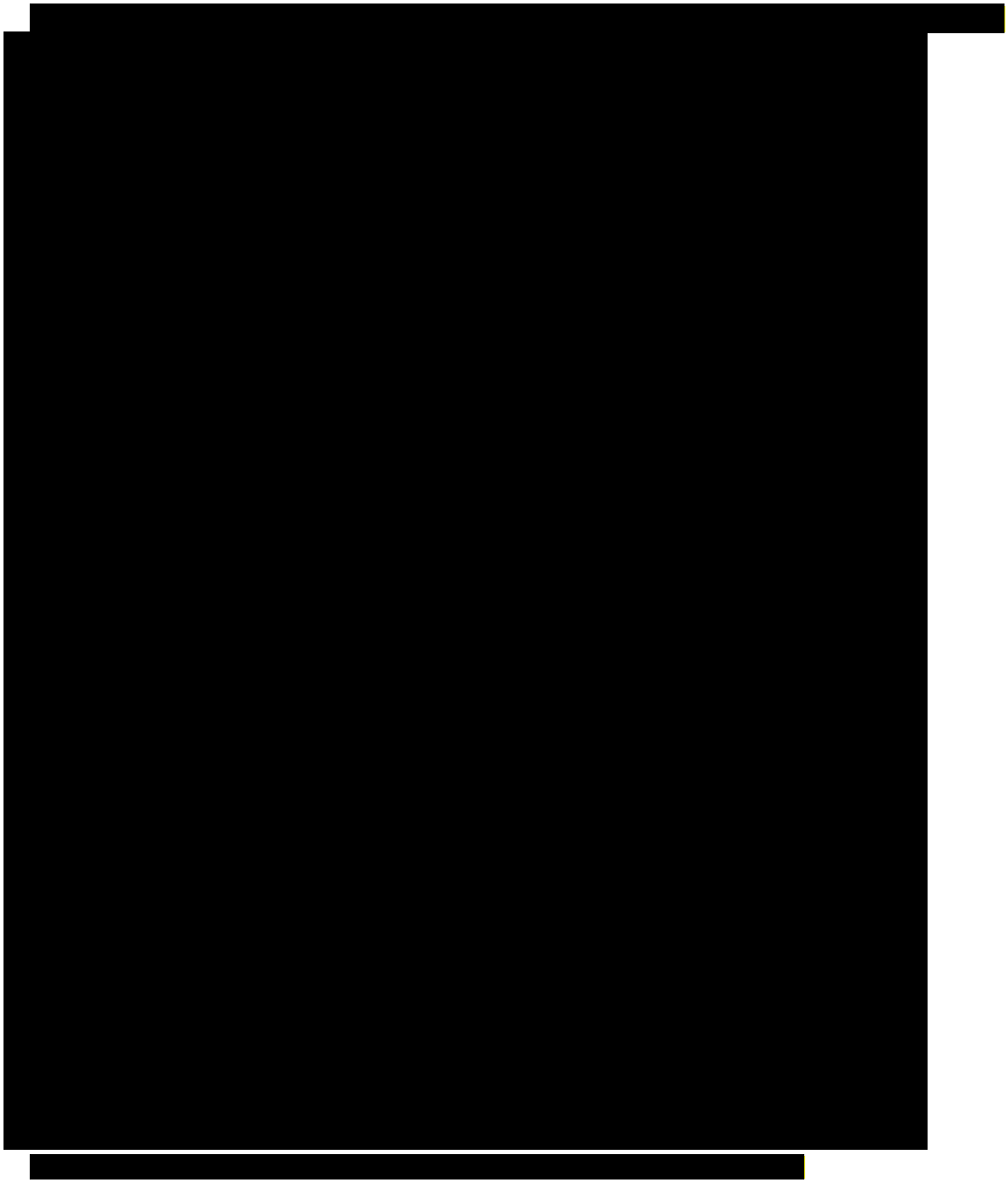

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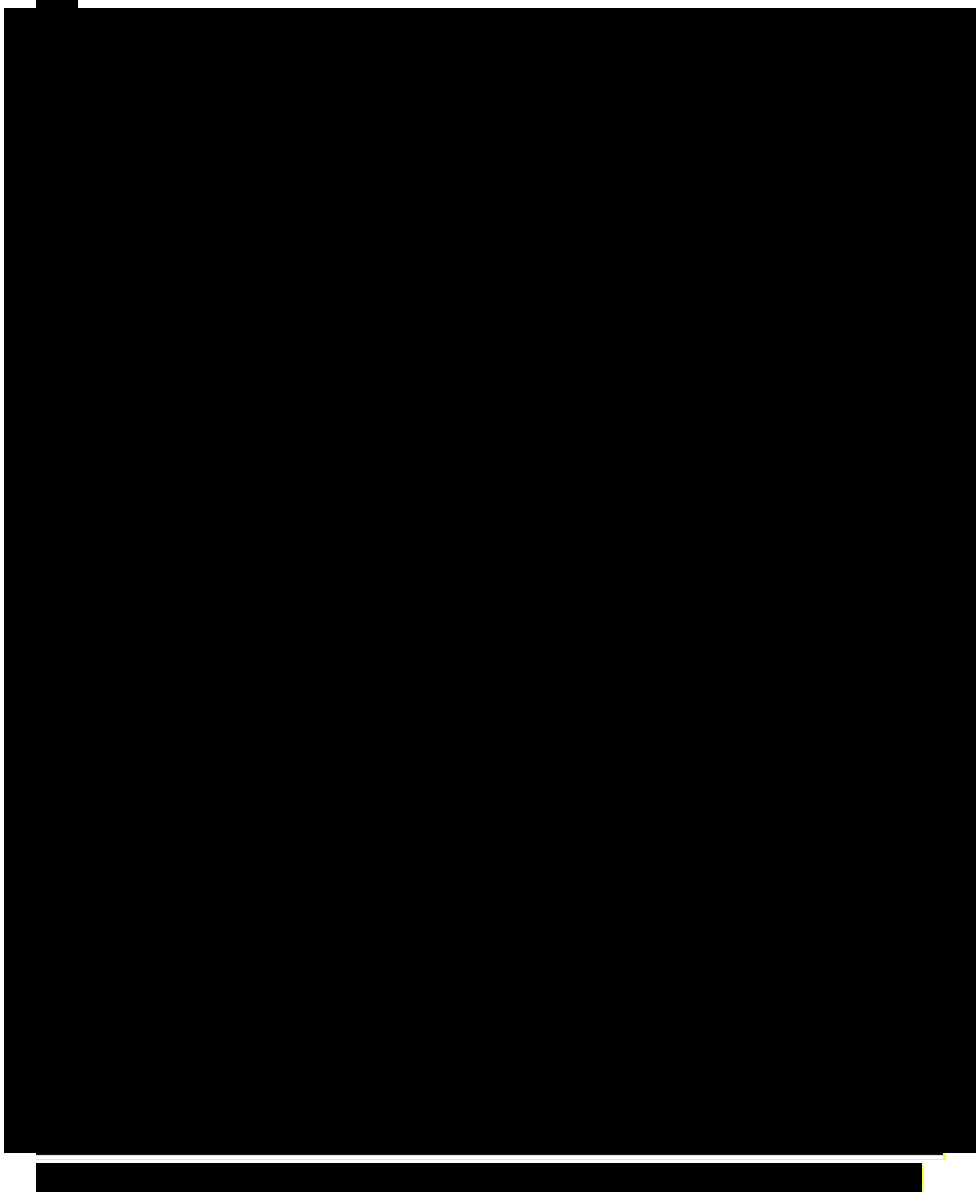

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18.1.2.2 Independent extrapolation models

This section reports the survival estimates using independent extrapolation models.

18.1.2.2.1 Nivo + rela

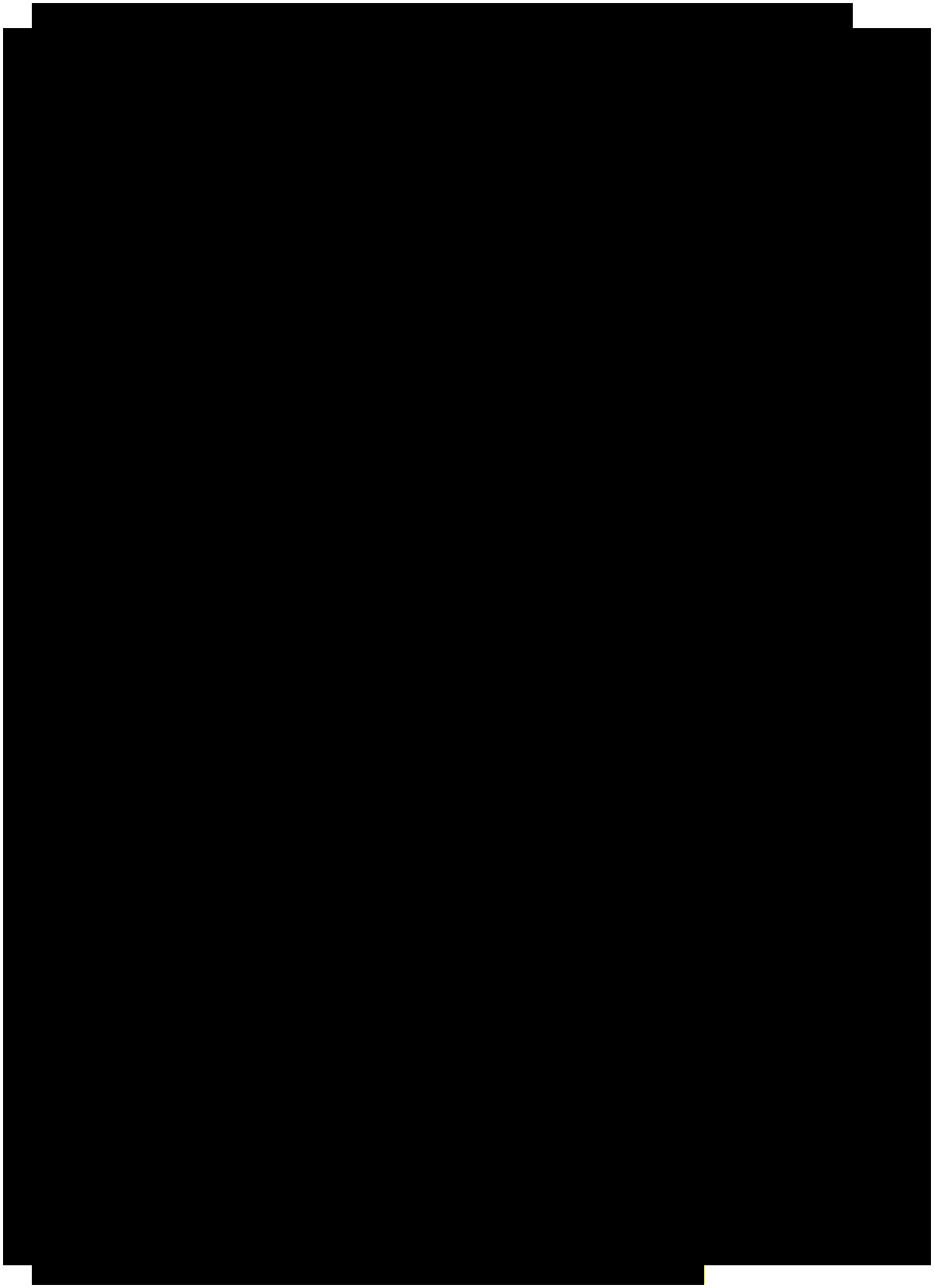
The goodness of fit statistics are presented in Table 52. In terms of both AIC and BIC, the best-fitting models are spline hazard 2 knots, spline odds 2 knots, and spline odds 1 knot. The spline models all outperform the standard parametric models in terms of AIC and BIC.

Table 52: Statistical goodness-of-fit indicators (AIC/BIC) values for independent parametric models fitted to PFS data for nivo+rela

Independent distributions	AIC	BIC
Spline hazard 2 knots	958.59	971.96
Spline odds 2 knots	961.42	974.79
Spline odds 1 knot	967.47	977.50
Spline normal 1 knot	968.75	978.78
Spline normal 2 knots	970.82	984.19
Spline hazard 1 knot	972.20	982.23
Generalized Gamma	979.59	989.61
Log-normal	1,007.52	1,014.20
Gompertz	1,009.25	1,015.93
Log-logistic	1,016.49	1,023.18
Weibull	1,044.57	1,051.26
Gamma	1,054.77	1,061.46
Exponential	1,073.99	1,077.33

Abbreviation: AIC, Akaike information criterion; BIC, Bayesian information criterion; nivo+rela, nivolumab + relatlimab; PFS, Progression-free survival.

Figure 43 and Figure 44 depicts the selected independent curves fit with the RELATIVITY-047 clinical trial data for nivo+rela. Visual inspection shows that standard parametric models fit the KM curve poorly. The spline models shows a better and more reasonable fit to the KM curve.



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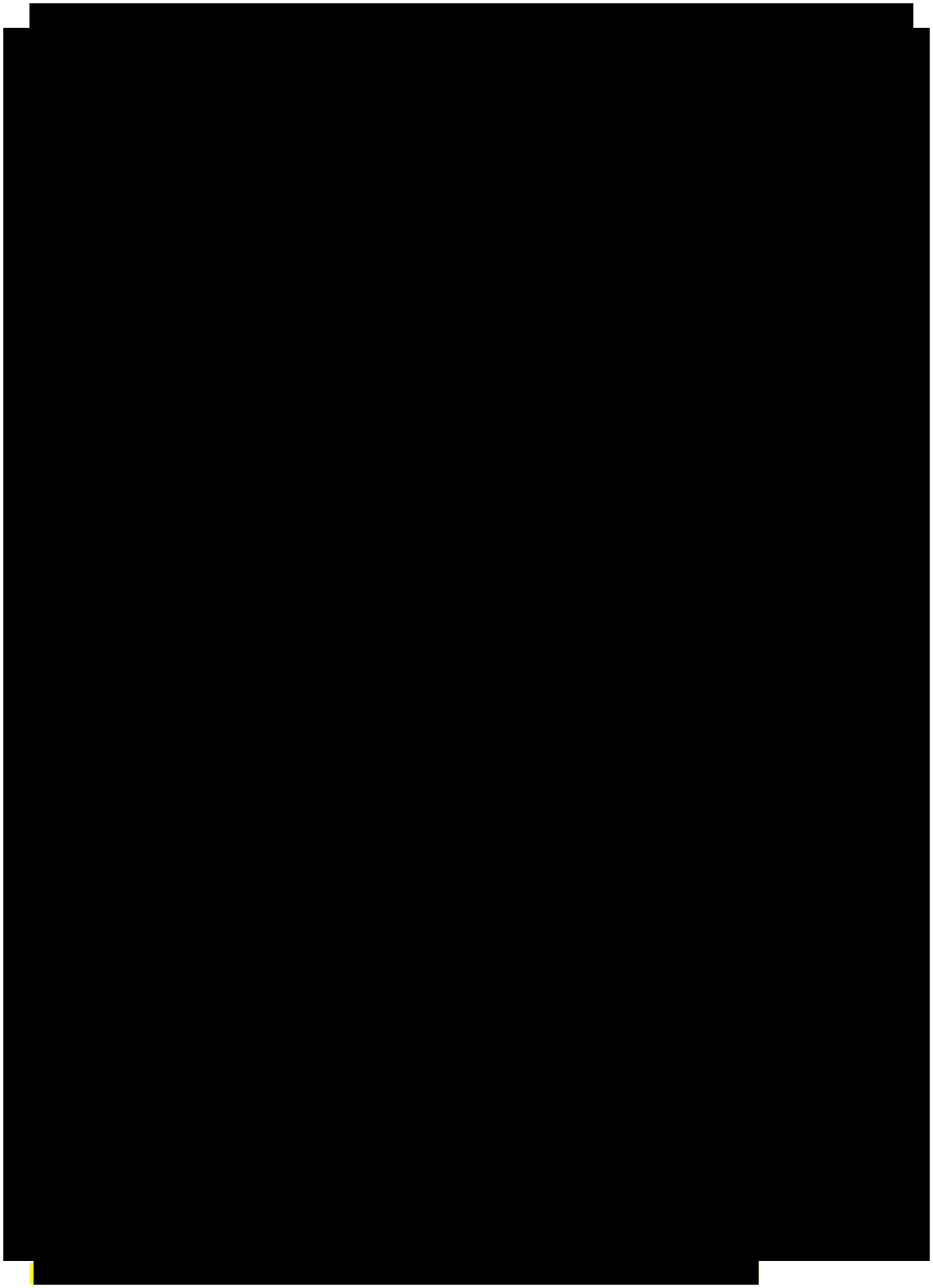

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18.1.2.2.2 Nivolumab monotherapy

The goodness of fit statistics are presented in Table 53. In terms of both AIC and BIC, the best-fitting models are spline odds 2 knots, spline normal 2 knots, and spline odds 1 knot, which all fall within 4 AIC points of one another. The spline models all outperform the standard parametric models in terms of AIC and BIC, with a large difference in AIC values (+34.97) between the best-fitting spline model and best-fitting standardised parametric model, suggesting standardised parametric models are a poor fit to the observed data and therefore may be inappropriate to model PFS from baseline.

Table 53: Statistical goodness-of-fit indicators (AIC/BIC) values for independent parametric models fitted to PFS data for nivolumab monotherapy

Independent distributions	AIC	BIC
Spline odds 2 knots	1003.66	1017.08
Spline normal 2 knots	1004.76	1018.19
Spline odds 1 knot	1006.14	1016.21
Spline hazard 1 knot	1010.63	1020.70
Spline hazard 2 knots	1012.80	1026.23
Spline normal 1 knot	1022.27	1032.34
Generalized Gamma	1038.62	1048.69
Gompertz	1060.73	1067.45
Log-logistic	1063.38	1070.09
Log-normal	1064.65	1071.36
Weibull	1120.95	1127.67
Gamma	1137.53	1144.24
Exponential	1156.13	1159.49

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

Figure 45 and Figure 46 illustrates the independent distributions for nivolumab monotherapy with the corresponding trial data. In line with the poor statistical fit to the observed data, the hazard plots show that all standardised parametric models poorly capture the initial drop in survival driven by the first per protocol tumour assessment. All spline models fit the KM data well, but were still unable to capture the tail.

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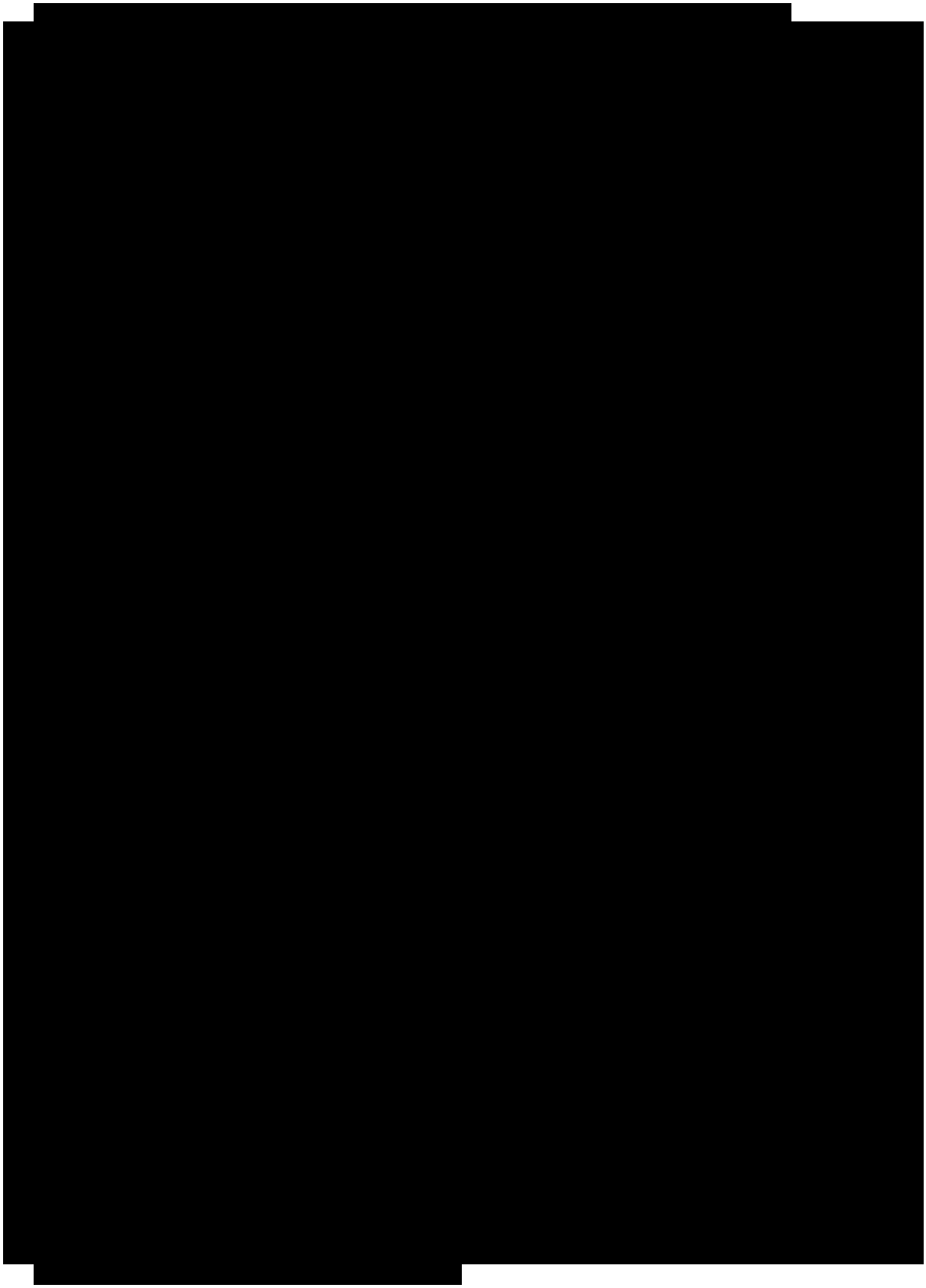

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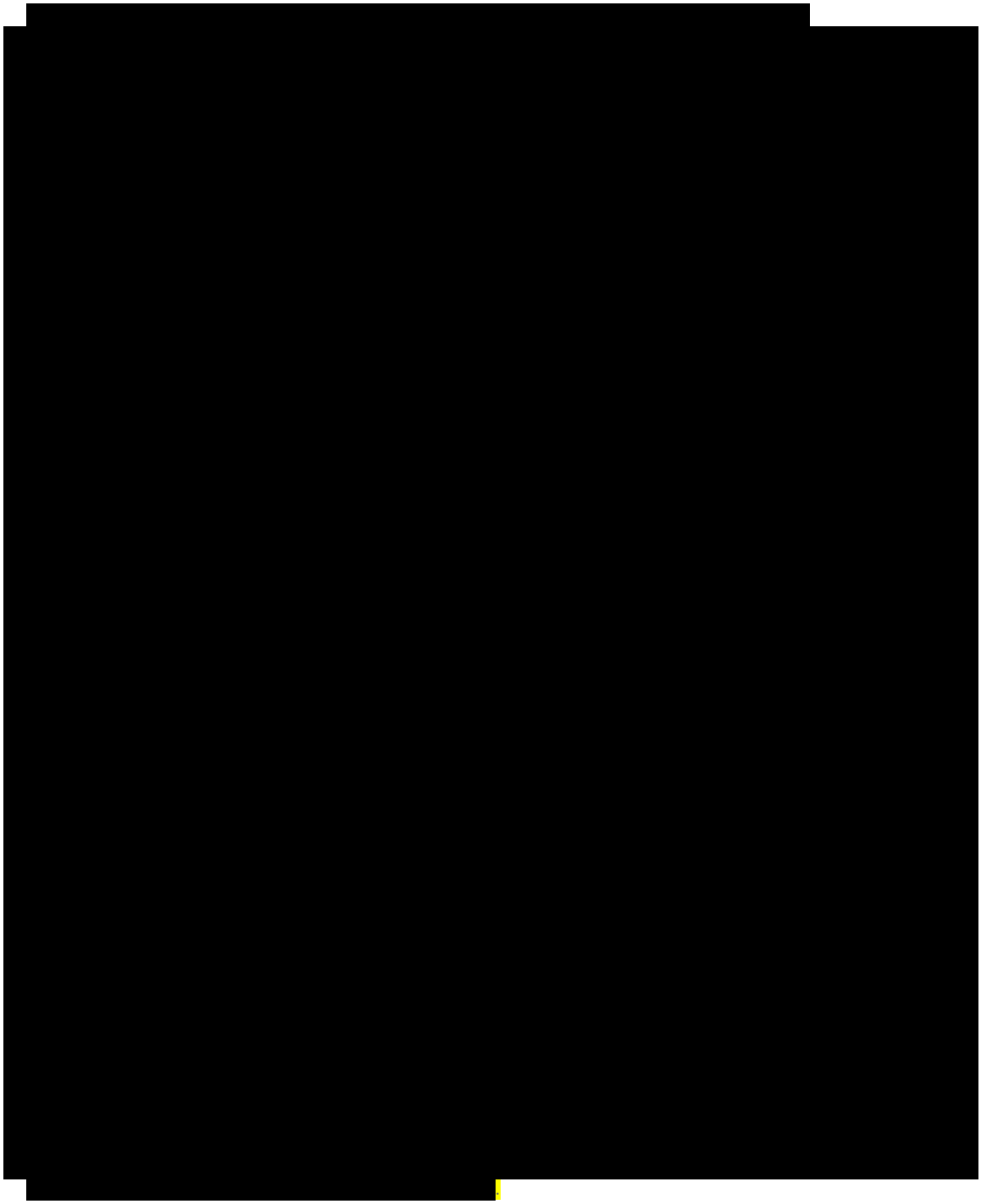

18.1.3 Conclusion

As shown in Figure 35, the PFS curves have a protocol driven divergence around 3 months, corresponding to the first assessment in the trial. Both independent and dependent extrapolations of the entire PFS curves fail to properly fit the KM curves due to this divergence. Therefore, a piecewise approach has been chosen for this submission, where the KM curves are used up until 3 months and extrapolations are applied thereafter (see section 8.3.2).

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19. Appendix G Literature search for HRQoL data

The direct, in-trial comparison available through the RELATIVITY-047 (see Section 7.1) study is presented to compare nivo+rela against nivolumab monotherapy. As such, no SLR is required for this application. For HRQoL data, please see Sections 7.1.6.1 and 8.4.

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20. Appendix H Mapping of HRQoL data

HRQoL data was collected in the RELATIVITY-047 trial—including EQ-5D-3L utility values—and were converted to EQ-5D-5L using Danish value sets as described below in section 20.4.

20.1 Analysis Population

[redacted]

20.2 Schedule of assessments

[redacted]

20.3 Completion rates

[redacted]

Visit	EQ-5D-3L descriptive system	
	Nivo+rela	Nivolumab monotherapy
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
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[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]

Visit	EQ-5D-3L descriptive system	
	Nivo+rela	Nivolumab monotherapy
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
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Visit	EQ-5D-3L descriptive system	
	Nivo+rela	Nivolumab monotherapy
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
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20.4 Calculation of Danish EQ-5D Utility Values

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20.5 Descriptive analyses of utility values

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Table 55: Summary statistics for EQ-5D-5L utilities using the Denmark value set, ITT

	Nivo+rela				Nivolumab monotherapy				Overall			
	N	Mean (SD)	Median (IQR)	Min - Max	N	Mean (SD)	Median (IQR)	Min - Max	N	Mean (SD)	Median (IQR)	Min - Max
Total	[redacted]											
Progression status												
PF	[redacted]											
PD	[redacted]											
Treatment status												
On treatment	[redacted]											
Off treatment	[redacted]											
Time to death												
Death more than 12 months away	[redacted]											
Death more than 6 months away but less than 12 months	[redacted]											
Death more than 1 month away	[redacted]											

	Nivo+rela				Nivolumab monotherapy				Overall			
	N	Mean (SD)	Median (IQR)	Min - Max	N	Mean (SD)	Median (IQR)	Min - Max	N	Mean (SD)	Median (IQR)	Min - Max
but less than 6 months												
Death within 1 month	[redacted]											
Unknown												

Abbreviations: N, total number of assessments across all patients and visits; IQR, Interquartile range; ITT, intent-to-treat; Min, Minimum; Max, Maximum; PF, Progression-free; PD, Progressed disease; SD, Standard deviation.

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20.6 Mixed effects models and Least Squares means

[redacted]

Level	Estimated mean	95% CI
[redacted]		

[redacted]

Parameter	Coefficient	Standard error	95% CI	P-value
[redacted]				
Progression status				
[redacted]				

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[redacted]

Level	Estimated mean	95% CI
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]

[redacted]

[redacted]

[redacted]

Parameter	Coefficient	Standard error	95% CI	P-value
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Progression status				
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Treatment arm				
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

[redacted]

[redacted]

Level	Estimated mean	95% CI
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]

[redacted]

[redacted]

[redacted]

Parameter	Coefficient	Standard error	95% CI	P-value
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Progression status				
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Treatment arm				
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Progression status: Treatment arm				
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

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[redacted]

Level	Estimated mean	95% CI
[redacted]		

[redacted]

Model	AIC
[redacted]	

[redacted]

Model	AIC	BIC	logLik	Chisq	Df	p.value
[redacted]						

[redacted]

Parameter	Coefficient	Standard error	95% CI	P-value
[redacted]				
Treatment status				
[redacted]				

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[redacted]

Level	Estimated mean	95% CI
[redacted]		
[redacted]		

[redacted]

[redacted]

[redacted]

Parameter	Coefficient	Standard error	95% CI	P-value
[redacted]				
Treatment status				
[redacted]				
[redacted]				
Treatment arm				
[redacted]				
[redacted]				

[redacted]

[redacted]

Level	Estimated mean	95% CI
[redacted]		
[redacted]		
[redacted]		
[redacted]		

[redacted]

[redacted]

[redacted]

Parameter	Coefficient	Standard error	95% CI	P-value
[redacted]				
Treatment status				
[redacted]				
[redacted]				
Treatment arm				
[redacted]				
[redacted]				
Treatment status: Treatment arm				
[redacted]				
[redacted]				

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[redacted]

Level	Estimated mean	95% CI
[redacted]		

[redacted]

Model	AIC
[redacted]	

[redacted]

Model	AIC	BIC	logLik	Chisq	Df	p.value
[redacted]						

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21. Appendix I Probabilistic sensitivity analyses

[redacted]

Parameter cluster	Parameters	Distribution
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]

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