Medicinrådet

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

Vers. 2.0

Bilagsoversigt

1. Ansøgers notat til Rådet vedr. nivolumab + relatlimab
2. Amgros' forhandlingsnotat vedr. nivolumab + relatlimab
3. Ansøgning vedr. nivolumab + relatlimab

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Virum d. 24.04.25

Til Medicinrådet

Bristol Myers Squibbs tilbagemelding på udkast til vurderingsrapport for nivolumab + relatlimab til behandling af fremskredent melanom hos PD-L1-negative patienter

Bristol Myers Squibb (BMS) imødeser Medicinrådets anbefaling vedr. nivolumab + relatlimab (herefter nivo+rela) til behandling af fremskredent melanom hos PD-L1-negative patienter planlagt til 21. maj 2025.

Indledningsvist vil BMS anerkende Medicinrådet for at acceptere revurderingen af sagen og det glæder BMS, at Medicinrådet i hovedanalysen er enig i størstedelen af BMS' antagelser.

BMS har dog to væsentlige kommentarer til den foreliggende vurderingsrapport, relateret til opgørelsen og beregningerne af omkostningerne ved efterfølgende behandlinger og ændring af dosis for nivolumab monoterapi:

1) **Vedr. Medicinrådets beregninger af omkostninger ved efterfølgende behandling**

BMS finder det nødvendigt at fremhæve Medicinrådets tilgang til opgørelse af efterfølgende behandling i omkostningsanalysen, der medfører et ubalanceret resultat.

I BMS' base case er efterfølgende behandling ikke medtaget i omkostningsanalysen, da omkostninger hertil ikke forventes at variere betydeligt i dansk klinisk praksis uagtet om en patient modtager nivo+rela eller nivolumab+ipilimumab (herefter nivo+ipi). For at undersøge betydningen af efterfølgende behandling, har BMS inkluderet en følsomhedsanalyse, hvor omkostningerne til efterfølgende behandlinger bliver inkluderet på baggrund af, hvad patienterne modtog som efterfølgende behandling i de to relevante studier. Resultatet heraf viser, at inklusion af efterfølgende behandling medfører lavere omkostninger for nivo+rela sammenlignet med nivo+ipi. I studierne modtog en sammenlignelig andel af patienterne efterfølgende systemisk behandling. Forskellen i omkostningerne til efterfølgende behandling drives primært af ipilimumab monoterapi og BRAF/MEK inhibitors. Selvom en større andel af nivo+rela patienter efterfølgende modtog ipilimumab monoterapi betyder den større andel af nivo+ipi patienter, der modtog BRAF/MEK inhibitors, at omkostningerne til efterfølgende behandling samlet er størst for nivo+ipi.

Medicinrådet vælger i vurderingsrapporten ikke at beskrive BMS' tilgang til at opgøre omkostninger til efterfølgende behandling på trods af, at den er baseret på faktiske studiedata. Medicinrådet vælger i stedet at benytte egne antagelser for efterfølgende behandling, uden at referere til studiedata. Medicinrådet antager, at efterfølgende behandling udelukkende består af ipilimumab monoterapi for nivo+rela og udelukkende af pembrolizumab for nivo+ipi. Dette på trods af at både guidelines beskriver BRAF/MEK inhibitors som efterfølgende behandling til nivo+ipi og data fra Dansk Melanom Database viser, at BRAF/MEK inhibitors i dansk klinisk praksis er efterfølgende behandling i over 50% af tilfældene (DAMMED rapport 2023). Ved at udelade BRAF/MEK inhibitors i omkostningsanalysen beregner man altså en urealistisk lav omkostning ved efterfølgende behandling for nivo+ipi. I Medicinrådets analyse antages det, at over dobbelt så mange patienter vil kunne modtage efterfølgende behandling efter nivo+rela. Denne antagelse er ikke underbygget af argumenter og afspejler ikke studiedata, der netop viser at andelen var sammenlignelig mellem de to behandlinger. Medicinrådet inkluderer ipilimumab monoterapi som efterfølgende behandling for nivo+rela, og antager her, at patienterne vil modtage det samme antal doser ipilimumab, som patienter der modtager ipilimumab i 1. linje. Det er alt andet lige usandsynligt, at

patienter i 2. linje vil kunne tolerere samme antal doser, hvilket betyder at omkostningerne til efterfølgende behandling for nivo+rela yderligere overestimeres. Medicinrådet beskriver i vurderingsrapporten, at omkostningerne til efterfølgende behandling er usikre, men vælger fortsat at medtage dem i deres hovedanalyse.

2) **Vedr. Medicinrådets ændring af dosis i den sundhedsøkonomiske analyse**

Medicinrådet vælger i deres sundhedsøkonomiske analyse at ændre dosis for nivolumab monoterapi, så denne tager udgangspunkt i andelen af patienter fra RELATIVITY-047 med en vægt < 80 kg. BMS anerkender Medicinrådets praksisændring for udregning af vægten, selvom det for de fleste tidligere vurderinger har været gennemsnitsvægt fra studiet. Samtidig antager BMS at samme praksis for udregning af vægt vil blive benyttet fremadrettet for andre lægemidler, så Medicinrådet ikke forskelsbehandler.

Samlet betyder Medicinrådets tilgang, at omkostningerne til efterfølgende behandling systematisk bliver overestimeret for nivo+rela sammenlignet med nivo+ipi. Dertil kommer praksisændringen for udregningen af vægten for nivolumab monoterapi, som øger omkostningerne til nivo+rela.

BMS anmoder derfor om, at vurderingsrapporten justeres så hovedanalysen afspejler den faktiske usikkerhed omkring efterfølgende behandling, der derfor bør udelades. En følsomhedsanalyse kan benyttes til at analysere usikkerheden, men denne bør afspejle data og dansk klinisk praksis. Det vil sige, at en sammenlignelig andel af patienterne modtager efterfølgende behandling og BRAF/MEK inhibitors inkluderes.

Vi håber, Medicinrådet vil tage vores kommentarer i betragtning og justere vurderingsrapporten i overensstemmelse hermed for at sikre en retvisende evaluering af nivo+rela til behandling af fremskredent melanom hos PD-L1-negative patienter.

Med venlig hilsen,

Nicolai Fik
Market Access Direktør
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23.04.2025
DBS/KLE

Forhandlingsnotat

Dato for behandling i Medicinrådet	21.05.2025
Leverandør	Bristol Myers Squibb
Lægemiddel	Opdualag (nivolumab + relatlimab)
Ansøgt indikation	Fremskredent melanom hos PD-L1-negative patienter.
Nyt lægemiddel / indikationsudvidelse	Nyt lægemiddel (kombinations lægemiddel)

Prisinformation

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

Tabel 1: Forhandlingsresultat betinget af en anbefaling i Medicinrådet

Lægemiddel	Styrke (pakningsstørrelse)	AIP (DKK)	Nuværende SAIP, (DKK)	Nuværende rabat ift. AIP	Forhandlet SAIP (DKK)	Forhandlet rabat ift. AIP
Opdualag	240+80 mg, 1stk. htgl.	49.540,18	[redacted]	[redacted]	[redacted]	[redacted]

Prisen er betinget af Medicinrådets anbefaling.

Aftaleforhold

Amgros har allerede en aftale på Opdualag og i aftalen kan prisen justeres. [redacted]

Konkurrencesituationen

Nuværende behandling af patienter med fremskredent melanom der er PD-L1 negative, og som ikke har modtaget tidligere systemisk behandling, er for langt de fleste patienter kombinationsbehandling med Opdivo (nivolumab) + Yervoy (ipilimumab). Denne behandling efterfølges af vedligeholdelsesbehandling med Opdivo monoterapi.

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

Lægemiddel	Styrke	Pakningsstørrelse	Dosering	Pris pr. pakning (SAIP, DKK)	Lægemiddeludgift (SAIP, DKK)		
					Pr. stof	Total periode	Total 12 måneder
Opdualag	240 mg nivolumab + 80 mg relatlimab	1 stk.	480 mg nivolumab og 160 mg relatlimab i.v. hver 4. uge*	[redacted]			[redacted]
Opdivo - Yervoy Uge 1-12	Opdivo: 40 mg/4 ml	1 stk.	1 mg/kg nivolumab i.v. og 3 mg/kg ipilimumab i.v. hver 3. uge i 12 uger*	[redacted]	[redacted]	[redacted]	[redacted]
	Yervoy: 5 mg/ml	10 ml		[redacted]	[redacted]		
Opdivo monoterapi	Opdivo: 40 mg/4 ml	1 stk.	6 mg/kg i.v. hver 4. uge fra uge 13*	[redacted]		[redacted]	

*Jf. udkast til vurderingsrapport, tabel 9 s. 40. Gennemsnitsvægt for behandlede patienter er 66,3 kg. jf. rapporten s. 40.

Status fra andre lande

Tabel 4: Status fra andre lande

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

Konklusion

[redacted]

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

Color scheme for text highlighting	
Color of highlighted text	Definition of highlighted text
	Confidential information
[Other]	[Definition of color-code]

Contact information

Contact information	
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Table of contents

Tables and Figures

Abbreviations

Abbreviation	Description	Abbreviation	Description
BIRC	Blinded Independent Review Committee	IPTW	Inverse Probability of Treatment Weighting
BMS	Bristol Myers Squibb	ITC	Indirect Treatment Comparison
BOR	Best Overall Response	ITT	Intention-to-treat
BRAF	B-Raf Proto-Oncogene	LAG	Lymphocyte Activation Gene
CHMP	Committee for Medicinal Products for Human Use	LDH	Lactate Dehydrogenase Levels
CTCAE	Common Terminology Criteria for Adverse Events	MHC	Major Histocompatibility
CTLA	Cytotoxic T-lymphocyte associated protein 4	NA	Not Applicable / Not available
DBL	Data Base Lock	NOMA	Norwegian Medical Products Agency
DCO	Data Cut Off	ORR	Objective Response Rate
DKK	Danish Krona	OS	Overall Survival
DMC	Danish Medicines Council	PFS	Progression Free Survival
DMCG	Danske Multidisciplinære Cancer Grupper	PPP	Pharmacy Purchasing Price
DRG	Disease Related Group	PRO	Patient Reported Outcomes
ECOG	Eastern Cooperative Oncology Group	QALY	Quality Adjusted Life Years
EMA	European Medicines Agency	SAE	Serious Adverse Events
EORTC	European Organization for Research and Treatment of Care	SLR	Systematic Literature Review

FACT-M	Functional Assessment of Cancer Therapy-Melanoma	SMD	Standardized Mean Difference
FDC	Fixed Dose Combination	TCR	T-Cell Receptor
HSUV	Health State Utility Value	TOI	Trial Outcome Index
ICER	Incremental Cost Effectiveness Ratio	ULN	Upper Limit of Normal
INV	Investigator	VAS	Visual Analogue Scale
IPD	Individual Patient-level Data		
IPT	Inverse Probability of Treatment		

1. Regulatory information on the medicine

Overview of the medicine	
Proprietary name	Opdualag™
Generic name	Nivolumab and relatlimab
Therapeutic indication as defined by EMA	Nivolumab and relatlimab is indicated for the first-line treatment of advanced (unresectable or metastatic) melanoma in adults and adolescents 12 years of age and older with tumour cell PD-L1 expression < 1%. The market authorisation in Europe is valid since September 2022.
Marketing authorization holder in Denmark	Bristol Myers Squibb
ATC code	L01FY02
Combination therapy and/or co-medication	No
(Expected) Date of EC approval	15/09/2022
Has the medicine received a conditional marketing authorization?	No
Accelerated assessment in the European Medicines Agency (EMA)	N/A

Overview of the medicine	
Orphan drug designation (include date)	No
Other therapeutic indications approved by EMA	No
Other indications that have been evaluated by the DMC (yes/no)	No, no other indications have been evaluated by the DMC.
Joint Nordic assessment (JNHB)	Are the current treatment practices similar across the Nordic countries (DK, FI, IS, NO, SE)? Yes. Is the product suitable for a joint Nordic assessment? No. If no, why not? This is a re-assessment and there are ongoing processes in the other Nordic countries which is why a Joint Nordic assessment is not applicable.
Dispensing group	BEGR
Packaging – types, sizes/number of units and concentrations	One vial of 20 mL (12 mg/ml nivolumab + 4 mg/ml relatlimab) contains 240 mg of nivolumab and 80 mg of relatlimab.

2. Summary table

Summary	
Therapeutic indication relevant for the assessment	Nivolumab and relatlimab, hereafter referred to as nivo+rela, is indicated for the first-line treatment of advanced (unresectable or metastatic) melanoma in adults and adolescents 12 years of age and older with tumour cell PD-L1 expression < 1%.
Dosage regiment and administration	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 an intravenous infusion over 30 minutes. This dose is established for adolescent patients weighing at least 30 kg.
Choice of comparator	The comparator is nivolumab and ipilimumab, hereafter referred to as nivo+ipi, a PD-1 and CTLA-4 inhibitor. According to the Danish treatment guidelines for melanoma [1, 2], the recommended standard of care for the relevant population of this application is combination checkpoint immunotherapy with PD-1 plus CTLA-4 inhibitors.
Prognosis with current treatment (comparator)	Melanoma accounts for most deaths caused by cutaneous cancers. While survival rates are high for localized melanoma,

Summary	
	2-year survival rates drop to 18-40% for metastatic disease (estimated survival rates for stage IV) [3].
Type of evidence for the clinical evaluation	Due to lack of head-to-head trials comparing nivo+rela and nivo+ipi regimens, the clinical evaluation is based on the indirect treatment comparison (ITC) by Long et al. that utilise patient-level data from RELATIVITY-047 and CheckMate 067 trials [4]
Most important efficacy endpoints (Difference/gain compared to comparator)	The estimated hazard ratio (HR) (95% CI) for overall survival (OS) in the ITC analysis of nivo+rela versus nivo+ipi was 1.01 (0.74, 1.37); for progression free survival (PFS) the estimated HR was 1.16 (0.89, 1.51) and for objective response rate (ORR) the estimated HR was 1.22 (0.89, 1.68).
Most important serious adverse events for the intervention and comparator	All-causality serious adverse events (SAEs) were reported in 39.07% of the patients treated with nivo+rela and 73.78% of the patients treated with nivo+ipi (absolute difference of 34.70%). Drug-related SAEs were reported in 16.90% of the patients treated with nivo+rela and 50.65% of the patients treated with nivo+ipi (absolute difference of 33.74%).
Impact on health-related quality of life	Clinical documentation: No ITC was conducted for the health-related quality of life (HRQoL). The RELATIVITY-047 trial measured HRQoL with the EuroQol Five-dimension three levels (EQ-5D-3L), the derived utility index and visual analogue scale (EQ-VAS) and the Functional Assessment of Cancer Therapy-Melanoma (FACT-M) questionnaire. The CheckMate 067 trial analysed HRQoL through the European Organization for Research and Treatment of Care Core Quality of Life (EORTC QLQ-C30) and EQ-5D-3L utility index and EQ-VAS. In RELATIVITY-047, EQ-5D-3L utility index scores for both treatment groups showed slight improvements, with no significant difference between nivo+rela and nivolumab alone, and changes stayed within clinically meaningful thresholds. The least squares (LS) mean changes from baseline, showed no significant differences between nivo+rela and nivolumab indicating that melanoma-specific QoL measured by FACT-M was relatively stable. For CheckMate 067 the EQ-5D-3L utility index showed minimal and non-significant changes between nivo+ipi and nivolumab alone. The VAS score declined slightly more in the nivo+ipi group, but the difference was not clinically meaningful. The HQoL remained generally stable across treatment arms, with the EORTC QLQ-C30. Health economic model: Since the type of economic analysis submitted is a cost-minimisation analysis, the impact on health-related quality of life is not included, but the HRQoL outcomes are presented descriptively for the respective studies.

Summary	
Type of economic analysis that is submitted	A cost-minimisation analysis of the intervention (nivo+rela) and the comparator (nivo+ipi) was conducted.
Data sources used to model the clinical effects	No clinical effect was modelled as the efficacy is considered equivalent between intervention (nivo+rela) and the comparator (nivo+ipi) [4].
Data sources used to model the health-related quality of life	N/A
Life years gained	N/A
QALYs gained	N/A
Incremental costs	502,795 DKK
ICER (DKK/QALY)	N/A
Uncertainty associated with the ICER estimate	N/A
Number of eligible patients in Denmark	100 new patients would be eligible for treatment, of which approximately [redacted] are expected to receive nivo+rela each year in Denmark.
Budget impact (in year 5)	25,132,825 DKK

3. The patient population, intervention, choice of comparator(s) and relevant outcomes

3.1 The medical condition

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 [5]. 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 [6]. In some cases, melanoma is diagnosed as metastatic without a known primary site, which is called unknown primary melanoma [7]. 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 tumorigenesis [8].

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 [6]. 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 1 [9].

Table 1 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 [9] (The original and primary source for this information is the AJCC Cancer Staging Manual, 8th Edition [2017], published by Springer International Publishing [10]).

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). Data reported from the Danish melanoma database shows that the percentage of patients with melanoma in the metastatic stage (stage IV) is stable over time in Denmark [11, 12]. The percentage of patients with stage IV melanoma reported in 2023 in Denmark is 0.4% [12].

Worldwide, most patients with melanoma can expect to survive more than five years after diagnosis; this is also seen in Denmark. However, the survival rate for patients with an advanced stage disease is lower than for those with earlier stages [13]. Data from Denmark on survival by the AJCC's 8th edition stages confirm that survival rates decrease in the advanced stages of the disease (see Table 2).

Table 2 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: [3]

3.2 Patient population

The relevant Danish patient population for this application consists of adults and adolescents 12 years of age and older with advanced (unresectable or metastatic) melanoma with tumour cell programmed death-ligand 1 (PD-L1) expression <1% that are eligible for first line treatment (1L).

In Denmark, melanoma is the fourth most common cancer in women and the fifth most common in men [14]. The average annual incidence between 2017 and 2021 was 1,405 new cases in women and 1,333 new cases in men [15]. The prevalence of the disease in 2022 was approximately 40,295 patients [14]. The most recent incidence and prevalence data from the NORDCAN database for melanoma in Denmark is from 2022: data from 2018 to 2022 are presented in Table 3 [14].

In the DMC protocol for treatment guidelines for first line treatment for unresectable or metastatic malignant melanoma 2020 [16], 100 patients are estimated to be PD-L1<1% yearly. Nivo+rela will be an alternative treatment option for those patients who are candidates to nivo+ipi due to PD-L1<1%, but have no central nervous system metastases. In addition, patients who today receive PD-1 inhibitor monotherapy due to e.g. fragile general condition and low/no tolerability of nivo+ipi, are also candidates for nivo+rela as an alternative treatment option. In total, 100 patients per year are eligible for nivo+rela, as shown in Table 4, however, the treatment choice will depend on the clinical assessment of the patient.

Table 3 Incidence and prevalence in the past 5 years (2018-2022)

Year	2018	2019	2020	2021	2022
Incidence in Denmark	2,805	2,750	2,711	2,910	3,029
Prevalence in Denmark	33,330	35,033	36,684	38,494	40,295

Source: [14]

Table 4 Estimated number of patients eligible for treatment

Year	Year 1	Year 2	Year 3	Year 4	Year 5
Number of patients in Denmark who are eligible for nivo+rela treatment in the coming years	100	100	100	100	100

Source: [16]

3.3 Current treatment options

Metastatic melanoma is the most aggressive skin cancer, and its incidence has been rising over time. Metastatic melanoma is the leading cause of death in the form of cutaneous malignancy [3, 8, 15, 17, 18]. In Denmark, the 4-year survival for patients with stage IV, is between 40% and 50% [12]. In the last few years, novel targeted therapies and checkpoint immunotherapy have improved overall survival (OS) and progression-free survival (PFS) rates [19]. Unfortunately, some patients are still only experiencing limited OS benefit [19].

In October 2018 the Danish Medicines Council decided to initiate the process of producing a national treatment guideline for unresectable or metastatic melanoma [20]. The process has been on hold since 2021. However, the Danish Cancer Society and the Danish Multidisciplinary Cancer Group (DMCG) provide recommendations for this patient population [1, 2]. For the treatment of metastatic or unresectable melanoma, immunotherapy with PD-1 inhibitors (nivolumab monotherapy and pembrolizumab monotherapy), programmed cell death protein 1 (PD-1) plus cytotoxic T lymphocyte antigen 4 (CTLA-4) inhibitors (nivolumab and 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 DMCG recommend the following [1, 2]:

- **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 can 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 can 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 can be considered; in patients with non-aggressive disease (small tumour burden, slow disease growth, comorbidity and/or fragile general condition), a PD-1 inhibitor can be used.

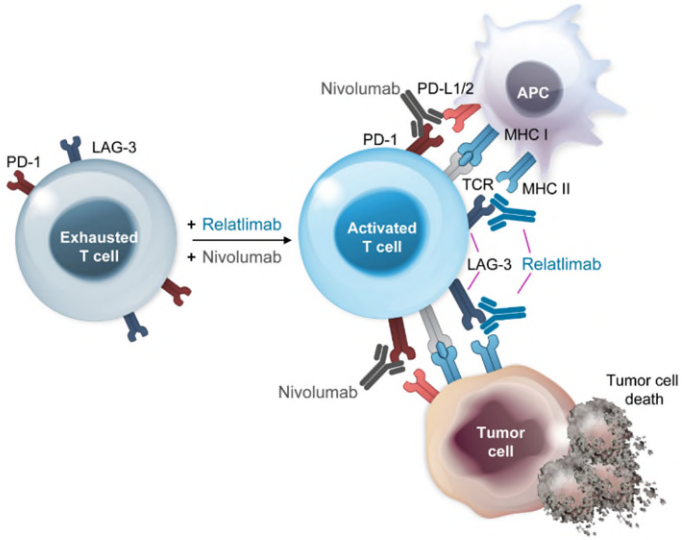
For second line (2L) treatment of unresectable or metastatic melanoma, different options are available depending on factors such as: severity of disease, physician assessment, patient's health state and preferences. Treatment options include targeted therapy, hyperthermic regional perfusion therapy in arms or legs, or palliative treatment with chemotherapy or radiotherapy [1].

3.4 The intervention

Nivo+rela received a positive opinion from the Committee for Medicinal Products for Human Use (CHMP) in July 2022 and obtained approval by the European Commission in September 2022 [21]. 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% [21].

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 programmed death ligand 2 (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 [22]. Relatlimab is an immunoglobulin G4 lymphocyte activation gene (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 1) [23, 24].

Figure 1 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: [23]

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. An overview of nivo+rela is presented in Table 5.

Table 5 Overview of the intervention

Overview of intervention	
Therapeutic indication relevant for the assessment	Nivolumab and relatlimab is indicated for the first-line treatment of advanced (unresectable or metastatic) melanoma in adults and adolescents 12 years of age and older with tumour cell PD-L1 expression < 1%.
Method of administration	Intravenous infusion
Dosing	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 an intravenous infusion over 30 minutes. This dose is established for adolescent patients weighing at least 30 kg [25].
Dosing in the health economic model (including relative dose intensity)	The cost-minimisation analysis uses a dose of nivo+rela of 480 mg nivo + 160 mg rela per administration. The mean number of doses (11.4) received by patients in RELATIVITY-047 is used in the cost-minimisation analysis (see section 11).

Overview of intervention	
Should the medicine be administered with other medicines?	No
Treatment duration / criteria for end of treatment	Treatment with nivo+rela should be continued as long as clinical benefit is observed or until treatment is no longer tolerated by the patient. Based on Danish clinical practice for immunotherapy and the first DMC assessment of nivo+rela, a maximum duration of treatment of two years is expected [26].
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 (e.g. companion diagnostics). How are these included in the model?	Testing for PD-L1 is standard practice for both stage IV and inoperable stage III melanoma and used for treatment decision making.. Thus, the test is not included in the cost-minimisation [27].
Package size(s)	1 vial of 20 ml containing 240 mg nivolumab and 80 mg relatlimab.

3.4.1 The intervention in relation to Danish clinical practice

Nivo+rela is expected to be used as a 1L treatment option for adults and adolescents 12 years of age and older with advanced (unresectable or metastatic) melanoma with tumour cell PD-L1 expression < 1% in the 1L setting in Denmark. The introduction of nivo+rela will be an additional treatment option in the existing treatment algorithm.

3.5 Choice of comparator(s)

Nivo+ipi is used as the comparator in this application since this is the current standard of care in patients with metastatic or unresectable melanoma with PD-L1 negative expression (<1%) and regardless of BRAF status. In accordance with the Danish treatment guidelines for melanoma [1, 2] (see Section 3.3), treatment with a PD-1 inhibitor (nivolumab monotherapy or pembrolizumab monotherapy) should be considered the 1L option for patients with unresectable or metastatic melanoma that do not tolerate treatment with nivo+ipi. The present application focuses on nivo+ipi as the comparator.

An overview of nivo+ipi is presented in Table 6.

Table 6 Overview of the comparator

Overview of comparator	
Generic name	Nivolumab / ipilimumab
ATC code	L01FF01 / L01FX04
Mechanism of action	Nivolumab binds to the PD-1 receptor and blocks its interaction with PD-L1 and PD-L2. The PD-1 receptor is a negative regulator of T-cell activity that has been shown to be involved in the control of T-cell immune responses. Engagement of PD-1 with the ligands PD-L1 and PD-L2 results in inhibition of T-cell proliferation and cytokine secretion. Nivolumab potentiates T-cell responses, including anti-tumour responses, through blockade of PD-1 binding to PD-L1 and PD-L2 ligands. Cytotoxic T lymphocyte antigen 4 (CTLA-4) is a key regulator of T-cell activity. Ipilimumab is a CTLA-4 immune checkpoint inhibitor that blocks T-cell inhibitory signals induced by the CTLA-4 pathway, increasing the number of reactive T-effector cells which mobilize to mount a direct T-cell immune attack against tumour cells. CTLA-4 blockade can also reduce T-regulatory cell function, which may contribute to an anti-tumour immune response. Ipilimumab may selectively deplete T-regulatory cells at the tumour site, leading to an increase in the intratumoural T-effector/T-regulatory cell ratio which drives tumour cell death. Combined nivolumab (anti-PD-1) and ipilimumab (anti-CTLA-4) mediated inhibition results in improved anti-tumour responses in metastatic melanoma.
Method of administration	Intravenous infusion

Overview of comparator	
Dosing	In adults and adolescents 12 years of age and older and weighing at least 50 kg, the recommended dose is 1 mg/kg nivolumab over 30 minutes in combination with 3 mg/kg ipilimumab over 30 minutes administered intravenously every 3 weeks for the first 4 doses. This is then followed by a second phase in which nivolumab monotherapy is administered intravenously at either 240 mg every 2 weeks over 30 minutes or at 480 mg every 4 weeks over 60 minutes. For the monotherapy phase, the first dose of nivolumab should be administered: • 3 weeks after the last dose of the combination of nivolumab and ipilimumab if using 240 mg every 2 weeks; or • 6 weeks after the last dose of the combination of nivolumab and ipilimumab if using 480 mg every 4 weeks. In adolescents 12 years of age and older and weighing less than 50 kg, the recommended dose is 1 mg/kg nivolumab over 30 minutes in combination with 3 mg/kg ipilimumab over 30 minutes administered intravenously every 3 weeks for the first 4 doses. This is then followed by a second phase in which nivolumab monotherapy is administered intravenously at either 3 mg/kg every 2 weeks over 30 minutes or 6 mg/kg every 4 weeks over 60 minutes. For the monotherapy phase, the first dose of nivolumab should be administered: • 3 weeks after the last dose of the combination of nivolumab and ipilimumab if using 3 mg/kg every 2 weeks; or • 6 weeks after the last dose of the combination of nivolumab and ipilimumab if using 6 mg/kg every 4 weeks [28].
Dosing in the health economic model (including relative dose intensity)	in the cost-minimisation analysis the dosing of nivolumab+ipilimumab is nivolumab 1 mg/kg and ipilimumab 3 mg/kg in the combination phase and in the nivo monotherapy phase, 6 mg/kg once every four weeks. The mean number of doses received by patients in CheckMate-067 is used in the cost-minimisation analysis, 3.1 doses in nivo+ipi combination phase and 6.25 doses in the nivo monotherapy phase (see section 11).
Should the medicine be administered with other medicines?	No

Overview of comparator	
Treatment duration/ criteria for end of treatment	Treatment with nivolumab, either as a monotherapy or in combination with ipilimumab or other therapeutic agents, should be continued as long as clinical benefit is observed or until treatment is no longer tolerated by the patient. In Danish clinical practice the maximum treatment duration is two years [2].
Need for diagnostics or other tests (i.e. companion diagnostics)	Tumour cell PD-L1 expression, is currently assessed in Danish clinical practice and recommended to be assessed by the Danish Multidisciplinary Cancer Group in the case of stage IV disease [27].
Package size(s)	Nivolumab 10 mg/mL concentrate for solution for infusion: • 40 mg/4 mL • 100 mg/10 mL • 120 mg/12 mL • 240 mg/24 mL Ipilimumab 5 mg/ml concentrate for solution for infusion: • 50 mg/10 ml • 200 mg/40 ml

3.6 Cost-effectiveness of the comparator(s)

The relevant comparator for this assessment, combination treatment with nivo+ipi is indicated for the treatment of advanced (unresectable or metastatic) melanoma and has not been assessed by the DMC as a treatment option in metastatic melanoma. However, the current treatment guidelines in Denmark for patients with metastatic or unresectable melanoma with negative PD-L1 expression (<1%) recommend combination immunotherapy with PD-1 plus CTLA-4 inhibitors, such as nivo+ipi [2]. This recommendation by DMCG has been valid since the guidelines were published in 2019 [29].

Nivo+ipi have previously been assessed by “Nye metoder” (NOMA) in Norway [30] and by the National Institute for Health and Care Excellence (NICE) [31] for use in advanced melanoma. Both NOMA and NICE recommended this combination treatment for advanced melanoma [30, 31]. Based on these previous assessments, BMS finds it reasonable to assume treatment with nivo+ipi, as per current Danish clinical practice, is cost-effective. Thus, no supplementary analysis is included in this application.

3.7 Relevant efficacy outcomes

3.7.1 Definition of efficacy outcomes included in the application

The key efficacy outcomes included in this submission are OS, PFS and objective response rate (ORR) (Table 7).

Table 7 Efficacy outcome measures relevant for the application

Outcome measure	Time point*	Definition	How was the measure investigated/method of data collection
Overall survival (OS) [4]	Minimum follow up 33 months	Time between randomization and death	
Progression-free survival (PFS) [4]	Minimum follow up 33 months	Date of first progression or death due to any cause, whichever occurred first	BIRC and Investigator assessed (RECIST v1.1)
Objective response rate (ORR) [4]	Minimum follow up 33 months	Proportion of patients achieving partial response or better as best overall response	Investigator assessed

* Time point for data collection used in analysis (follow up time for time-to-event measures)

Abbreviations: BIRC, Blinded independent review committee, ITC, indirect treatment comparison

Validity of outcomes

The key efficacy outcomes presented in this submission are relevant endpoints used to evaluate clinical efficacy in oncology, including melanoma. OS is universally recognized as being unambiguous, unbiased, with a defined endpoint of paramount clinical relevance, and positive results provide confirmatory evidence that a given treatment extends the life of a patient. PFS is commonly used in oncology research as a direct or surrogate measure of clinical benefit for drug approvals. OS is the gold standard primary endpoint to evaluate the outcome of any drug, biologic, intervention, or procedure that is assessed in oncologic clinical trials. ORR is commonly used as an endpoint to assess the clinical benefit for drug approvals.

4. Health economic analysis

A cost-minimisation analysis was performed for this submission based on the results of an indirect treatment comparison (ITC), showing that the efficacy of the nivo+rela and nivo+ipi are similar (See further section 7).

4.1 Model structure

The cost-minimisation analysis compared the costs associated with treatment with nivo+rela and nivo+ipi in patients with previously untreated metastatic or unresectable melanoma and with tumour cell PD-L1 expression < 1%. The following treatment-associated costs were included in the analysis:

- Medicine acquisition costs
- Medicine administration costs
- Management of adverse events
- Patient time and transportation costs

All other costs (e.g., disease management costs, subsequent treatment costs and palliative care costs) were based on similar efficacy assumed to be equivalent between nivo+rela and nivo+ipi and were therefore not included in the analysis.

4.2 Model features

Table 8 shows the features of the economic model.

Table 8 Features of the economic model

Model features	Description	Justification
Patient population	Adults and adolescents 12 years of age and older with previously untreated metastatic or unresectable melanoma and with tumour cell PD-L1 expression < 1%.	Same population as described in section 3.2.
Perspective	Limited societal perspective.	According to DMC guidelines.
Time horizon	One year.	The cost-minimisation analysis compares costs based on average number of doses received from the Relativity-047 trial and the CM-067 trial. As the average treatment durations were less than a year, all relevant cost differences are captured within the one-year time horizon.
Cycle length	NA.	NA.
Half-cycle correction	NA.	NA.
Discount rate	No discount rate was applied.	The time horizon is 1 year.
Intervention	Opdualag® (nivo+rela)	NA.

Model features	Description	Justification
Comparator(s)	Nivo+ipi.	See section 3.5.
Outcomes	Total costs and difference in the costs associated with treatment with nivo+rela and nivo+ipi.	These are the standard outcomes in a cost-minimisation model.

Abbreviations: NA=not applicable.

5. Overview of literature

5.1 Literature used for the clinical assessment

No randomized, head-to-head trial comparing nivo+rela (the intervention) and nivo+ipi (the comparator) exists. RELATIVITY-047 and CheckMate 067 are the only relevant trials in the comparison of nivo+rela and nivo+ipi in adult patients with previously untreated, unresectable or metastatic melanoma with PD-L1 expression levels <1% [32, 33].

As the data owner of both trials, BMS has access to the necessary individual patient-level data (IPD). A recently published ITC by Long et al. [4] supported by BMS, using IPD from both trials includes a comprehensive analysis of the comparison between nivo+rela and nivo+ipi. The literature included in the clinical assessment is not based on a systematic literature review (SLR), as the ITC represents the most relevant comparison of these treatments.

In this assessment, the focus is on the PD-L1 <1% subgroup results, representing the population in scope. Additionally, some results in this assessment are based on degrees of freedom (DoF) adjustments, following the framework used in Long et al. [4], ensuring consistency and reliability in the analysis.

An overview of the literature for efficacy and safety (RELATIVITY-047 and CheckMate 067) is presented in Table 9.Table 9 Relevant literature included in the assessment of efficacy and safety

Reference (Full citation incl. reference number)*	Trial name*	NCT identifier	Dates of study (Start and expected completion date, data cut-off and expected data cut-offs)	Used in comparison of*
Long et al. Overall Survival and Response with Nivolumab and Relatlimab in Advanced Melanoma. NEJM Evid. 2023	RELATIVITY-047	NTC03470922	Study start (Actual): 2018-04-11 Study Completion (Estimated): 2025-12-16	Nivo+rela arm used for ITC for the PD-L1 <1% subgroup

Reference (Full citation incl. reference number)*	Trial name*	NCT identifier	Dates of study (Start and expected completion date, data cut-off and expected data cut-offs)	Used in comparison of*
Apr;2(4):EVIDoa2200239 [32]			Data cut-off 2021-10-28	
Tawbi HA, et al Relatlimab and Nivolumab versus Nivolumab in Untreated Advanced Melanoma. N Engl J Med. 2022 Jan 6;386(1):24-34. doi: 10.1056/NEJMoa2109970. PMID: 34986285; PMCID: PMC9844513. [34]	RELATIVITY-047	NTC03470922	Study start (Actual): 2018-04-11 Study Completion (Estimated): 2025-12-16 Data cut-off 2021-03-09	Nivo+rela arm used for ITC for the PD-L1 <1% subgroup
Wolchok et al, Long-Term Outcomes With Nivolumab Plus Ipilimumab or Nivolumab Alone Versus Ipilimumab in Patients With Advanced Melanoma, 2021 [33]	CheckMate 067	NTC01844505	Study start (Actual): 2013-06-11 Completion (Actual): 2024-04-19	Nivo+ipi arm used for ITC for the PD-L1 <1% subgroup
Larkin et al, Combined Nivolumab and Ipilimumab or Monotherapy in Untreated Melanoma, 2015 [35]	CheckMate 067	NTC01844505	Study start (Actual): 2013-06-11 Completion (Actual): 2024-04-19	Nivo+ipi arm used for ITC for the PD-L1 <1% subgroup
Long et al, First-Line Nivolumab Plus Relatlimab Versus Nivolumab Plus Ipilimumab in Advanced Melanoma: An Indirect Treatment Comparison Using RELATIVITY-047 and CheckMate 067 Trial Data, 2024 [4]	RELATIVITY-047, CheckMate 067	NTC03470922, NTC01844505	Data cutoff RELATIVITY-047: 2023-10-19 Database lock Check Mate 067: 2021-11-12, follow-up time truncated at 2017-04-13 to align the two trials	Nivo+rela versus nivo+ipi, population. for the PD-L1 <1% subgroup

* If there are several publications connected to a trial, include all publications used.

5.2 Literature used for the assessment of health-related quality of life

In the RELATIVITY-047 trial health related quality of life (HRQoL) data were collected by the EQ-5D-3L descriptive system and the EQ VAS and in addition the disease specific instrument Functional Assessment of Cancer Therapy-Melanoma (FACT-M). In the CheckMate 067 trial HRQoL data were collected through EQ-5D-3L and the EQ VAS and the disease specific instrument, European Organization for Research and Treatment of Care Core Quality of Life (EORTC QLQ-C30).

A methodological meaningful comparison between the trials was not applicable, this assessment will therefore include HRQoL results for RELATIVITY-047 (for nivo+rela) and CheckMate 067 (for nivo+ipi), both compared to nivolumab monotherapy respectively. An overview of the relevant literature included in the documentation of HRQoL is shown in Table 10.

Table 10 Relevant literature included for (documentation of) health-related quality of life

Reference (Full citation incl. reference number)	Health state/Disutility	Reference to where in the application the data is described/applied
Schadendorf D, Tawbi H, Lipson EJ, Stephen Hodi F, Rutkowski P, Gogas H, Lao CD, Grob JJ, Moshyk A, Lord-Bessen J, Hamilton M, Guo S, Shi L, Keidel S, Long GV. Health-related quality of life with nivolumab plus relatlimab versus nivolumab monotherapy in patients with previously untreated unresectable or metastatic melanoma: RELATIVITY-047 trial. Eur J Cancer. 2023 Jul;187:164-173. doi: 10.1016/j.ejca.2023.03.014. Epub 2023 Mar 22. PMID: 37167764 [36]	N/A	See section 10
Schadendorf D, Larkin J, Wolchok J, Hodi FS, Chiarion-Sileni V, Gonzalez R, Rutkowski P, Grob JJ, Cowey CL, Lao C, Wagstaff J, Callahan MK, Postow MA, Smylie M, Ferrucci PF, Dummer R, Hill A, Taylor F, Sabater J, Walker D, Kotapati S, Abernethy A, Long GV. Health-related quality of life results from the phase III CheckMate 067 study. Eur J Cancer. 2017 Sep;82:80-91. doi: 10.1016/j.ejca.2017.05.031. Epub 2017 Jun 23. PMID: 28651159; PMCID: PMC5737813 [37]	N/A	See section 10

5.3 Literature used for inputs for the health economic model

A cost-minimisation analysis was conducted comparing drug acquisition costs, administration costs, adverse event cost and cost for patient and caregivers time and transportation. These costs were based on publicly available sources, i.e.

medicinpriser.dk [38] for the drug acquisition costs and for the administration cost as well as adverse event management the relevant DRG were used with the 2024 weight from Sundhedsdatastyrelsen [39, 40]. In addition, patient transportation cost and patient time were included, based on the unit costs from DMC, Værdisætning af Enhedsomkostninger, 2024 [41].

Table 11 Relevant literature used for input to the health economic model

Reference (Full citation incl. reference number)	Input/estimate	Method of identification	Reference to where in the application the data is described/applied
Publicly available sources/literature	Drug cost Administration cost Adverse event management Transportation cost & Patient time	According to DMC guidelines	Section 11

6. Efficacy

6.1 Efficacy of relatlimab plus nivolumab compared to nivolumab + ipilimumab for first-line treatment of advanced (unresectable or metastatic) melanoma in adults and adolescents 12 years of age and older with tumour cell PD-L1 expression < 1%

6.1.1 Relevant studies

The efficacy is based on the ITC published by Long et al. [4] that utilise trial data from RELATIVITY-047 and CheckMate 067. Data from RELATIVITY-047 were from the database lock (DBL) of October 19, 2023, with a minimum follow-up time of 33 months for the overall population and [redacted] months for nivo and nivo+rela in the PD-L1<1/non quantifiable population (BMS data on file [42]). For CheckMate 067 outcomes, a 10-year follow-up is available [43]. However, to make data comparable for the ITC, it was necessary to truncate data from CheckMate 067 at the DBL of November 12, 2021, with minimum follow-up time of 36 months. The Long et al. [4] ITC includes the ITT population of the two trials, with a subgroup analysis including PD-L1 <1%. As the focus in this application is on the subgroup with PD-L1 <1%, results from the ITC for that specific subgroup will be presented (BMS data on file [44]). An overview of the study designs for the respective studies, RELATIVITY-047 (nivo+rela) and CheckMAte-067 (nivo+ipi), included in the comparison are presented in Table 12. The studies are further described in detail in Appendix A. Efficacy results from the respective study are

presented in 6.1.4 and 6.1.5 and in section 7.1.3 the efficacy results from comparative analysis are presented.

No differences in survival outcomes between the nivo mono arms in CheckMate 067 and RELATIVITY-047 were observed in all randomized patients, despite any potential differences in subsequent treatment, due to different in chronologic timing of enrolment of the two trials (Long, et al. 2024). The same conclusions are assumed for the PDL1<1% patient population.

Table 12 Overview of study design for studies included in the comparison

Trial name, NCT-number (reference)	Study design	Study duration	Patient population	Intervention	Comparator	Outcomes and follow-up period
A Study of Relatlimab Plus Nivolumab Versus Nivolumab Alone in Participants With Advanced Melanoma (RELATIVITY-047) NCT03470922 [32, 34, 36]	Randomised (1:1), parallel assignment, quadruple masked, phase 2-3 trial	Treatment continued until the occurrence of disease progression, unacceptable adverse effects, or withdrawal of consent	12 years of age or older, had previously untreated, histologically confirmed, unresectable stage III or IV melanoma (RECIST 1.1), LAG-3 and PD-L1 expression, received specified treatment (see in [34])	Relatlimab + Nivolumab 160 mg of relatlimab and 480 mg of nivolumab in a fixed-dose combination. Administered in a single 60-minute intravenous infusion every 4 weeks	Nivolumab 480 mg of nivolumab. Administered in a single 60-minute intravenous infusion every 4 weeks	Progression Free Survival (PFS) From randomization to date of first documented tumour progression or death (up to approximately 33 months) Overall Survival (OS) From randomization to the date of death (up to approximately 3 years) Overall Response Rate (ORR) From randomization up to approximately 3 years
Phase 3 Study of Nivolumab or Nivolumab Plus Ipilimumab Versus Ipilimumab Alone in Previously Untreated Advanced	Randomised (1:1:1), parallel assignment, quadruple masked, phase 3 trial	Until documented disease progression, discontinuation due to toxicity, withdrawal of consent or the study end	18 years or older, histologically confirmed stage III (unresectable) or stage IV melanoma, with biomarker analysis.	Nivolumab 1 mg/kg plus ipilimumab 3 mg/kg once every 3 weeks (four doses) followed by nivolumab 3 mg/kg once every 2 weeks	Nivolumab 3 mg/kg once every 2 weeks, or Ipilimumab 3 mg/kg once every 3 weeks (four doses)	PFS: From randomization until disease progression or death, whichever occurred first (assessed up to February 2015, approximately 20 months) OS: From randomization to date of death (Assessed up to September 2016, approximately 39 months) Rate of Overall Survival, Time Frame: 6, 12, and 24 months Rate of Progression-Free Survival, Time Frame: 6, 12, and 24 months Objective Response Rate (ORR) Per Investigator Assessment: From randomization until date of disease progression or the date of subsequent

Trial name, NCT-number (reference)	Study design	Study duration	Patient population	Intervention	Comparator	Outcomes and follow-up period
Melanoma (CheckMate 067) NCT01844505 [33, 37, 45]			Treatment naïve patients. ECOG performance status (PS) 0 or 1			anti-cancer therapy, whichever occurs first (Assessed up to February 2015, approximately 20 months) Progression-Free Survival Based on PD-L1 Expression Level: From randomization until disease progression or death from any cause, whichever occurs first (Assessed up to September 2016, approximately 39 months)

6.1.2 Comparability of studies

The ITC by Long et al. [4] included a propensity score model to generate inverse probability of treatment weighting (IPTW), which adjusted for any imbalances in the distribution of baseline characteristics between the two trials. The distribution of baseline characteristics was compared between the weighted cohorts using a standardised mean difference (SMD) of <0.2 to indicate balance between treatments [4].

Patients were matched by baseline characteristics, and altogether 13 patients were excluded due to missing covariates [4]. Patient characteristics were weighed by geographic region, previous adjuvant therapy, and melanoma subtype, as prior they were unbalanced between the two treatments (SMD ≥0.2) and tumour PD-L1 expression approached the threshold (SMD = 0.18). After weighting, effective sample sizes were 339 for the nivo+rela group and 297 for the nivo+ipi group in the ITT population [4]. For the relevant population with PD-L1 <1% the effective sample sizes were 185 and 158, respectively.

PFS, OS, and ORR are presented in this assessment per subgroup PD-L1 <1%, (results presented in section 7.1.3).

6.1.2.1 Comparability of patients across studies

In Table 13 below, baseline data are presented separately from the respective trials for the ITT populations.

As the relevant patient population in this application consists of the subjects with PD-L1 <1%, the baseline characteristics amongst patients with PD-L1 <1%/non quantifiable before and after weighting are presented in Table 14.

In addition, as the comparative analysis of safety in this assessment is based on the ITT population, the patient baseline characteristics from the ITC for the unweighted and weighted data are presented in Table 15 [4].

Table 13 Baseline characteristics of patients in studies included in the comparative analysis of efficacy and safety (ITT population)

	RELATIVITY-047 [32]		CheckMate 067 [35]		
	Nivo+rela (n=355)	**Nivo (n=359)**	**Nivo (n=316)**	**Nivo+ipi (n=314)**	**Ipi (n=315)**
Age – median (range) yr	63 (20–94)	62 (21–90)	NR	NR	NR
Age – mean (range) yr	NR	NR	59 (25–90)	59 (18–88)	61 (18–89)
Female — no. (%)	145 (40.8)	153 (42.6)	114 (36.1)	108 (34.4)	113 (35.9)
ECOG Performance status — no. (%)					
0	236 (66.5)	242 (67.4)	238 (75.3)	230 (73.2)	224 (71.1)
1	119 (33.5)	117 (32.6)	77 (24.4)	83 (26.4)	91 (28.9)
2	NR	NR	1 (0.3)	0	0
PD-L1 expression					
>=1% (positive)	146 (41.1)	147 (40.9)	80 (25.3)	68 (21.7)	75 (23.8)
<1% (negative)	209 (58.9)	212 (59.1)	208 (65.8)	210 (66.9)	202 (64.1)
***BRAF* status — no. (%)**					

	RELATIVITY-047 [32]		CheckMate 067 [35]		
	Nivo+rela (n=355)	Nivo (n=359)	Nivo (n=316)	Nivo+ipi (n=314)	Ipi (n=315)
Mutation	136 (38.3)	139 (38.7)	100 (31.6)	101 (32.2)	97 (30.8)
Wild type / No mutation	219 (61.7)	220 (61.3)	216 (68.4)	213 (67.8)	218 (69.2)

Abbreviations: BRAF, B-Raf Proto-Oncogene; ECOG=Eastern Cooperative Oncology Group; NR=Not reported; PD-L1= Programmed Death-Ligand 1; yr= years; no=number

Table 14 Baseline characteristics of patients in the indirect treatment comparison included in the comparative analysis of efficacy (patients with PD-L1 <1%/non quantifiable) (BMS data on file [44])

	Before weighting[1]			After IPT-weighting [2,3]			Before weighting[1]			After IPT-weighting [2,3]		
	Nivo+rela (N = 204)	Nivo+ipi (N = 152)	SMD[b]	Nivo+rela (N = 185)	Nivo+ipi (N = 158)	SMD[b]	Nivo (047) N = 209	Nivo (067) N = 137	SMD[b]	Nivo (047) N = 178	Nivo (067) N = 148	SMD[b]
Demographics	60.41 ± 14.91		0.044			0.134			0.165			0.021
Age (years)		61.03 ± 12.96		59.73 ± 15.18	61.62 ± 12.87		60.91 ± 14.19	58.56 ± 14.22		59.93 ± 14.58	60.24 ± 14.36	
Sex			0.111			0.006			0.064			0.084
Male	115 (56.37%)	94 (61.84%)		58.18%	57.86%		120 (57.42%)	83 (60.58%)		58.73%	54.59%	
Female	89 (43.63%)	58 (38.16%)		41.82%	42.14%		89 (42.58%)	54 (39.42%)		41.27%	45.41%	

Geographic region			0.335			0.142			0.495			0.154
Rest of World	189 (92.65%)	124 (81.58%)		90.91%	86.42%		193 (92.34%)	102 (74.45%)		88.40%	83.04%	
USA	15 (7.35%)	28 (18.42%)		9.09%	13.58%		16 (7.66%)	35 (25.55%)		11.60%	16.96%	
Geographic region (detailed)[4], n (%)			0.975			0.908			1.102			0.938
Australia/New Zealand	16 (7.84%)	14 (9.21%)		7.36%	9.61%		16 (7.66%)	8 (5.84%)		7.26%	8.13%	
Europe	102 (50.00%)	100 (65.79%)		51.33%	70.17%		103 (49.28%)	80 (58.39%)		48.00%	63.77%	
Latin America	63 (30.88%)	0 (0.00%)		28.72%	0.00%		66 (31.58%)	0 (0.00%)		29.25%	0.00%	
USA/Canada	20 (9.80%)	32 (21.05%)		11.15%	15.94%		20 (9.57%)	47 (34.31%)		13.76%	27.07%	
Rest of World	3 (1.47%)	6 (3.95%)		1.45%	4.27%		4 (1.91%)	2 (1.46%)		1.73%	1.03%	
Disease characteristics			0.171			0.052			0.266			0.043
Time from advanced melanoma diagnosis until index date (years)	2.71 ± 4.29	3.40 ± 3.78		3.04 ± 4.76	3.26 ± 3.65		2.96 ± 4.37	4.38 ± 6.18		3.57 ± 5.32	3.80 ± 5.36	

Prior adjuvant therapy			0.484			0.166			0.664			0.242
Not received	184 (90.20%)	109 (71.71%)		85.53%	79.22%		196 (93.78%)	95 (69.34%)		89.71%	81.26%	
Received	20 (9.80%)	43 (28.29%)		14.47%	20.78%		13 (6.22%)	42 (30.66%)		10.29%	18.74%	
Metastasis stage			0.049			0.025			0.132			0.094
M0, M1 and normal LDH level	131 (64.22%)	94 (61.84%)		63.00%	64.21%		131 (62.68%)	77 (56.20%)		61.19%	56.56%	
M1 and elevated LDH level	73 (35.78%)	58 (38.16%)		37.00%	35.79%		78 (37.32%)	60 (43.80%)		38.81%	43.44%	
AJCC disease stage			0.067			0.073			0.230			
Stage III	20 (9.80%)	12 (7.89%)		8.13%	10.23%		11 (5.26%)	15 (10.95%)		5.96%	8.24%	0.118
Stage IV	184 (90.20%)	140 (92.11%)		91.87%	89.77%		197 (94.26%)	122 (89.05%)		93.74%	91.76%	
Melanoma subtype			0.421			0.254			0.419			0.195
Acral	27 (13.24%)	8 (5.26%)		9.60%	7.13%		29 (13.88%)	5 (3.65%)		10.03%	6.02%	
Cutaneous												

Mucosal	132 (64.71%)	121 (79.61%)		67.82%	78.25%		143 (68.42%)	113 (82.48%)		72.44%	78.82%	
Other	18 (8.82%)	15 (9.87%)		10.34%	8.22%		20 (9.57%)	13 (9.49%)		9.23%	9.72%	
	27 (13.24%)	8 (5.26%)		12.24%	6.40%		17 (8.13%	6 (4.38%)		8.31%	5.44%	
ECOG performance status			0.195			0.091			0.131			0.026
0	135 (66.18%)	114 (75.00%)		68.67%	72.83%		140 (66.99%)	100 (72.99%)		68.59%	69.78%	
≥ 1	69 (33.82%)	38 (25.00%)		31.33%	27.17%		69 (33.01%)	37 (27.01%)		31.41%	30.22%	
LDH category 1			0.046			0.009			0.112			0.079
≤ ULN	128 (62.75%)	92 (60.53%)		61.82%	62.25%		126 (60.29%)	75 (54.74%)		58.87%	54.94%	
> ULN	76 (37.25%)	60 (39.47%)		38.18%	37.75%		83 (39.71%)	62 (45.26%)		41.13%	45.06%	
LDH category 2			0.069			0.061			0.163			0.032
> 2 X ULN	21 (10.29%)	19 (12.50%)		12.36%	10.41%		22 (10.53%)	22 (16.06%)		12.63%	13.72%	
2 X ULN	183 (89.71%)	133 (87.50%)		87.64%	89.59%		187 (89.47%)	115 (83.94%)		87.37%	86.28%	
BRAF mutation			0.164			0.033			0.151			0.038
	125 (61.27%)	105 (69.08%)		63.64%	65.23%		130 (62.20%)	95 (69.34%)		63.10%	64.91%	

Mutation wild-type	79 (38.73%)	47 (30.92%)		36.36%	34.77%		79 (37.80%)	42 (30.66%)		36.90%	35.09%	
Mutation positive												
Liver metastasis[5]			0.172			0.008			0.229			0.085
No liver metastases	154 (75.49%)	103 (67.76%)		72.13%	71.75%		163 (77.99%)	93 (67.88%)		75.25%	71.48%	
Liver metastases	50 (24.51%)	49 (32.24%)		27.87%	28.25%		46 (22.01%)	44 (32.12%)		24.75%	28.52%	
Tumor burden[6]			0.189			0.104			0.143			0.167
≤ 31 mm	61 (29.90%)	33 (21.71%)		27.76%	24.59%		58 (27.75%)	30 (21.90%)		27.47%	21.27%	
> 31 mm and ≤ 97 mm	96 (47.06%)	79 (51.97%)		47.08%	52.23%		101 (48.33%)	69 (50.36%)		46.82%	54.36%	
> 97 mm	47 (23.04%)	40 (26.32%)		25.16%	23.18%		50 (23.92%)	38 (27.74%		25.71%	24.37%	

Data sources: CheckMate 067 trial (database lock: November 12, 2021), RELATIVITY-047 trial (database lock: October 19, 2023)

Abbreviations: AJCC: American Joint Committee on Cancer, ECOG PS: Eastern Cooperative Oncology Group Performance Status, Ipi: ipilimumab, IPT: inverse probability of treatment, LDH: lactate dehydrogenase, M: metastasis, Nivo: nivolumab, PD-L1: programmed cell death ligand 1, Rela: relatlimab, ULN: upper limit of normal.

Notes: [1] IPT weights with stabilization and truncation at the 5th and 95th percentiles are used [2] N per arm reflects the effective sample size after weighting. [3] IPT weights obtained from the overall population reweighting were applied; no further reweighting has been conducted within the subgroup. [4] Besides 'Australia/New Zealand', 'Europe', and 'United States/Canada', other regions where patients were recruited from include 'Rest of World' (Israel [CheckMate 067 trial]; Israel and Russia [RELATIVITY-047 trial]) and 'Latin America' (RELATIVITY-047 trial). [5] Liver metastasis was derived from patients that had liver metastases at screening per investigator for both trials. [6] Tumor burden was assessed per investigator and categorized as the quartiles from the checkMate 067 trial (<= Q1 [31 mm], > Q1 [31 mm] and <= Q3 [97 mm], and > Q3 [97 mm]) to match definitions between trials. Those without reported tumor burden were omitted from this analysis due to small sample size.

Table 15 Baseline characteristics of patients in the indirect treatment comparison included in the comparative analysis of safety (ITT) [4]

	Before weighting [a]			After weighting [a]		
	Nivo+rela (n = 349)	Nivo+ipi (n = 307)	SMD[b]	Nivo+rela (n = 339)	Nivo+ipi (n = 297)	SMD[b]
Age, years, mean ± SD	60.94 ± 14.05	59.50 ± 3.63	0.105	60.50 ± 14.17	60.35 ± 13.61	0.011
Sex						
Male	206 (59.03%)	201 (65.47%)	0.133	61.05%	62.17%	0.023
Female	143 (40.97%)	106 (34.53%)		38.95%	37.83%	
Geographic region						
Rest of world	312 (89 40%)	246 (80.13%)	0.026	86.16%	84.63%	0.043
USA	37 (10.60%)	61 (19.87%)		13.84%	15.37%	
Time from advanced melanoma diagnosis until index date, years, mean ± SD	2.85 ± 4.86	3.57 ± 4.48	0.154	3.20 ± 5.44	3.36 ± 4.17	0.033
Prior adjuvant therapy						
Not received	315 (90.26%)	236 (7. 87%)	0.367	85.80%	82.97%	0.078
Received	34 (9.74%)	71 (23.13%)		14.20%	17.03%	

AJCC disease stage						
Stage III	34 (9.74%)	16 (5.21%)	0.173	7.91%	7.07%	0.032
Stage IV	315 (90.26%)	291 (94.79%)		92.09%	92.93%	
ECOG performance status						
≥1	116 (33 24%)	83 (27 04%)	0.135	30.40%	29.05%	0.03
0	233 (66.76%)	224 (72 96%)		69.60%	70.95%	
BRAF mutation status						
Wild-type	215 (61 60%)	206 (67.10%)	0.115	63.43%	63.83%	0.008
Mutant	134 (38.40%)	101 (32.90%)		36.57%	36.17%	
Tumor PD-L1 expression						
<1% or nonquantifiable	204 (58.45%)	152 (49.51%)	0.18	54.51%	53.09%	0.028
≥1 %	145 (41.55%)	155 (50.49%)		45.49%	46.91%	

Abbreviations: ECOG, Eastern Cooperative Oncology Group; ; PD-L1, programmed cell death ligand 1

[a] The analysis sets for unweighted population included all patients randomized to nivolumab and relatlimab in the RELATIVITY-047 trial or nivolumab and ipilimumab in the CheckMate 067 trial who had values for all covariates included in the propensity score model. In the weighted population, the number of patients per treatment group reflected the effective sample size after weighting.

[b] A threshold SMD of < 0.2 was used to indicate balance between treatments.

6.1.3 Comparability of the study population(s) with Danish patients eligible for treatment

The only model (cost-minimisation) baseline input related to patient characteristics was body weight of 79.7 kg used for the dosing of the treatments, and was derived from the RELATIVITY-047 trial (Table 16).

The patient baseline characteristics in RELATIVITY-047 are expected to be similar to those of Danish patients. Baseline characteristics e.g. age, gender and BRAF mutation, as presented by Ellebaek et al [46] in a descriptive and retrospective population-based study in Denmark in metastatic melanoma patients, show that the disease characteristics are similar to those in REALATIVITY-047 [46].

Table 16 Characteristics in the relevant Danish population and in the health economic model

	Value in Danish population (reference)	Value used in health economic model
Patient weight	79.7 kg assumed to be similar to average weight of patients in RELATIVITY-047	79.7 kg

6.1.4 Efficacy – results per RELATIVITY-047

Between April 2018 and December 2020, a total of 421 patients with PD-L1 <1% were randomly assigned to receive nivo+rela (n=209) or nivo monotherapy (n=212) [32] in the RELATIVITY-047 study.

The OS and PFS results from the RELATIVITY-047 for the PD-L1 <1% population are presented in Table 17, based on a data base lock of October 19, 2023, at a minimum follow-up of 33.0 months for the overall population and [redacted] months for nivo and nivo+rela in the PD-L1<1/non quantifiable population (BMS data on file [42]). This is the data cut-off (DCO) used in the ITC. At this 3-year (33 months) minimum follow up, nivo+rela showed a median OS of [redacted] months and a median PFS of [redacted] months.

Figure 2 and Figure 3 [47] shows the Kaplan-Meier curves of OS and PFS for the PD-L1 <1% population .

Table 17 Efficacy results from the RELATIVITY-047 trial with 3 year follow up for all randomised subjects with PD-L1<1%/non quantifiable [42]

	Nivo+rela (N=209)	Nivo (N=212)	Hazard ratio, 95% CI
Median OS months (95% CI)	[redacted]	[redacted]	[redacted]
Median BIRC assessed PFS months (95% CI)	[redacted]	[redacted]	[redacted]

Abbreviations: BIRC, Blinded independent review committee; NR, not reached; CI, confidence interval; OS, overall survival; PFS, progression-free survival

Abbreviations: BIRC,Blinded independent review committee; BMS-986213,nivo+rela; CI,confidence interval; PD-L1, programmed death ligand 1

6.1.5 Efficacy – results per CheckMate 067

In the CheckMate 067 study, at the time of the DCO on 12, November 2021, the minimum follow-up for the study was 90 months (7.5 years). Data from this DCO is presented as it is the most recent with PD-L1 <1% subgroup results available. Results for the PD-L1 <1% subgroup (n=353) are presented in Table 18 and the Kaplan-Meier curves for OS and PFS in the PD-L1 <1% subjects are presented in Figure 4 and Figure 5 respectively [48, 49]. At the 7.5-year (90 months) minimum follow up, the combination nivo+ipi showed a median OS of [redacted] and a median PFS of [redacted] (Table 18).

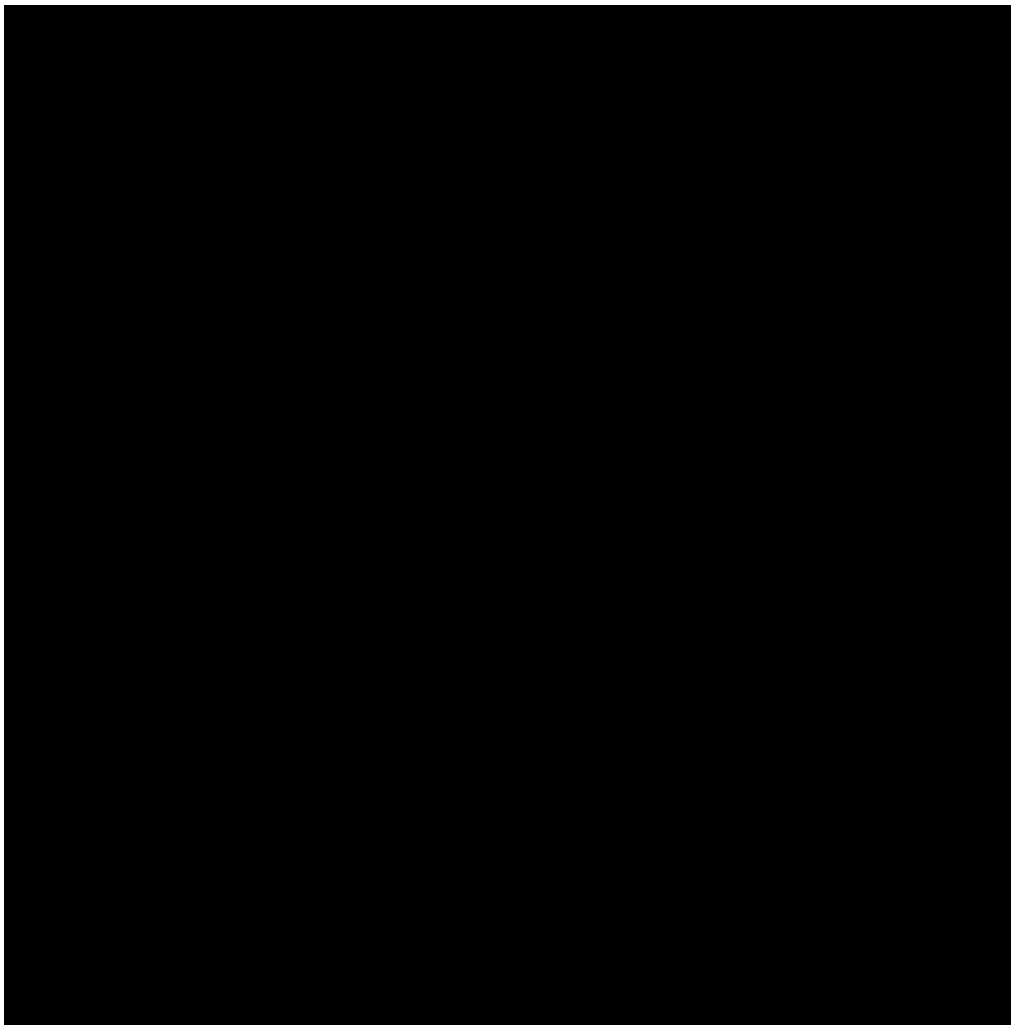
Table 18 Efficacy results from the CheckMate 067 trial with 7.5 year follow up for all randomised subjects with PD-L1<1%/non quantifiable

	Nivo+ipi (n=123)	Nivo (n=117)	Hazard ratio (95% CI)
Median OS (95% CI)	[redacted]	[redacted]	
Median investigator-assessed PFS (95% CI)	[redacted]	[redacted]	[redacted]

Abbreviations: OS,Overall survival; PFS, progression-free survival; NA, Not available

Note: Symbols represent censored observations DBL: 12-NOV-2021 (7.5 Year)

Source: BMS data on file [48-51]



7. Comparative analyses of efficacy

7.1.1 Differences in definitions of outcomes between studies

The key outcomes included in the comparative analysis were described in section 3.7 and includes OS, PFS and ORR as defined in Long et. al [4]. The ITC adjustment was done on the ITT population and results for the key outcomes are presented for the ITT population before and after weighing [4] and for the relevant PD-L1 <1% subgroup.

7.1.2 Method of synthesis

In the ITC, data from RELATIVITY-047 were analysed using DCO of October 19, 2023 (the latest available at the time of the analysis), with a minimum follow-up time of 33 months.

Data for CheckMate 067 were analysed using a DCO of November 12, 2021, with a	**Nivo (CM**	**Nivo + ipi (CM**	**Nivo (Relativity**	**Nivo + Rela (Relativity**

minimum follow-up time of 90 months (7.5 years) [4]. To best align the follow-up times between the two trials, the follow-up time for CheckMate 067 was truncated at the date of April 13, 2017, corresponding to the CheckMate 067 DCO of May 24, 2017[4]. Patients without an event were censored on the date of truncation, resulting in a minimum follow-up time of 36 months. Patients in the CheckMate 067 arms who did not have an event by April 13, 2017 were censored at this date [4]. Please see below summary statistics of follow-up time and treatment duration for the PD-L1 <1%/non-quantifiable subgroup. Minimum was defined from randomization to clinical cut-off (Last Patient Last Visit, LPLV). The minimum follow-up (randomization to clinical cut-off) reflects the shortest observation time among patients still in the study at the cut-off. The median, mean, maximum was defined from randomization to death or last known alive date. The median follow-up (time from randomization to death/last known alive date) is influenced by deaths or loss to follow-up. Due to these different definitions of follow-up times, some mean and median follow-up times appear shorter than the minimum follow-up in the table.**Follow-up, months**	**067, data cut-off April 13, 2017)**	**067, data cut-off April 13, 2017)**	**047, data cut-off Oct 19, 2023)**	**047, data cut-off Oct 19, 2023)**
Minimum (randomization to clinical cutoff)	[redacted]	[redacted]	[redacted]	[redacted]
Median (randomization to death or last known alive date)	[redacted]	[redacted]	[redacted]	[redacted]
Mean (randomization to death or last known alive date)	[redacted]	[redacted]	[redacted]	[redacted]
Maximum (randomization to death or last known alive date)	[redacted]	[redacted]	[redacted]	[redacted]

Source: BMS data on file, 2025.

Please find below the median treatment duration for the PD-L1 <1%/non-quantifiable subgroup from the treatment arms in the RELATIVITY 047 and CM 067 trials.

	Nivo (CM	**Nivo + ipi**	**Nivo (Relativity**	**Nivo + Rela**

	067, data cut-off April 13, 2017)	(CM 067, data cut-off April 13, 2017)	047, data cut-off Oct 19, 2023)	(Relativity 047, data cut-off Oct 19, 2023)
Median duration of treatment (95% CI), months	[redacted]			

Source: BMS data on file, 2025.

A propensity score model was used to generate IPTW, which adjusted for any imbalances in the distribution of baseline characteristics between the two trials [4]. The Table 19 below includes a summary of the distribution of IPT weights amongst patients in the nivo+ipi arm (CheckMate-067 trial) and nivo+rela arm (RELATIVITY-047 trial). IPT weights with stabilization and truncation at the 5th and 95th percentiles are used.

The probability of treatment was estimated through binary logistic regression separately for nivo + rela vs. nivo + ipi and captures patients' probability of being included in the CA224-047 trial vs. the CheckMate 067 trial.

Covariates in the model included age group, sex, geographic, time from advanced melanoma diagnosis until randomization, prior adjuvant therapy, LDH category, disease stage, melanoma subtype, ECOG PS, BRAF mutation status, PD-L1 expression, liver metastasis, and tumour burden. Patients were matched by baseline characteristics, and altogether 13 patients were excluded due to missing covariate [4].

Table 19 Summary statistics for IPT weights

	Nivo + Ipi (n = 307)	Nivo + Rela (n = 349)
Weight		
Mean ± SD	[redacted]	[redacted]
Median	[redacted]	[redacted]
Range	[redacted]	[redacted]
Missing / N (%)	[redacted]	[redacted]

Source: BMS data on file

The sample includes a subset of patients with non-missing values on all covariates included in the binary logistic regression model. IPT weights obtained from the overall

population (ITT) reweighting were applied; no further reweighting has been conducted within the subgroup. After weighting, effective sample sizes were 339 for the nivo+rela group and 297 for the nivo+ipi group in the ITT population and for the relevant population with PD-L1 <1%/non quantifiable the effective sample sizes were 204 and 152 and 185 and 158, for nivo+rela and nivo+ipi before and after weighting respectively [4].

An overview of the analysis populations (ITT) in the ITC is given in Table 20 below including the sample size of the nivo arms from RELATIVITY-047 and CheckMate 067 respectively.

Table 20 Analysis populations

Analysis populations		
ITT	Nivo + Rela (RELA-047)	N= 355
	Nivo + Ipi (CM067)	N= 314 Safety population N=313
	Nivo mono (RELA-047)	N= 359
	Nivo mono (CM067)	N= 316
ITC- Unweighted sample (patients with no missing data)	Nivo + Rela (RELA-047 ITC)	N= 349
	Nivo + Ipi (CM067 ITC)	N= 307
	Nivo mono (RELA-047)	355
	Nivo mono (CM067)	303
ITC- ESS in weighted sample	Nivo + Rela (RELA-047 ITC)	N= 339
	Nivo + Ipi (CM067 ITC)	N= 297
	Nivo mono (RELA-047)	N= 338
	Nivo mono (CM067)	N= 288

OS and PFS were estimated with Kaplan-Meier method and compared for nivo+rela vs nivo+ipi in a Cox regression model using HRs before and after IPT weighting. Violations to the proportional hazards assumption were assessed and dismissed using the Schoenfeld residual test, as indicated by a *P* value of <.05.

The Schoenfeld residual plots before and after weighting are also supportive of proportional hazards, as can be seen from the flat smoothed trend line. The Schoenfeld residual plots for OS and PFS before and after weighting are included in Appendix C.

Complete ORRs were compared in a logistic regression model using odds ratios (ORs) also before and after weighting [4].

The results in the following sections are presented for the key outcomes before and after IPT weighting for the ITT population and for the PD-L1<1% subpopulation analysis, to show any difference in results for baseline imbalances between the two arms prior to any statistical adjustments were made and when they were adjusted to account for differences in between the study populations and the robustness of the results.

For AEs please see section 9.

7.1.3 Results from the comparative analysis

The results from the ITC showed that overall, OS, PFS per INV and ORR were similar between nivo+rela and nivo+ipi arms for the PD-L1 <1%/non quantifiable group before and after the IPT weighting (Table 21) [44].

Table 21 Results from the comparative analysis of nivo+rela vs. nivo+ipi in adult patients with tumour cell PD-L1 expression < 1%/not quantifiable [44]

Outcome measure	Nivo+rela unweighted	Nivo+ipi unweighted	HR/OR (95% CI)	Nivo+rela weighted	Nivo+ipi weighted	HR/OR (95% CI)
OS events	107/204	72/152		107/185	72/158	
Median OS months (95% CI)	38.3 (24.5, NR)	NR (27.6, NR)	HR 1.04 (0.77, 1.41)	43.0 (26.9, NR)	NR (26.4, NR)	HR 1.01 (0.74, 1.37)
PFS per INV events	140/204	91/152		140/185	91/158	
Median PFS per INV months (95% CI)	6.9 (4.5, 10.1)	11.0 (6.7, 20.0)	HR 1.20 (0.92, 1.56)	6.5 (4.5, 10.1)	9.9 (6.7, 16.5)	HR 1.16 (0.89, 1.51)
ORR per INV events	80/204	65/152		71/185	68/158	
ORR per INV %	39.2	42.8	OR 0.86 (0.64; 1.17)	38.4	43.0	OR 0.82 (0.60; 1.13)

Abbreviations: CI, confidence interval; OS, overall survival; PFS, progression free survival; ORR, objective response rate; INV, investigator

Note: N per arm reflects the effective sample size after weighting. IPT weights obtained from the overall population reweighting were applied; no further reweighting has been conducted within the subgroup.

7.1.4 Efficacy – results per OS

The OS for the PD-L1 <1%/non quantifiable subjects was similar between nivo+rela and nivo+ipi before and after weighting (Table 22)[44]. The median OS for nivo+rela was 38.3 months (95% CI 24.5, NR) and 43.0 (95% CI 26.9, NR) before and after weighting [44].

The Kaplan-Meier plots for OS in the PD-L1 <1%/non quantifiable subjects before and after weighting are presented in Figure 6 below [44].

Table 22 Overall survival before and after application of IPT weighting in subjects with PD-L1 <1%/non-quantifiable [44]

	Before IPT weighing		After IPT weighting	
	Nivo+rela (N =204)	Nivo+ipi (N = 152)	Nivo+rela (N = 185)	Nivo+ipi (N = 158)
Number of events	107	72	107	72
Median OS months (95% CI)	38.3 (24.5, NR)	NR (27.6, NR)	43.0 (26.9, NR)	NR (26.4, NR)
12 months OS (95% CI)	0.74 (0.68, 0.80)	0.69 (0.61, 0.76)	0.74 (0.67; 0.80)	0.69 (0.60; 0.76)
16 months OS (95% CI)	0.69 (0.62, 0.75)	0.66 (0.58, 0.73)	0.70 (0.63, 0.76)	0.66 (0.57, 0.73)
24 months OS (95% CI)	0.61 (0.52, 0.68)	0.58 (0.51, 0.64)	0.59 (0.52, 0.66)	0.60 (0.51, 0.68)
28 months OS (95% CI)	0.56 (0.49, 0.62)	0.58 (0.50, 0.65)	0.57 (0.49, 0.63)	0.57 (0.49, 0.65)
36 months OS (95% CI)	0.51 (0.44, 0.58)	0.54 (0.46, 0.61)	0.52 (0.44, 0.59)	0.53 (0.45, 0.61)

Figure 6 Kaplan-Meier plots of overall survival before weighting (A) and after weighting (B) for subjects with PD-L1 <1%/non-quantifiable [44]

7.1.5 Efficacy – results per PFS

Overall, in the PD-L1 <1%/non quantifiable subjects the PFS per INV was similar between nivo+rela and nivo+ipi before and after weighting (Table 23)[44]. The median PFS for nivo+rela was 6.9 months (95% CI 4.5, 10.1) and 6.5 months (4.5, 10.1) before and after weighting [44].

The Kaplan-Meier plots for PFS in the PD-L1 <1%/non quantifiable subjects before and after weighting are presented in Figure 7 [44].

Table 23 Progression free survival per investigator before and after application of IPT weighting in subjects with PD-L1 <1%/non-quantifiable [44]

	Before IPT weighing		After IPT weighting	
	Nivo+rela (N =204)	Nivo+ipi (N =152)	Nivo+rela (N = 185)	Nivo+ipi (N = 158)
Number of events	140	91	140	91
Median PFS months (95% CI)	6.9 (4.5, 10.1)	11.0 (6.7, 20.0)	6.5 (4.5, 10.1)	9.9 (6.7, 16.5)
12 months PFS (95% CI)	0.40 (0.33, 0.47)	0.47 (0.39, 0.55)	0.40 (0.33, 0.47)	0.45 (0.36, 0.53)
16 months PFS (95% CI)	0.36 (0.29, 0.43)	0.44 (0.36, 0.52)	0.36 (0.29, 0.43)	0.42 (0.33, 0.50)
24 months PFS (95% CI)	0.32 (0.25, 0.39)	0.38 (0.30, 0.46)	0.32 (0.25, 0.39)	0.36 (0.28, 0.45)
28 months PFS (95% CI)	0.30 (0.24, 0.37)	0.38 (0.29, 0.46)	0.30 (0.24, 0.37)	0.35 (0.27, 0.44)
36 months PFS (95% CI)	0.30 (0.23, 0.36)	0.36 (0.28, 0.44)	0.30 (0.23, 0.37)	0.34 (0.26, 0.42)

Figure 7 Kaplan-Meier plots of PFS per Investigator before weighting (A) and after weighting (B) for subjects with PD-L1 <1%/non-quantifiable [44]

7.1.6 Efficacy – results per ORR

Confirmed ORR per INV was assessed in the subgroup of PD-L1 <1%/non quantifiable subjects (Table 24)[52]. The ORR was similar between nivo+rela and nivo+ipi before and after weighting was 39.2% and 42.8% in the nivo+rela arm and 38.4% and 43.0% in the nivo+ipi arm respectively.

Table 24 ORR in the PD-L1 <1%/non quantifiable patient subgroup before and after the application of weighting [52]

	Before IPT weighing		After IPT weighting	
	Nivo+rela (N = 204)	Nivo+ipi (N = 152)	Nivo+rela (N = 185)	Nivo+ipi (N = 158)
Confirmed ORR per INV %	39.2	42.8	38.4	43.0
CR, n (%)	[redacted]	[redacted]	[redacted]	[redacted]
PR, n (%)	[redacted]	[redacted]	[redacted]	[redacted]
OR (95% CI)	0.86 (0.64; 1.17)		0.82 (0.60; 1.13)	

7.1.7 Subgroup analysis

The subgroup analysis for PD-L1 <1% subjects after IPT weighting showed that results were consistent among subgroups (Figure 8)[53].

8. Modelling of efficacy in the health economic analysis

8.1 Presentation of efficacy data from the clinical documentation used in the model

Not applicable.

8.1.1 Extrapolation of efficacy data

Not applicable.

8.1.1.1 Extrapolation of [effect measure 1]

Not applicable.

Table 25 Summary of assumptions associated with extrapolation of [effect measure]

Method/approach	Description/assumption
NA.	NA.

8.1.1.2 Extrapolation of [effect measure 2]

Not applicable.

8.1.2 Calculation of transition probabilities

Not applicable.

Table 26 Transitions in the health economic model

Health state (from)	Health state (to)	Description of method	Reference
NA.	NA.		
	NA.		

8.2 Presentation of efficacy data from [additional documentation]

Not applicable.

8.3 Modelling effects of subsequent treatments

Subsequent treatment for nivo+rela and nivo+ ipi and the nivo mono arms in RELATIVITY-047 and CheckMate 067 are shown below in Table 27 and Table 28 (PDL1<1%/non-quantifiable patients).

Table 27 Subsequent treatment in Relativity 047, PDL1<1%/non-quantifiable patients

	Number of subjects (%)	
	[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]

Note: Subject may have received more than one type of subsequent therapy.

Table 28 Subsequent treatment in CM 067, PDL1<1%/non-quantifiable patients

	Number of subjects (%)	
	[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]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]

[redacted]

Note: Subject may have received more than one type of subsequent therapy.

The cost analysis included a scenario with subsequent therapies added for nivo+rela and nivo+ipi respectively. A user-modifiable distribution of multiple subsequent treatments was included in the model.

The share of patients receiving subsequent systemic treatment including immunotherapy was assumed based on RELATIVITY-047 and CheckMate 067, with 43.5% (n=91, the proportion in REALTIVITY-047 that received subsequent systemic therapy, see Table 27) in the nivo+rela arm and 47.8% for nivo+ipi (n=76, equivalent to the sum of

patients who received both subsequent immunotherapy and subsequent systemic therapy, 34.0% (n=22) and 13.8% (n=54), see Table 28).

Table 29 below, present the assumptions made for the distributions of type of subsequent treatments by initial treatment. Based on the proportion for subsequent systemic and immunotherapy in the respective trial, the share for each treatment was re-calculated to only include systemic and immunotherapy treatment and was then re-distributed proportionally to only include the relevant subsequent treatment for Denmark: nivo mono, ipi mono, pembro mono and dabrafenib plus trametinib.

Note that in RELATIVITY-047 and CheckMate 067, subject may have received more than one type of subsequent therapy.

Table 29 Distribution of subsequent treatments applied in the cost analysis

Drug	Nivo+rela (n= 91)	Nivo+ipi (n = 76)	Nivo+rela	Nivo+ipi
	Re-calculated		Re-distributed	
Nivolumab mono	13%	8%	19.0%	10.0%
Ipilimumab mono	14%	4%	20.6%	5.0%
Pembrolizumab mono	7%	18%	9.5%	23.3%
Dabrafenib + Trametinib combination	35%	49%	50.8%	61.7%
Total (re-distributed)	-	-	100%	100%

Section 11.6 include the assumptions made in the cost analysis on treatment cost and duration.

8.4 Other assumptions regarding efficacy in the model

Not applicable.

8.5 Overview of modelled average treatment length and time in model health state

Not applicable.

Table 30 Estimates in the model

	Modelled average [effect measure] (reference in Excel)	Modelled median [effect measure] (reference in Excel)	Observed median from relevant study
NA.	NA.	NA.	NA.

Table 31 Overview of modelled average treatment length and time in model health state, undiscounted and not adjusted for half cycle correction (adjust the table according to the model)

Treatment	Treatment length [months]	Health state 1 [months]	Health state 2 [months]
NA.	NA.	NA.	NA.

9. Safety

9.1 Safety data from the clinical documentation

The safety population consisted of the ITT population (regardless of PD-L1 expression) since the AEs are expected not to differ based on PD-L1 status. The overall safety data from the ITC before and after application of weighting are presented in Table 32 below. In addition the detailed safety data from the ITT populations of CheckMate 067 [54] and RELATIVITY-047 [55] with the latest available data are presented in the Table 33 and Table 34 respectively. For the health economic model the IPT weighted grade 3-4 AE's from the ITC was used (see Table 36).

Table 32 Overview of safety events, median follow-up for nivo+rela 33.8 months [3-years follow-up] and median follow-up for nivo+ipi 37 months [3-years follow-up]

	Before IPT weighing			After IPT weighting		
	Nivo + Rela (N = 349)	Nivo + Ipi (N = 307)	Difference, % (95 % CI)	Nivo+rela (N=339)	Nivo+ipi (N=297)	Difference, % (95 % CI)
Number of adverse events, n	N.A	N.A	N.A	N.A	N.A	N.A
All-causality AEs n (%)	346 (99.14%)	306 (99.67%)	0.53%	99.08%	99.68%	0.61%
Number of serious adverse events*, n	N.A	N.A	N.A	N.A	N.A	N.A
All cause serious adverse events*, n (%)	137 (39.26%)	223 (72.64%)	33.38%	39.07%	73.78%	34.70%
Number of CTCAE grade ≥ 3 events, n	N.A	N.A	N.A	N.A	N.A	N.A
Number of drug-related select AEs grade ≥ 3	51 (14.61%)	97 (31.60%)	N.A	N.A	N.A	N.A
Number of adverse reactions, n	N.A	N.A	N.A	N.A	N.A	N.A
Number and proportion of patients with drug related SAE, n (%)	57 (16.33%)	150 (48.86%)	32.53%	16.90%	50.65%	33.74%
Number and proportion of patients who had a dose reduction, n (%)	N/A	N/A	N/A	N/A	N/A	N/A

Number and proportion of patients who discontinue treatment regardless of reason, n (%)	80 (22.92%)	149 (48.53%)	25.61%	23.24%	51.07%	27.82%
Number and proportion of patients who discontinue treatment due to adverse events, n (%)	60 (17.19%)	121 (39.41%)	22.22%	17.40%	41.05%	23.66%

Abbreviations: N.A, not available

Sources: [4]

Table 33 Treatment-Related Adverse Events*, study CheckMate 067, 10 years follow-up [54]

Event†	Nivo+ipi (N=313)		Nivo (N=313)		Ipi (N=311)	
	Any grade	Grade 3 or 4	Any grade	Grade 3 or 4	Any grade	Grade 3 or 4
Any treatment-related adverse event — no. (%)	300 (95.8)	196 (62.6)	272 (86.9)	77 (24.6)	268 (86.2)	92 (29.6)
Rash	100 (31.9)	12 (3.8)	79 (25.2)	2 (0.6)	71 (22.8)	6 (1.9)
Pruritus	114 (36.4)	6 (1.9)	76 (24.3)	1 (0.3)	118 (37.9)	1 (0.3)
Vitiligo	28 (8.9)	0	33 (10.5)	1 (0.3)	16 (5.1)	0
Dry skin	16 (5.1)	0	18 (5.8)	0	11 (3.5)	0
Maculopapular rash	38 (12.1)	6 (1.9)	18 (5.8)	2 (0.6)	38 (12.2)	1 (0.3)
Fatigue	121 (38.7)	13 (4.2)	114 (36.4)	3 (1.0)	90 (28.9)	3 (1.0)
Asthenia	30 (9.6)	1 (0.3)	26 (8.3)	1 (0.3)	16 (5.1)	2 (0.6)
Pyrexia	60 (19.2)	2 (0.6)	21 (6.7)	0	21 (6.8)	1 (0.3)
Chills	22 (7.0)	0	12 (3.8)	0	10 (3.2)	0

Diarrhea	146 (46.6)	35 (11.2)	71 (22.7)	11 (3.5)	107 (34.4)	18 (5.8)
Nausea	88 (28.1)	7 (2.2)	42 (13.4)	0	54 (17.4)	2 (0.6)
Vomiting	48 (15.3)	7 (2.2)	22 (7.0)	1 (0.3)	25 (8.0)	1 (0.3)
Constipation	12 (3.8)	0	20 (6.4)	0	16 (5.1)	0
Abdominal pain	28 (8.9)	1 (0.3)	19 (6.1)	0	28 (9.0)	2 (0.6)
Dry mouth	20 (6.4)	0	15 (4.8)	0	7 (2.3)	0
Colitis	44 (14.1)	27 (8.6)	8 (2.6)	3 (1.0)	37 (11.9)	26 (8.4)
Headache	35 (11.2)	2 (0.6)	24 (7.7)	0	26 (8.4)	1 (0.3)
Dizziness	19 (6.1)	0	16 (5.1)	0	12 (3.9)	0
Arthralgia	45 (14.4)	2 (0.6)	36 (11.5)	1 (0.3)	27 (8.7)	0
Myalgia	18 (5.8)	1 (0.3)	16 (5.1)	1 (0.3)	9 (2.9)	0
Increased lipase	45 (14.4)	34 (10.9)	31 (9.9)	19 (6.1)	18 (5.8)	12 (3.9)
Increased amylase	27 (8.6)	9 (2.9)	22 (7.0)	8 (2.6)	15 (4.8)	4 (1.3)
Increased ALT	64 (20.4)	31 (9.9)	15 (4.8)	5 (1.6)	13 (4.2)	6 (1.9)
Hypothyroidism	62 (19.8)	1 (0.3)	34 (10.9)	0	15 (4.8)	0
Hyperthyroidism	36 (11.5)	3 (1.0)	14 (4.5)	0	3 (1.0)	0
Hypophysitis	25 (8.0)	5 (1.6)	2 (0.6)	1 (0.3)	12 (3.9)	5 (1.6)
Decreased appetite	61 (19.5)	4 (1.3)	35 (11.2)	1 (0.3)	41 (13.2)	1 (0.3)
Cough	26 (8.3)	1 (0.3)	19 (6.1)	2 (0.6)	15 (4.8)	0
Dyspnea	36 (11.5)	3 (1.0)	18 (5.8)	1 (0.3)	12 (3.9)	0
Pneumonitis	24 (7.7)	6 (1.9)	6 (1.9)	1 (0.3)	5 (1.6)	1 (0.3)

Treatment-related adverse event leading to discontinuation — no. (%)	140 (44.7)	105 (33.5)	49 (15.7)	29 (9.3)	52 (16.7)	47 (15.1)
Patients who died due to study drug toxicity	2 (0.6)**		1 (0.3)††		1 (0.3)‡	

*ALT denotes alanine aminotransferase, AST aspartate aminotransferase. †Shown are treatment-related adverse events of any grade that occurred in at least 5% of patients in any treatment group, and within 100 days of the last treatment dose, grouped by organ system class. The severity of adverse events was graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events version 4.0.**Cardiomyopathy (n=1) and liver necrosis (n=1), both more than 100 days after last dose. (ie, nivolumab plus ipilimumab)††Neutropenia, within 100 days after last dose. (ie, nivolumab)‡Colon perforation, within 100 days after last dose.(ie, ipilimumab)

Sources: [54]

Table 34 AE Summary, study RELATIVITY-047, median follow-up of 33.8 months [3-years follow-up][55]

	Nivo+rela (N=355)		Nivo (N=359)	
	Any grade	**Grade 3 or 4**	**Any grade**	**Grade 3 or 4**
Any AE	352 (99.2)	164 (46.2)	345 (96.1)	141(39.3)
TRAE	302 (85.1)	78 (22.0)	263 (73.3)	43 (12.0)
Leading to discontinuation	63 (17.7)	34 (9.6)	35 (9.7)	14 (3.9)
TRAEs in ≥5% of patients				
Pruritus	93 (26.2)	0	61 (17.0)	2 (0.6)
Fatigue	84 (23.7)	5 (1.4)	47 (13.1)	1 (0.3)
Rash	61 (17.2)	3 (0.8)	54 (15.0)	2 (0.6)
Diarrhea	60 (16.9)	5 (1.4)	39 (10.9)	2 (0.6)
Hypothyroidism	59 (16.6)	0	47 (13.1)	0
Arthralgia	56 (15.8)	3 (0.8)	34 (9.5)	1 (0.3)

Vitiligo	49 (13.8)	0	44 (12.3)	0
Asthenia	32 (9.0)	1 (0.3)	18 (5.0)	0
Nausea	32 (9.0)	0	18 (5.0)	0
Increased ALT	31 (8.7)	5 (1.4)	17 (4.7)	2 (0.6)
Increased AST	31 (8.7)	5 (1.4)	10 (2.8)	1 (0.3)
Myalgia	30 (8.5)	1 (0.3)	18 (5.0)	0
Decreased appetite	28 (7.9)	0	10 (2.8)	0
Infusion-related reaction	24 (6.8)	0	13 (3.6)	1 (0.3)
Hyperthyroidism	23 (6.5)	0	24 (6.7)	0
Treatment-related deaths[a]	4 (1.1)		2 (0.6)	

Data are No. (%) unless otherwise specified. Abbreviations: AE, adverse event; TRAE, treatment-related AE

[a]Treatment-related deaths: nivolumab plus relatlimab (n=4): hemophagocytic lymphohistiocytosis, acute edema of the lung, pneumonitis, and multi organ failure; nivolumab (n=2): sepsis and myocarditis, and worsening pneumonia**.** No new treatment-related deaths were reported since the last database lock

Sources: [55]

The most frequent all cause serious adverse events (SAEs) of RELATIVITY-047 (nivo+rela arm) and CheckMate 067 (nivo+ipi arm) studies are presented in Table 35. Based on the DBL 9 March 2021, also presented in the nivo+real EPAR [21], overall, 34% of patients in rela+nivo experienced a SAE (any grade)[56]. The most frequently reported (≥ 1% of subjects) any-grade SAEs were, malignant neoplasm progression (3.7%), adrenal insufficiency, myocarditis, back pain, colitis, and diarrhoea (1.1% each)[56]. For the DBL of REALATIVITY-047 with 3 years follow up, the frequency of SAEs was not reported, therefore the March 2021 DBL was used. In REALTIVITY-047 with the 3-year follow up of all AE (any grade), in all treated subjects (n=355), no severe (grade ≥3) AE were reported in ≥5% [57]. For CheckMate 067, the 3-year follow up for SAE's were used, overall SAE's was reported in 72% in the nivo+ipi arm with the most frequently reported SAE's were diarrhoea (11%), colitis (10%), pyrexia (8%) and malignant neoplasm progression (5%)[58].

A summary of all reported SAE's are presented in detail in the Appendix E, separately for each study.

Table 35 Serious adverse events with frequency of ≥ 5%, studies RELATIVITY-047 and CheckMate 067 presented separately

	RELATIVITY-047[1]	CheckMate 067[1]
Adverse events	**Nivo+rela (N=355)**	**Nivo+ipi (N=313)**
Colitis, n (%)	[redacted]	[redacted]
Diarrhoea, n (%)	[redacted]	[redacted]
Malignant neoplasm progression, n (%)	[redacted]	[redacted]
Pyrexia, n (%)	[redacted]	[redacted]

[1]Includes events reported between first dose and 30 days after last dose of study therapy.

Source: [56, 58]

The safety data included in cost-minimisation analysis were the adverse grade 3 or 4 AEs from ITC (Table 36) [59].

Table 36 Adverse events used in the health economic model

Adverse events	Intervention	Comparator		
	Frequency used in economic model for nivo+rela	Frequency used in economic model for nivo+ipi	Source	Justification
Anemia	2.67%	1.1%	Table 3 in ITC supplementary material: [59]	Grade 3 or 4 AEs, 36 months follow-up, IPT weighting
Arthralgia	1.71%	0.6%	Same as above	Same as above
Asthenia	0.29%	0.8%	Same as above	Same as above
Back pain	1.71%	0.6%	Same as above	Same as above
Constipation	0.58%	0.3%	Same as above	Same as above
Cough	0.25%	0.2%	Same as above	Same as above
Decreased appetite	0.50%	2.2%	Same as above	Same as above
Diarrhea	2.75%	12.4%	Same as above	Same as above

Adverse events	Intervention	Comparator		
Fatigue	1.84%	6.3%	Same as above	Same as above
Headache	0.27%	0.8%	Same as above	Same as above
Hypothyroidism	0.00%	0.3%	Same as above	Same as above
Nausea	0.57%	3.4%	Same as above	Same as above
Pruritus	0.00%	2.2%	Same as above	Same as above
Pyrexia	0.00%	1.4%	Same as above	Same as above
Rash	1.03%	3.4%	Same as above	Same as above
UTI	1.23%	0.9%	Same as above	Same as above
Vitiligo	0.00%	0.00%	Same as above	Same as above

9.1.1 Comparative analysis of adverse events in CheckMate 067 and RELATIVITY-047

A direct comparison of safety outcomes for the PD-L1-negative subgroup between nivo+rela and nivo+ipi is not available. A naïve cross-trial comparison of the ITT populations from RELATIVITY-047 (Tawbi et al. [55]) and CheckMate 067 (Wolchok et al. [54]) is summarised below. AEs are not expected to differ based on PD-L1 status.

Grade 3-4 AEs occurred in 18.9% of patients in the nivo + rela arm in RELATIVITY-047, whereas 62.6% of patients experienced grade 3-4 AEs in the nivo + ipi arm of CheckMate 067. SAEs were reported in 39.26% of patients in the nivo + rela arm of RELATIVITY-047, with 16.33% considered drug-related, whereas in the nivo + ipi arm of CheckMate 067, SAEs were observed in 72.64% of patients, with 48.86% considered drug-related.

In RELATIVITY-047, 22.92% of patients discontinued treatment due to AEs in the nivo + rela arm, with 17.19% of discontinuations being drug-related. In CheckMate 067, 48.53% of patients in the nivo + ipi arm discontinued treatment due to AEs, with 39.41% being drug-related. No treatment-related deaths were reported for nivo + rela in RELATIVITY-047, whereas in CheckMate 067, two treatment-related deaths occurred in the nivo + ipi arm (in 0.6% of the safety population), due to cardiomyopathy (1 case) and liver necrosis (1 case).

Grade 3-4 AEs and treatment-related deaths were not assessed in the ITC. However, overall safety results from the ITC confirms that nivo + ipi has a less favorable AE profile compared to nivo+rela. Before weighting, SAEs were 33.38% higher in nivo + ipi compared to nivo + rela, increasing to 34.70% after weighting. Drug-related SAEs were 32.53% higher before weighting and 33.74% higher after weighting. Treatment

discontinuations due to AEs increased from 25.61% before weighting to 27.82% after weighting, while drug-related treatment discontinuations increased from 22.22% to 23.66% after weighting.

Both the naïve and ITC-adjusted comparisons indicate that nivo + rela has a lower incidence of SAEs, TRAEs and lower treatment discontinuation rates compared to nivo + ipi, with no reported treatment-related deaths of nivo+rela reported in RELATIVITY-047.

9.2 Safety data from external literature applied in the health economic model

Not applicable.

Table 37 Adverse events that appear in more than X % of patients

Adverse events	Intervention (N=x)			Comparator (N=x)			Difference, % (95 % CI)	
	Number of patients with adverse events	Number of adverse events	Frequency used in economic model for intervention	Number of patients with adverse events	Number of adverse events	Frequency used in economic model for comparator	Number of patients with adverse events	Number of adverse events
Adverse event, n	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A

Abbreviation: N/A, not applicable.

10. Documentation of health-related quality of life (HRQoL)

The CheckMate 067 trial analysed HRQoL through the EORTC QLQ-C30 questionnaire, EQ-5D utility index and visual analogue scale (EQ-VAS) [37]. The RELATIVITY-047 trial measured HRQoL with the Functional Assessment of Cancer Therapy-Melanoma (FACT-M), EQ-5D-3L utility index and EQ-VAS [36]. Please find the description of the specific instrument in the relevant sections below.

The main patient reported outcome (PRO) measures were different between the relevant trials, (EORTC QLQ-C30 and FACT-M) and therefore not directly comparable. No ITC of HRQoL of the EQ-VAS or EQ-5D utility indices has been carried out between the trials. For this reason, in the current application we focus on describing the PRO

outcomes comparing nivo+rela to nivo monotherapy according to results from RELATIVITY-047, and nivo+ipi to nivo monotherapy according to CheckMate 067.

Table 38 Overview of included HRQoL instruments

Measuring instrument	Source	Utilization
EQ-5D-3L and EQ-VAS	RELATIVITY-047, CheckMate 067	Descriptive, using the EQ-5D utility index
Functional Assessment of Cancer Therapy-Melanoma (FACT-M)	RELATIVITY-047	Descriptive
European Organization for Research and Treatment of Care Core Quality of Life Questionnaire (EORTC QLQ-C30)	CheckMate 067	Descriptive

10.1 Presentation of the health-related quality of life EQ-5D-3L and EQ-VAS and utility index

10.1.1 Study design and measuring instrument

The EQ-5D-3L is a generic and preference-weighted measure for capturing health-related QoL on the assessment day. It is a self-reported instrument with five domains evaluated: mobility, self-care, usual activities, pain/discomfort, and anxiety/depression. Each domain is divided into three severity levels. The EQ-5D summary or utility index is a composite score derived from the results of the five dimensions, using a single summary index score (utility index) which is a value set based on population norms. The value typically ranges from 0 (dead) to 1 (full health), but it is possible to have a value lower than 0 (worse than dead state) [60]. The EQ-5D Visual Analogue Scale (EQ-VAS) is a self-reported measure, where patients are asked to rate their overall health on a single scale from 0 to 100. 0 represents the worst possible health imaginable, while 100 represents the best health imaginable [60].

10.1.2 Data collection

In RELATIVITY-047 HRQoL data were collected at baseline (after randomisation, but prior to the first dose of study treatment) and before dosing at each 4-week treatment cycle thereafter until disease progression or treatment discontinuation. During the post-treatment period, all HRQoL assessments were performed at two follow-up safety visits (generally at 30 days and 100 days from the last dose), while FACT-M MS and EQ-5D-3L were also assessed at subsequent follow-up survival visits. Data analysis included all on-treatment and posttreatment data from visits with at least 10 patients in each treatment group [36]. Missing data handling was not described further in the report. In CheckMate 067 HRQoL was collected in all randomised patients and assessed at weeks 1 and 5 of

each 6-week cycle for the first 6 months, and then once every 6 weeks thereafter as well as at two visits in the follow-up period. No adjustment was made for missing data when scoring the EQ-5D index or the EQ-5D VAS and no imputation was used to handle missing data for the longitudinal analysis [36].

Table 39 Pattern of missing data and completion: RELATIVITY-047 EQ-5D-3L, adapted from supplementary materials of [36]

Time point	HRQoL population N	Missing N (%)	Expected to complete N	Completion N (%)	HRQoL population	Missing N (%)	Expected to complete N	Completion N (%)
	Nivo+rela N = 355				Nivo N = 359			
	Number of patients at randomization	Number of patients for whom data is missing (% of patients at randomization)	Number of patients "at risk" at time point X	Number of patients who completed (% of patients expected to complete)	Number of patients at randomization	Number of patients for whom data is missing (% of patients at randomization)	Number of patients "at risk" at time point X	Number of patients who completed (% of patients expected to complete)
Baseline	355	11 (3.1)	355	344 (96.9)	359	8 (2.2)	359	351 (97.8)
Week 36	355	188 (53)	183	167 (91.3)	359	205 (57.1)	162	154 (95.1)
Week 72	355	268 (75.5)	94	87 (92.6)	359	261 (72.7)	103	98 (95.1)
Week 108	355	319 (89.9)	40	36 (90)	359	305 (85)	55	54 (98.2)
Week 144	355	333 (93.8)	25	22 (88)	359	325 (90.5)	36	34 (94.4)
Week 152	355	343 (96.6)	12	12 (100)	359	334 (93)	26	25 (96.2)
Safety visit 1	355	239 (67.3)	279	116 (41.6)	359	250 (69.6)	267	109 (40.8)

Time point	HRQoL population N	Missing N (%)	Expected to complete N	Completion N (%)	HRQoL population	Missing N (%)	Expected to complete N	Completion N (%)
	Nivo+rela N = 355				Nivo N = 359			
Safety visit 2	355	272 (76.6)	216	83 (38.4)	359	280 (78)	198	79 (39.9)
Survival visit 1	355	291 (82)	174	64 (36.8)	359	288 (80.2)	160	71 (44.4)

In Table 40 EQ-5D utility index and VAS completion rates are shown for the CheckMate 067 trial, separately for the three treatment arms. Baseline completion rate is based on subjects having any baseline data with no post-baseline data requirement. Then, baseline plus ≥1 shows the number of patients with non-missing PRO data at baseline and data from ≥1 post-baseline visit. Follow-up visit 1 is 30 days from the last dose (plus/minus 7 days), follow-up visit 2 was 84 days (plus/minus 7 days) from follow-up visit 1 [37].

Table 40 Pattern of missing data and completion in the CheckMate 067 trial for EQ-5D [37]

Time point	HRQoL population N	Missing N (%)	Expected to complete N	Completion N (%)	HRQoL population N	Missing N (%)	Expected to complete N	Completion N (%)	HRQoL population N	Missing N (%)	Expected to complete N	Completion N (%)
	Nivo	N= 316			Nivo+ipi	N= 314			Ipi	N= 315		
Baseline	316	34 (10.7)	316	282 (89.2)	314	24 (7.6)	314	290 (92.3)	315	37 (11.7)	315	278 (88.2)
Baseline plus ≥1	316	49 (15.5)	316	267 (84.4)	314	40 (12.7)	314	274 (87.2)	315	57 (18)	315	258 (81.9)
Week 5	316	89 (28.1)	302	227 (75.1)	314	134 (42.6)	293	180 (61.4)	315	97 (30.7)	300	218 (72.6)
Week 7	316	79 (25)	291	237 (81.4)	314	132 (42)	276	182 (65.9)	315	99 (31.4)	291	216 (74.2)
Week 11	316	118 (37.3)	271	198 (73)	314	201 (64)	226	113 (50)	315	152 (48.2)	244	163 (66.8)
Week 13	316	123 (38.9)	249	193 (77.5)	314	208 (66.2)	201	106 (52.7)	315	186 (59)	205	129 (62.9)
Week 17	316	160 (50.6)	220	156 (70.9)	314	231 (73.5)	164	83 (50.6)	315	212 (67.3)	158	103 (65.1)
Week 19	316	153 (48.4)	205	163 (79.5)	314	217 (69.1)	155	97 (62.5)	315	218 (69.2)	144	97 (67.3)
Week 23	316	183 (57.9)	188	133 (70.7)	314	227 (72.2)	137	87 (63.5)	315	239 (75.8)	118	76 (64.4)

Time point	HRQoL population N	Missing N (%)	Expected to complete N	Completion N (%)	HRQoL population N	Missing N (%)	Expected to complete N	Completion N (%)	HRQoL population N	Missing N (%)	Expected to complete N	Completion N (%)
	Nivo	N= 316			Nivo+ipi	N= 314			Ipi	N= 315		
Week 25	316	174 (55)	182	142 (78)	314	217 (69.1)	130	97 (74.6)	315	241 (76.5)	111	74 (66.6)
Week 31	316	195 (61.7)	164	121 (73.7)	314	222 (70.7)	125	92 (73.6)	315	265 (84.1)	87	50 (57.4)
Week 37	316	204 (64.5)	152	112 (73.6)	314	225 (71.6)	119	89 (74.7)	315	267 (84.7)	75	48 (64)
Week 43	316	216 (68.3)	145	100 (68.9)	314	240 (76.4)	114	74 (64.9)	315	271 (86)	65	44 (67.6)
Week 49	316	224 (70.8)	128	92 (71.8)	314	249 (79.2)	97	65 (67)	315	275 (87.3)	58	40 (68.9)
Week 55	316	253 (80)	100	63 (63)	314	266 (84.7)	72	48 (66.6)	315	291 (92.3)	43	24 (55.8)
Week 61	316	278 (87.9)	58	38 (65.5)	314	285 (90.7)	42	29 (69)	315	298 (94.6)	28	17 (60.7)
Week 67	316	303 (95.8)	21	13 (61.9)	314	298 (94.9)	22	16 (72.7)	315	306 (97.1)	13	9 (69.2)
Week 73	316	313 (99)	4	3 (75)	314	308 (98)	9	6 (66.6)	315	315 (100)	2	0 (0)
Week 79	316	314 (99.3)	2	2 (100)	314	313 (99.6)	2	1 (50)	315	315 (100)	0	NA

Time point	HRQoL population N	Missing N (%)	Expected to complete N	Completion N (%)	HRQoL population N	Missing N (%)	Expected to complete N	Completion N (%)	HRQoL population N	Missing N (%)	Expected to complete N	Completion N (%)
	Nivo	N= 316			Nivo+ipi	N= 314			Ipi	N= 315		
Follow-up 1c	316	220 (69.6)	104	96 (92.3)	314	209 (66.5)	108	105 (97.2)	315	191 (60.6)	136	124 (91.1)
Follow-up 2c	316	258 (81.6)	62	58 (93.5)	314	218 (69.4)	99	96 (96.9)	315	218 (69.2)	103	97 (94.1)

10.1.3 HRQoL results

The results presented below are from published sources. Since the type of economic analysis submitted is a cost-minimisation analysis, the impact on HRQoL is not included as an outcome, but the EQ-5D outcomes are presented descriptively for the respective studies in the following section. As such, Danish preference weights where not derived.

10.1.3.1 EQ-5D utility index and VAS results from RELATIVITY-047

Below on Figure 9 shows the least squares (LS) mean changes from baseline on treatment in the mixed model with repeated measures (MMRM) analysis. Data from all on-treatment visits with ≥ 10 patients in each treatment group are included; dashed lines represent clinically meaningful change as defined by the minimally important difference (MID). The changes of LS mean of the scores show an initial deterioration followed by an improvement, most changes are confined within the MID thresholds [36].

Figure 9 Least squares changes from baseline on treatment in the MMRM analysis for the EQ-5D-3L health utility index (B), and EQ-VAS (C) in RELATIVITY-047 [36]

CI, confidence interval; EQ-VAS, EQ-5D-3L visual analogue scale; LS, least squares; MID, minimal important difference; MMRM, mixed-effect model for repeated measures; NIVO, nivolumab; RELA, relatlimab.

Table 41 HRQoL EQ-5D-3L summary statistics (adapted from supplementary materials of [36] Table S3, Table S4)

	Nivolumab + relatlimab		Nivolumab		Nivolumab + relatlimab vs. nivolumab	
	N	Mean (SE)	N	Mean (SE)	Difference (95% CI) p-value	
Mean baseline scores						
EQ-5D Utility index	315	0.78 (0.014)	323	0.78 (0.014)	0.000 (-0.038, 0.038) 1.000	
EQ-VAS	315	77.7 (1.087)	323	78.3 (1.079)	0.600 (-2.403, 3.603) 0.695	
Overall LS mean change from baseline to week 152						
	Mean score (95% CI)		Mean score (95% CI)		Difference in LS mean score (95% CI)	Prespecified MID for worsening
EQ-5D Utility index	−0.01 (−0.03 to 0.01)		−0.00 (−0.02 to 0.02)		0.01 (−0.03 to 0.01)	−0.08
EQ-VAS	2.23 (0.73 to 3.87)		2.87 (1.43 to 4.32)		−0.58 (−2.49 to 1.34)	-7

10.1.3.2 EQ-5D utility index and VAS results from CheckMate 067

Change in baseline in HRQoL for total quality-of-life population. The mean (SD) EQ-5D utility index score (labelled B in the figure below) at baseline was 0.803 (0.219) for nivolumab, 0.779 (0.234) for nivolumab + ipilimumab, and 0.791 (0.226) for ipilimumab; mean (SD) EQ-5D VAS score (labelled C on the figure below) at baseline was 75.9 (18.5) for nivolumab, 74.0 (19.9) for nivolumab + ipilimumab, and 75.8 (18.3) for ipilimumab. Clinical significance is denoted by the horizontal dashed lines, and it was determined by the MID value for each test, which was 0.8 points for EQ-5D utility index, and 7 points for EQ-5D VAS. No clinically meaningful difference occurred between the arms [37].

Figure 10 Change in baseline in EQ-5D utility index and VAS in CheckMate 067 [37]

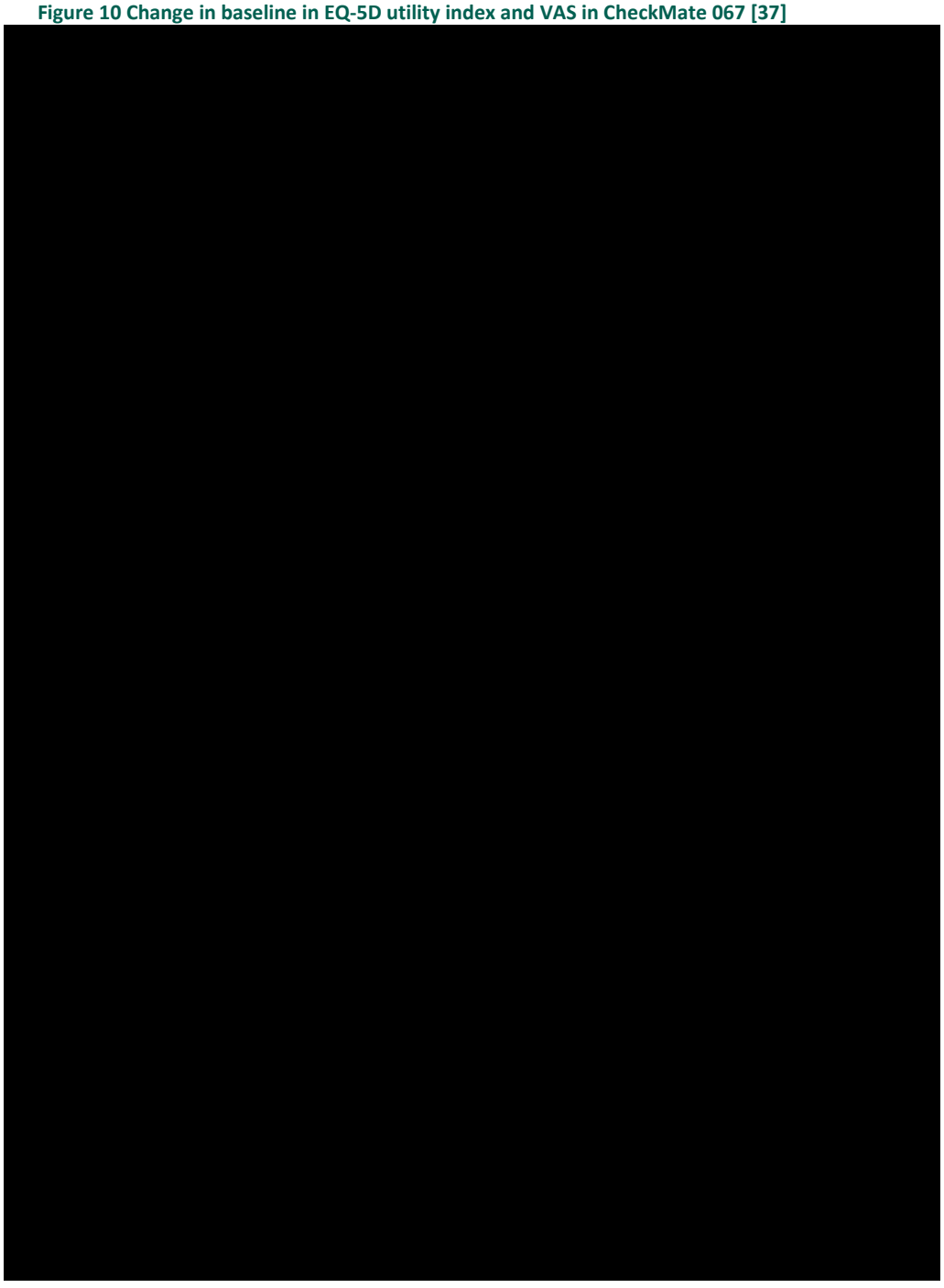


Table 42 HRQoL EQ-5D utility index and VAS summary statistics [37]

	Nivolumab + ipilimumab			Nivolumab			Nivolumab + ipilimumab vs. nivolumab	
	N	Mean start values (SE)	LS mean change (SE), p-value	N	Mean start values (SE)	LS mean change (SE), p-value	Mean change difference (95% CI) p-value	Standard mean difference (95% CI) p-value
Utility index	239	0.785 (0.015)	-0.019 (0.011), 0.096	264	0.803 (0.014)	0.001 (0.010), 0.957	-0.020 (95% CI: -0.049, 0.009) p=0.957	-0.089
VAS	239	74.1 (1.300)	-3.4 (1.0), <0.001b	264	75.9 (1.139)	-1.7 (0.9), 0.047b	-1.700 (95% CI: -4.337, 0.937) p=0.047	-0.088

10.1.3.3 Comparative analysis of EQ-5D-3L and EQ-VAS in CheckMate 067 and RELATIVITY-047

A comparison of HRQoL measures was not included in the ITC. However, a qualitative review of CheckMate 067 and RELATIVITY-047 indicates generally stable EQ-5D utility index and VAS scores across treatment arms, with no clinically meaningful differences between combination and monotherapy regimens within each trial. In both studies, an initial decline in EQ-5D utility index and VAS scores was observed after treatment initiation, followed by stabilisation or minor improvement over time. In the post-treatment period, RELATIVITY-047 showed a transient decline in both EQ-5D utility index and EQ-VAS, which later recovered. In contrast, CheckMate 067 did not report a significant decline in EQ-VAS after treatment discontinuation, suggesting potential differences in post-treatment HRQoL trajectories between the trials. The observed changes in EQ-5D utility index and VAS in both studies remained within predefined minimal important difference thresholds, confirming that no meaningful worsening of HRQoL occurred during the trial periods.

10.2 Presentation of the health-related quality of life Functional Assessment of Cancer Therapy-Melanoma (FACT-M)

10.2.1 Study design and measuring instrument

The primary HRQoL end points of interest in the RELATIVITY-047 trial were FACT-M total, FACT-M Trial Outcome Index, FACT-general (FACT-G) total, FACT-M melanoma subscale (MS) [36]. The FACT-M questionnaire assesses the effects of disease symptoms on functioning and well-being and includes all 27 items from the FACT-General (FACT-G) questionnaire (covering general, cancer-related HRQoL concepts of physical, functional, emotional, and social/family well-being), and a 16-item disease-specific melanoma subscale (MS) [61, 62].

The Functional Assessment of Cancer Therapy-Melanoma (FACT-M) is a patient-reported outcome measure specifically designed to assess the quality of life in individuals diagnosed with melanoma. The tool evaluates physical, emotional, social, and functional well-being as well as melanoma-specific dimensions, including symptoms, treatment side effects, and concerns about disease progression [63].

The FACT-M total score is comprised of the FACT-G physical, functional, emotional, and social/family well-being subscales and the MS. The FACT-M Trial Outcome Index (TOI) and FACT-G general physical well-being module question 5 (GP5; “I am bothered by side effects of treatment”) were evaluated as additional end points. The FACT-M TOI is the sum of physical well-being, functional well-being, and MS scores. GP5 is as a single-item overall summary measure of treatment toxicity burden and is rated on a 5-point Likert scale [64].

10.2.2 Data collection

HRQoL data were collected at baseline (after randomisation, but prior to the first dose of study treatment) and before dosing at each 4-week treatment cycle thereafter until disease progression or treatment discontinuation because of unacceptable toxicity, withdrawal of consent, end of study, or death. During the posttreatment period, all HRQoL assessments were performed at two follow-up safety visits (generally at 30 [± 7] days and 100 [± 7] days from the last dose), and only the FACT-M MS and EQ-5D-3L were assessed at subsequent follow-up survival visits (generally 3 months [± 14 days] after follow-up visit 2 and every 3 months [± 14 days] thereafter) [36]

Table 43 Pattern of missing data and completion rates of FACT-M at selected, representative timepoints (adapted from supplementary materials of [36])

Time point	HRQoL population N	Missing N (%)	Expected to complete N	Completion N (%)	HRQoL population N	Missing N (%)	Expected to complete N	Completion N (%)
	Nivo+rela	**N=355**			**Nivo**	**N=359**		
	Number of patients at randomization	Number of patients for whom data is missing (% of patients at randomization)	Number of patients "at risk" at time point X	Number of patients who completed (% of patients expected to complete)	Number of patients at randomization	Number of patients for whom data is missing (% of patients at randomization)	Number of patients "at risk" at time point X	Number of patients who completed (% of patients expected to complete)
Baseline	355	14 (3.9)	355	341 (96.1)	359	17 (4.7)	359	342 (95.3)
Week 36	355	186 (52.4)	183	169 (92.3)	359	207 (57.7)	162	152 (93.8)
Week 72	355	270 (76.1)	94	85 (90.4)	359	261 (72.7)	103	98 (95.1)
Week 108	355	319 (89.9)	40	36 (90)	359	305 (85)	55	54 (98.2)
Week 144	355	332 (93.5)	25	23 (92)	359	325 (90.5)	36	34 (94.4)
Week 152	355	344 (96.9)	12	11 (91.7)	359	334 (93)	26	25 (96.2)

Time point	HRQoL population N	Missing N (%)	Expected to complete N	Completion N (%)	HRQoL population N	Missing N (%)	Expected to complete N	Completion N (%)
	Nivo+rela	N=355			Nivo	N=359		
Follow-up (post treatment)	355	243 (68.5)	279	112 (40.1)	359	255 (71)	267	104 (39)
Safety visit 1	355	274 (77.2)	216	81 (37.5)	359	281 (78.3)	198	78 (39.4)
Safety visit 2	355	290 (81.7)	174	65 (37.4)	359	292 (81.3)	160	67 (41.9)
Survival visit 1	355	14 (3.9)	355	341 (96.1)	359	17 (4.7)	359	342 (95.3)

10.2.3 HRQoL results

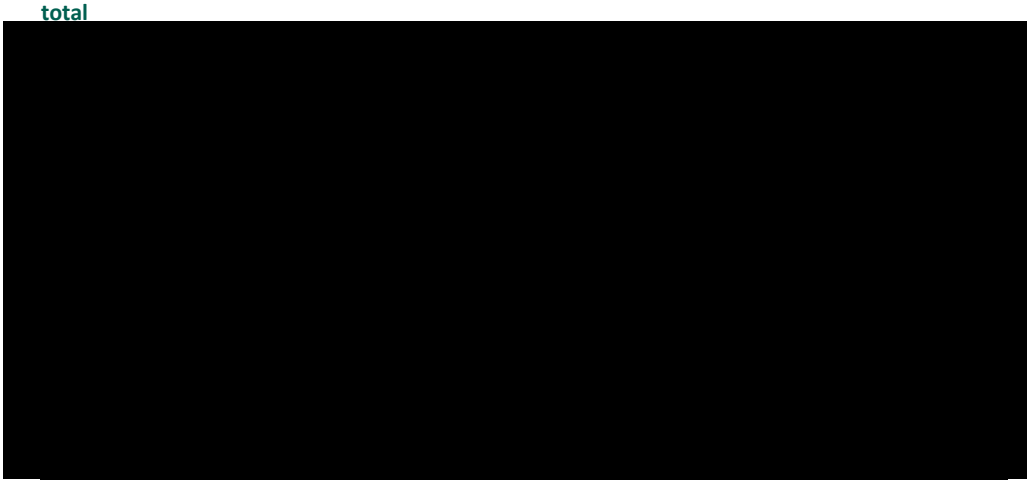
Table 44 shows the mean baseline FACT-M HRQoL scores. Standard error (SE) was replaced from the original table with standard deviation (SD). Patient disposition in FACT-M eligible population differs from the table above as it does not include 38 patients, who were excluded from the sample due to missing data [36]. Below the table Figure 11 is a graph displaying the mean change from baseline through the different data collection time points for both the intervention and comparator. Data from all on-treatment visits with ≥ 10 patients in each treatment group are included; dashed lines represent clinically meaningful change as defined by the minimal important difference [36].

Table 44 Mean baseline FACT-M summary statistics (adapted from supplementary materials of [36])

	Nivo+rela		Nivo		Nivo+rela vs. nivo
	N	Mean (SD)	N	Mean (SD)	Difference (95% CI) p-value
FACT-M	317	–	327	–	NA
FACT-M total	313	135.6 (24.1)	316	136.4 (22.9)	0.8 (-2.82, 4.42) ~0.666
FACT-M-TOI	314	95.6 (18.5)	318	96.4 (17.7)	0.8 (-2.02, 3.62) 0.576
FACT-G	313	82.6 (16.5)	317	82.8 (15.5)	0.2 (-2.31, 2.71) 0.876
FACT-M MS	316	53.0 (9.0)	325	53.7 (8.9)	0.7 (-0.69, 2.09) 0.322
Physical well-being	314	23.4 (5.1)	321	23.8 (5.0)	0.4 (-0.38, 1.18) 0.317
Social/family well-being	315	22.3 (5.4)	321	22.5 (5.1)	0.2 (-0.62, 1.02), 0.631
Emotional well-being	315	17.6 (4.3)	320	17.5 (4.4)	-0.1 (-0.79, 0.59) 0.770
Functional well-being	316	19.3 (6.5)	320	18.9 (6.3)	-0.4 (-1.40, 0.60), 0.437

Abbreviations: FACT, Functional Assessment of Cancer Therapy; FACT-G, Functional Assessment of Cancer Therapy-General; FACT-M, Functional Assessment of Cancer Therapy-Melanoma; HRQoL, health-related quality of life; MS, melanoma subscale; Nivo, nivolumab; Nivo+rela, nivolumab and relatlimab; SE, standard error; TOI, Trial Outcome Index;

Figure 11 LS mean changes from baseline on treatment in the MMRM analysis for the FACT-M total



Abbreviations: CI, confidence interval; EQ-VAS, EQ-5D-3L visual analogue scale; FACT-M, Functional Assessment of Cancer Therapy-Melanoma; LS, least squares; MID, minimal important difference; MMRM, mixed-effect model for repeated measures; NIVO, nivolumab; RELA, relatlimab.

10.3 Presentation of the health-related quality of life EORTC QLG Core Questionnaire (EORTC QLQ-C30)

10.3.1 Study design and measuring instrument

The EORTC QLQ-C30 is a self-administered, cancer-specific, 30-item questionnaire with a 1-week recall period. It incorporates five 2- to 5-item functional scales (physical, role, cognitive, emotional, and social), 3 2- to 3-item symptom scales (fatigue, pain, and nausea and vomiting), a 2-item global health status/QoL scale, and numerous single items that assess additional symptoms commonly reported by patients with cancer (e.g., dyspnoea, loss of appetite, insomnia, constipation, and diarrhoea) and the perceived financial impact of the disease. None of the items are shared between scales. All scales/items are linearly transformed to a 0 to 100 metric, with high functional scale scores representing high/healthy levels of functioning and high scores for symptom scales/items representing high levels of symptoms/problems [65, 66].The questionnaire was used according to its validation.

10.3.2 Data collection

HRQoL was assessed in all randomised patients at weeks 1 and 5 per 6-week cycle for the first 6 months, once every 6 weeks thereafter, and at two follow-up visits using the European Organization for Research and Treatment of Care Core Quality of Life Questionnaire (EORTC QLQ-C30) and EQ-5D questionnaire. In addition to the randomised population, patient subgroups, including BRAF mutation status, partial or complete response, treatment-related AEs of grade 3/4, and those who discontinued due to any reason and due to an AE, were investigated [37]. Missing items in the EORTC QLQ-C30 were imputed by using values equal to the average of the non-missing items for scales in which at least half of the items were completed. A scale in which fewer than half of the

items were completed was treated as missing and, once the instrument was scored, the missing data was not replaced [37]. In Table 45 completion rate is calculated using the number of patients with non-missing PRO data at baseline and data from ≥ 1 post-baseline visit, divided by the number of patients in the study at each respective time point.

At baseline completion rate is based on subjects having any baseline data with no post-baseline data requirement [37].

Table 45 Pattern of missing data and completion in CheckMate 067 trial, EORTC QLQ-C30 [37]

Time point	HRQoL population N	Missing N (%)	Expected to complete N	Completion N (%)	HRQoL population N	Missing N (%)	Expected to complete N	Completion N (%)	HRQoL population N	Missing N (%)	Expected to complete N	Completion N (%)
	Nivo	N= 316			Nivo+ipi	N= 314			Ipi	N= 315		
Baseline	316	32 (10.1)	316	284 (89.8)	314	24 (7.6)	314	290 (92.3)	315	36 (11.4)	315	279 (88.5)
Baseline plus ≥1	316	47 (14.8)	316	269 (85.1)	314	40 (12.7)	314	274 (87.2)	315	56 (17.7)	315	259 (82.2)
Week 5	316	88 (27.8)	302	228 (75.4)	314	132 (42)	293	182 (62.1)	315	95 (30.1)	300	220 (73.3)
Week 7	316	79 (25)	291	237 (81.4)	314	132 (42)	276	182 (65.9)	315	98 (31.1)	291	217 (74.5)
Week 11	316	118 (37.3)	271	198 (73)	314	201 (64)	226	113 (50)	315	152 (48.2)	244	163 (66.8)
Week 13	316	123 (38.9)	249	193 (77.5)	314	208 (66.2)	201	106 (52.7)	315	186 (59)	205	129 (62.9)
Week 17	316	160 (50.6)	220	156 (70.9)	314	231 (73.5)	164	83 (50.6)	315	212 (67.3)	158	103 (65.1)
Week 19	316	152 (48.1)	205	164 (80)	314	217 (69.1)	155	97 (62.5)	315	217 (68.8)	144	98 (68)
Week 23	316	183 (57.9)	188	133 (70.7)	314	227 (72.2)	137	87 (63.5)	315	239 (75.8)	118	76 (64.4)

Week 25	316	174 (55)	182	142 (78)	314	217 (69.1)	130	97 (74.6)	315	241 (76.5)	111	74 (66.6)
Week 31	316	195 (61.7)	164	121 (73.7)	314	222 (70.7)	125	92 (73.6)	315	265 (84.1)	87	50 (57.4)
Week 37	316	204 (64.5)	152	112 (73.6)	314	224 (71.3)	119	90 (75.6)	315	267 (84.7)	75	48 (64)
Week 43	316	216 (68.3)	145	100 (68.9)	314	240 (76.4)	114	74 (64.9)	315	271 (86)	65	44 (67.6)
Week 49	316	224 (70.8)	128	92 (71.8)	314	249 (79.2)	97	65 (67)	315	275 (87.3)	58	40 (68.9)
Week 55	316	253 (80)	100	63 (63)	314	266 (84.7)	72	48 (66.6)	315	291 (92.3)	43	24 (55.8)
Week 61	316	278 (87.9)	58	38 (65.5)	314	285 (90.7)	42	29 (69)	315	298 (94.6)	28	17 (60.7)
Week 67	316	303 (95.8)	21	13 (61.9)	314	298 (94.9)	22	16 (72.7)	315	306 (97.1)	13	9 (69.2)
Week 73	316	313 (99)	4	3 (75)	314	308 (98)	9	6 (66.6)	315	315 (100)	2	0 (0)
Week 79	316	314 (99.3)	2	2 (100)	314	313 (99.6)	2	1 (50)	315	315 (100)	0	NA
Follow-up 1c	316	220 (69.6)	104	96 (92.3)	314	209 (66.5)	108	105 (97.2)	315	191 (60.6)	136	124 (91.1)
Follow-up 2c	316	258 (81.6)	62	58 (93.5)	314	218 (69.4)	99	96 (96.9)	315	218 (69.2)	103	97 (94.1)

10.3.3 HRQoL results

Analyses were performed on all randomised patients with both a baseline and ≥ 1 post-baseline assessment. Subgroup analysis was also carried out.

Continuous data were described using descriptive statistics, and categorical data were summarised using counts and percentages. Mean changes from baseline at each time point were reported and assessed according to minimally important difference (MID) values, with statistical significance assessed at P ≤0.05. To assess longitudinal changes from baseline within and between each treatment, modelling was conducted using all observed data through week 55 via a mixed effects model for repeated measures (MMRM), including baseline PRO score and stratification factors as covariates. MMRM can give unbiased estimates with certain missing data contexts and can be more powerful than a two-sample t-test [37].

Slight deterioration from baseline started at week 5 and showed an overall trend toward stabilization from week 25. No clinically meaningful changes were observed in any treatment group while on treatment. Clinically meaningful deterioration was observed at week 7 for nivo+ipi for role functioning as well as the fatigue and appetite loss symptom scales [37].

In Table 46 additional columns were added to fit the outcomes from the trial: mean (SD) column contains the value at the start of the measurement, the following column contains the least squares mean change with standard error and p-value. Superscript *a* marks significant deterioration within arm.

To only present information relevant to this application, Table 46 below only includes a comparison of nivo+ipi vs nivo alone. The nivo+ipi vs ipi and nivo vs ipi comparisons have been excluded from this part.

Table 46 Nivo+ipi vs nivo EORTC QLQ C30 Function Scales global health status results (from supplementary materials of [37])

	Nivo+ipi			Nivo			Nivo+ipi vs nivo	
Domains	N	Mean start values (SD)	LS mean change (SE), *P* value	N	Mean start values (SD)	LS mean change (SE), *P* value	Mean change difference (95% CI), p-value	SMD (95% CI), P value
Global Health Status	239	70.9 (22.4)	-5.8 (1.0), <0.001[a]	266	74.7 (19.5)	-3.6 (0.9), <0.001[a]	-2.2 (−5.88,1.48), <0.001	-0.11 (−0.285,0.065), <0.001

In the graph below (Figure 12), mean (SD) EORTC QLQ-C30 global health score at baseline was 74.7 (19.4) for nivolumab, 70.7 (22.3) for nivo+ipi, and 73.5 (20.5) for

ipilimumab. Clinical significance, which is denoted by the horizontal dashed line at these points on the graph, was determined by the MID value and it was 10 points for EORTC QLQ-C30 [37]. Additionally, the included graph denotes overall response and rate of grade 3/4 adverse events as bars by treatment group.

Figure 12 Change in baseline in HRQoL for total quality-of-life population (from supplementary materials of [37])

In the analysis of data, the marked difference in the rate of grade 3/4 AEs observed in the three arms was not found to be causing a clinically meaningful difference in HRQoL. This may be explained by different factors, including drivers of HRQoL, or the fact that the instruments are designed to be used with patients who receive chemotherapy and may not detect the impact of the AEs observed with immunotherapy [37].

10.4 Health state utility values (HSUVs) used in the health economic model

The health economic analysis conducted for this submission was a cost-minimisation analysis, thus this section is not applicable.

10.4.1 HSUV calculation

N/A

10.4.1.1 Mapping

N/A

10.4.2 Disutility calculation

N/A

10.4.3 HSUV results

N/A

Table 47 Overview of health state utility values [and disutilities]

	Results [95% CI]	Instrument	Tariff (value set) used	Comments
N/A				

10.5 Health state utility values measured in other trials than the clinical trials forming the basis for relative efficacy

N/A

10.5.1 Study design

N/A

10.5.2 Data collection

N/A

10.5.3 HRQoL Results

N/A

10.5.4 HSUV and disutility results

N/A

Table 48 Overview of health state utility values [and disutilities]

	Results [95% CI]	Instrument	Tariff (value set) used	Comments
N/A				

Table 49 Overview of literature-based health state utility values

	Results [95% CI]	Instrument	Tariff (value set) used	Comments
N/A				

11. Resource use and associated costs

Cost parameters included in the cost-minimisation analysis were medicine acquisition and administration costs, costs associated with managing adverse events and non-medical costs in terms of patient and caregiver time and transportation cost. All costs are reported in DKK.

All other costs (e.g., disease management costs, subsequent treatment costs and palliative care costs) were assumed to be equivalent between nivo+rela and nivo+ipi and were therefore not included in the analysis.

11.1 Medicines - intervention and comparator

The mean number of doses received in the PD-L1 <1% populations that were randomized to nivo+rela and nivo+ipi from RELATIVITY-047 and CheckMate 067, respectively, were used in the cost-minimisation analysis. The two-year stopping rule was not included in either of the study protocols. Hence, in accordance with Danish clinical practice, the average doses were counted using a two-year stopping rule for both nivo+rela and nivo+ipi. Given that the minimum follow-up was more than two years for both studies, the data was fully matured.

The number of doses used in the cost-minimisation, treatment administration frequency and assumption on vial sharing are presented in Table 50. The acquisition costs are summarized in Table 51. Total vial sharing (no wastage) was assumed.

On average, PD-L1 <1% patients in RELATIVITY-047 randomised to nivo+rela received [redacted] doses of nivo+rela. Nivo+rela was administered every four weeks (Q4W). Thus, [redacted] doses of nivo+rela is used in the cost-minimisation.

On average, PD-L1 <1% patients in CheckMate 067 randomised to nivo+ipi received [redacted] doses of ipilimumab and [redacted] doses of nivolumab. In both CheckMate 067 and Danish clinical practice, nivo+ipi is administered as 1 mg/kg nivolumab plus 3 mg/kg ipilimumab Q3W for the first four doses followed by a monotherapy phase. In CheckMate 067 the nivolumab monotherapy was administrated as 3 mg/kg Q2W. However, in Danish clinical practice nivolumab monotherapy is administrated as 6 mg/kg Q4W. To estimate the number of doses used in Danish clinical practice the [redacted] nivolumab monotherapy doses (total doses minus combination doses: [redacted] from CheckMate 067 needs to be divided by two. In total, [redacted] doses of nivolumab + ipilimumab in combination and [redacted] doses of nivolumab monotherapy are used in the cost-minimisation analysis.

The average patient weight of 79.7 kg is used in the analysis, based on the average weight from Relativity-047, which was confirmed by the DMC [26].

Table 50 Medicines used in the model

Medicine	Dose	Relative dose intensity	Frequency	Vial sharing
Opdualag® (nivolumab + relatlimab)	480 mg nivolumab + 160 mg relatlimab per administration.	Not relevant as actual number of doses is used.	Every four weeks. In total [redacted] doses based on data from Relativity-047.	Not relevant
Ipilimumab	3 mg/kg	Not relevant as actual number of doses is used.	Every three weeks for up to 12 weeks. On average [redacted] doses based on data from CheckMate-067.	Yes
Nivolumab	1 mg/kg 6 mg/kg	Not relevant as actual number of doses is used.	In combination with ipilimumab (1 mg/kg) followed by six weeks break and hereafter every four weeks (6 mg/kg). On average [redacted] doses in combination phase and [redacted] doses in monotherapy phase based on data from CheckMate 067.	Yes

Table 51 Medicines used in the model (cost information)

Medicine	Strength	Package size	Pharmacy purchase price [DKK]
Opdualag® (nivolumab + relatlimab) (IV)	240 mg + 80 mg	1	49,540.18
Opdivo® (nivolumab) (IV)	100 mg	1	8,523.80
Yervoy® (ipilimumab) (IV)	200 mg	1	95,188.99

Abbreviations: IV, intravenous.

Source: Medicinpriser.dk – sourced on 16/09/2024 [38].

11.2 Medicine costs – co-administration

Not applicable.

11.3 Administration costs

An intravenous (IV) administration cost of 1,578 DKK was applied for all treatments per administration, based on the DRG 09MA98 (see Table 52) [39].

Table 52 Administration costs used in the model

Administration type	Frequency	Unit cost [DKK]	DRG code	Reference
Intravenous infusion	Dependent on the administration frequency of the different medicines and the total number of doses (see section 11.1)	1,578	09MA98 "MDC09 1-dagsgruppe, pat. mindst 7 år" derived from (DC439M) Malignant melanoma of the skin with metastases + (BWAA60) Medication by intravenous injection	Sundhedsdatastyrelsen 2025 [39].

11.4 Disease management costs

The costs of disease management are based on the assumption of similar efficacy and are therefore not included, as they would be the same.

Table 53 Disease management costs used in the model

Activity	Frequency	Unit cost [DKK]	DRG code	Reference
NA	NA	NA	NA	NA

11.5 Costs associated with management of adverse events

In the cost-minimisation analysis grade 3 or 4 adverse events are presented. See Table 36 in section 9.1 for the frequencies used in the model. Costs were sourced through Sundhedsdatastyrelsen Interaktiv DRG list [40].

Table 54 Cost associated with management of adverse events

Adverse event	DRG code	Aktionsdiagnose	Unit cost (DKK)

Anemia	16MA98	(DD630)Anæmi ved neoplastisk sygdom	2 208.00
Arthralgia	08MA17	(DM255)Ledsmerter	2 267.00
Asthenia	23MA03	(DR539)Utilpashed eller udmattelse UNS	5 271.00
Back pain	08MA98	(DM549)Rygsmerter UNS	1 684.00
Constipation	06MA11	(DK590)Forstoppelse	4 977.00
Cough	04MA98	(DR059)Hoste UNS	1 330.00
Decreased appetite	10MA98	(DR630)Appetitløshed	1 992.00
Diarrhea	06MA11	(DK591)Funktionel diarré	4 977.00
Fatigue	23MA03	(DR539)Utilpashed eller udmattelse UNS	5 271.00
Headache	23MA03	(DR519)Hovedpine UNS	5 271.00
Hypothyroidism	10MA01	(DE039)Hypothyroidisme UNS	1 790.00
Nausea	06MA11	(DR119B)Kvalme	4 977.00
Pruritus	09MA98	(DL298)Anden form for kløe	1 578.00
Pyrexia	18MA98	(DR509)Feber UNS	2 781.00
Rash	09MA98	(DR219)Hududslæt UNS	1 578.00
UTI	11MA98	DN390)Urinvejsinfektion uden angivelse af lokalisation	1 543.00
Vitiligo	09MA98	(DL809)Vitiligo	1 578.00

11.6 Subsequent treatment costs

In the base case analysis, costs of subsequent treatment are not included. This is based on the assumption that patients will receive similar subsequent treatment regimens regardless of whether they are treated with nivo+rela or nivo+ipi. However, a scenario

analysis was done to assess the cost impact of including subsequent treatment for both arms.

Table 55 presents the included medicines, dosing and the average time on subsequent treatment. The 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 for all subsequent therapies except for ipilimumab. For ipilumimab monotherapy the same assumption was made as for the initial treatment described in section 11.1. based on CheckMate 067.

Table 55 Medicines of subsequent treatments

Medicine	Dose	Relative dose intensity	Frequency	Vial sharing
Nivolumab mono	6 mg/kg every 4 weeks	Not relevant as actual number of doses is used.	[redacted]	Yes
Ipilimumab mono	3 mg/kg	Not relevant as actual number of doses is used.	[redacted]	Yes
Pembrolizumab mono	2 mg/kg ever 3 weeks	Not relevant as actual number of doses is used.	[redacted]	Yes
Dabrafenib + Trametinib combination	Dabrafenib, 150 mg (2x75 mg) twice daily (corresponding to a total daily dose of 300 mg). Trametinib, 2 mg once daily.	Not relevant as actual number of doses is used.	[redacted]	N/A

Table 56 Subsequent medicines used in the model (cost information)

Medicine	Strength	Package size	Pharmacy purchase price [DKK]
Opdivo® (nivolumab) (IV)	100 mg	1	8,524
Yervoy® (ipilimumab) (IV)	200 mg	1	95,189

Medicine	Strength	Package size	Pharmacy purchase price [DKK]
Pembrolizumab (IV)	25 mg/ml	4	21,574
Dabrafenib (oral)	75 mg	120	43,064
Trametinib (oral)	2 mg	30	44,916

Abbreviations: IV, intravenous.

Source: Medicinpriser.dk – sourced on 25/03/2025 [38].

11.7 Patient costs

The analysis adopted a limited societal perspective. This includes non-medical costs due to time and transportation spent due to treatment for the patient and caregiver. The costs were based on an hourly wage (DKK 188) taken from Værdisætning af Enhedsomkostninger 2024, by the DMC [41]. Transportation costs (DKK 140 per round trip) were also included [41]. The non-medical costs were applied according to the use of time each time patients had to be dosed. 100% of the patients were assumed to incur in non-medical costs, compared to only 50% of carers (Table 57).

Table 57 Patient costs used in the model

Activity	Unit cost [DKK]	Time spent [minutes, hours, days]
Patients (hourly rate)	188	Assumption: 0.5 hour for nivolumab + relatlimab administration. 1 hours for nivolumab + ipilimumab administration. 0.5 hour for nivolumab monotherapy administration. 100% of patients.
Transportation (round trip)	140	Same number of round trips as number of doses: [redacted] for nivolumab + relatlimab [redacted] for nivolumab + ipilimumab

11.8 Other costs (e.g. costs for home care nurses, out-patient rehabilitation and palliative care cost)

Not applicable.

12. Results

12.1 Base case overview

The base case settings for the cost-minimisation analysis of nivolumab + relatlimab and nivolumab + ipilimumab are presented in Table 58.

Table 58 Base case overview

Feature	Description
Comparator	Nivolumab + ipilimumab
Perspective	Limited societal
Type of model	Cost-minimisation
Time horizon	One year
Treatment line	First-line treatment of metastatic or unresectable melanoma with tumour cell PD-L1 expression < 1%.
Measurement and valuation of health effects	NA
Costs included	Medicine acquisition costs Medicine administration costs Costs associated with management of adverse events Patient costs
Dosage of medicine	Nivolumab + relatlimab has a fixed dose Nivolumab + ipilimumab dosing is based on weight
Average time on treatment	Number of doses from RELATIVITY-047 and CheckMate 067 are used instead of average time on treatment.
Parametric function for PFS	NA
Parametric function for OS	NA
Inclusion of waste	No
Average time in model health state	NA.

Feature	Description
Health state 1	
Health state 2	
Health state 3	
Death	

12.1.1 Base case results

Table 59 shows the cost-minimisation analysis results. The additional cost of nivo+rela was 503,334 DKK.

Table 59 Base case results

	Nivo+rela	Nivo+ipi	Difference
Medicine costs	1,129,516 DKK	628,590 DKK	500,926 DKK
Medicine costs – co-administration	NA.	NA.	NA.
Administration	17,989 DKK	14,754 DKK	3,235 DKK
Disease management costs	NA.	NA.	NA.
Costs associated with management of adverse events	496 DKK	1,462 DKK	-966 DKK
Subsequent treatment costs	NA.	NA.	NA.
Patient costs	3,203 DKK	3,064 DKK	139 DKK
Palliative care costs	NA.	NA.	NA.
Total costs	**1,151,204 DKK**	**647,871 DKK**	**503,334 DKK**
Life years gained (health state A)	NA.	NA.	NA.
Life years gained (health state B)	NA.	NA.	NA.
Total life years	NA.	NA.	NA.
QALYs (state A)	NA.	NA.	NA.
QALYs (state B)	NA.	NA.	NA.
QALYs (adverse reactions)	NA.	NA.	NA.
Total QALYs	NA.	NA.	NA.
Incremental costs per life year gained	NA.		

Incremental cost per QALY gained (ICER)	NA.

12.1.2 Scenario - Results including subsequent treatments

A cost comparison with subsequent treatments was assessed based on the different proportions and shares presented in section 8.3. The inclusion of subsequent treatments lowers the difference in cost comparison between the two treatments arm, with a saving of 114,686 DKK in favour of nivo + rela. The total cost comparison is a net additional cost of 388,648 DKK nivo + rela against nivo + ipi. The results are shown in table Table 60.

Table 60 Scenario - Subsequent treatment results

	Nivo+rela	Nivo+ipi	Difference
Medicine costs	1,129,516 DKK	628,590 DKK	500,926 DKK
Medicine costs – co-administration	NA.	NA.	NA.
Administration	17,989 DKK	14,754 DKK	3,235 DKK
Disease management costs	NA.	NA.	NA.
Costs associated with management of adverse events	496 DKK	1,462 DKK	-966 DKK
Subsequent treatment costs	358,609 DKK	473,294 DKK	-114,686 DKK
Patient costs	3,203 DKK	3,064 DKK	139 DKK
Palliative care costs	NA.	NA.	NA.
Total costs	**1,509,813 DKK**	**1,121,165 DKK**	**388,648 DKK**
Life years gained (health state A)	NA.	NA.	NA.
Life years gained (health state B)	NA.	NA.	NA.
Total life years	NA.	NA.	NA.
QALYs (state A)	NA.	NA.	NA.
QALYs (state B)	NA.	NA.	NA.
QALYs (adverse reactions)	NA.	NA.	NA.
Total QALYs	NA.	NA.	NA.
Incremental costs per life year gained	NA.		
Incremental cost per QALY gained (ICER)	NA.		

12.2 Sensitivity analyses

12.2.1 Deterministic sensitivity analyses

No sensitivity analyses were found to be relevant.

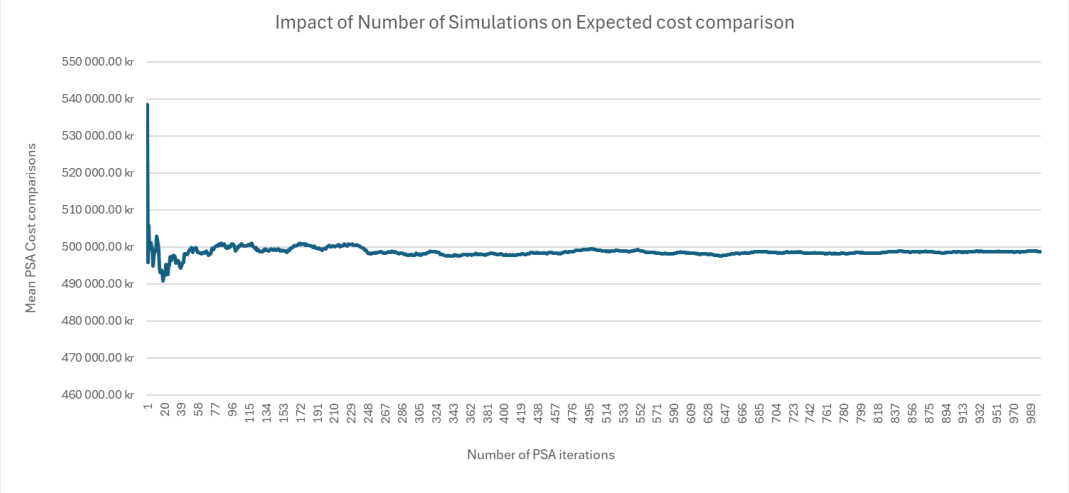
Table 61 One-way sensitivity analyses results

	Change	Reason / Rational / Source	Incremental cost (DKK)	Incremental benefit (QALYs)	ICER (DKK/QALY)
Base case	NA.	NA.	NA.	NA.	NA.

12.2.2 Probabilistic sensitivity analyses

A probabilistic sensitivity analysis (PSA) was performed to test the uncertainty of the parameters included in the cost comparison. The different distributions used and their specific are included in Appendix G. When the standard errors were unknown, it was assumed to be 10% of the mean deterministic value. The PSA was run for 1,000 iterations and the probabilistic results were consistent with the deterministic cost comparison, with a total difference of 498,730.96 DKK (95% CI 424,924 - DKK 571,318 DKK). Since the current analysis presented a cost minimisation model, both the relevant ICER scatter plot and cost-effectiveness acceptability curves (CEAC) were not available. In Figure 13, a convergence plot is presented for the estimated mean of the expected cost comparison as a function of the PSA iterations.

Figure 13 Convergence plot for the estimated total cost comparison



13. Budget impact analysis

A budget impact analysis was conducted and incorporated in the cost-minimisation analysis. A five-year projection was used in the analysis and costs were estimated for two scenarios:

Scenario 1) Nivo+rela is introduced as the 1L treatment of adults and adolescents 12 years of age and older with previously untreated metastatic or unresectable melanoma and with tumour cell PD-L1 expression < 1%.

Scenario 2) Nivo+rela is not introduced in the treatment algorithm.

Costs were estimated based on the expected number of eligible patients (described in section 3.2)The budget impact analysis was based on Pharmacy Purchasing Price (PPP) of all treatments. The following undiscounted costs (described in section 11) were included in the analysis:

- Medicine acquisition costs.
- Medicine administration costs.

Number of patients (including assumptions of market share)
As described in section 3.2, it was assumed that approximately 100 new patients would be eligible for treatment with nivo+rela each year. A constant number of eligible patients was assumed over the five-year period. Table 62 presents the estimated patient numbers for both scenarios one and two. The market share was assumed to be 50% in all years. The market share assumption is based on assumptions of clinical preferences.

Table 62 Number of new patients expected to be treated over the next five-year period if the medicine is introduced (adjusted for market share)

	Year 1	Year 2	Year 3	Year 4	Year 5
			Recommendation		
Nivo+rela	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Nivo+ipi	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
			Non-recommendation		
Nivo+rela	0	0	0	0	0
Nivo+ipi	100	100	100	100	100

Budget impact
The expected budget impact of introducing nivo+rela for the 1L treatment of adults and adolescents 12 years of age and older with previously untreated metastatic or unresectable melanoma and with tumour cell PD-L1 expression < 1% is presented in

Table 63. Nivo+rela is expected to have a budget impact of approximately DKK 25.1 million in year 5 after its introduction.

Table 63 Expected budget impact of recommending the medicine for the indication (DKK)

	Year 1	Year 2	Year 3	Year 4	Year 5
The medicine under consideration is recommended	89,640,349.7	89,640,349.7	89,640,349.7	89,640,349.7	89,640,349.7
The medicine under consideration is NOT recommended	64,480,605.0	64,480,605.0	64,480,605.0	64,480,605.0	64,480,605.0
Budget impact of the recommendation	25,159,744.7	25,159,744.7	25,159,744.7	25,159,744.7	25,159,744.7

14. List of experts

N/A

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Appendix A. Main characteristics of studies included

Table 64 and Table 65 show the main characteristics of the RELATIVITY-047 and CheckMate 067 studies, respectively.

Table 64 Main characteristic of studies included (RELATIVITY-047)

Trial name: RELATIVITY-047	NCT number: NCT03470922
Objective	The purpose of this study was to determine whether relatlimab in combination with nivolumab is more effective than nivolumab by itself in treating unresectable melanoma or melanoma that has spread.
Publications – title, author, journal, year	Long, G.V., et al., Overall Survival and Response with Nivolumab and Relatlimab in Advanced Melanoma. NEJM Evid, 2023. 2(4): p. EVIDoa2200239. Tawbi, H.A., et al., Relatlimab and Nivolumab versus Nivolumab in Untreated Advanced Melanoma. N Engl J Med, 2022. 386(1): p. 24-34. Schadendorf, D., et al., Health-related quality of life with nivolumab plus relatlimab versus nivolumab monotherapy in patients with previously untreated unresectable or metastatic melanoma: RELATIVITY-047 trial. Eur J Cancer, 2023. 187: p. 164-173.
Study type and design	Randomised (1:1), parallel assignment, quadruple masked, phase 2-3 trial.
Sample size (n)	Nivo+rela (n=355). Nivo (n=359).
Main inclusion criteria	• Participants must have histologically confirmed Stage III (unresectable) or Stage IV melanoma, per the AJCC staging system. • Participants must not have had prior systemic anticancer therapy for unresectable or metastatic melanoma. • Tumor tissue from an unresectable or metastatic site of disease must be provided for biomarker analyses.
Main exclusion criteria	• Participants must not have active brain metastases or leptomeningeal metastases. • Participants must not have uveal melanoma. • Participants must not have an active, known, or suspected autoimmune disease.
Intervention	Relatlimab + Nivolumab:

Trial name: RELATIVITY-047	NCT number: NCT03470922
	160 mg of relatlimab and 480 mg of nivolumab in a fixed-dose combination. Administered in a single 60-minute intravenous infusion every 4 weeks.
Comparator(s)	Nivolumab: 480 mg of nivolumab. Administered in a single 60-minute intravenous infusion every 4 weeks.
Follow-up time	Minimum follow-up time of 33 months. [redacted]
Is the study used in the health economic model?	No, a cost-minimisation analysis was conducted.
Primary, secondary and exploratory endpoints	**Endpoints included in this application:** The primary endpoint progression-free survival (PFS). PFS was defined as the time between the date of randomization and the date of first documented tumour progression, assessed by a blinded independent central review (BICR) (per RECIST v1.1 criteria), or death due to any cause, whichever occurs first. Subjects who die without a reported progression will be considered to have progressed on the date of their death. The secondary endpoint overall survival (OS). OS was defined as the time between the date of randomization and the date of death due to any cause. For subjects that are alive, their survival time will be censored at the date of last contact ("last known alive date"). **Other endpoints (not included in the application):** The secondary endpoint overall response rate (ORR). ORR is defined as the number of randomized subjects who achieve a best response of complete response (CR) or partial response (PR) based on BIRC assessments (using RECIST v1.1 criteria). Other pre-specified endpoints: • The number of participants experiencing adverse events (AEs). • The number of participants experiencing serious adverse events (SAEs). • The number of participants experiencing adverse events (AEs) leading to discontinuation. • The number of participant deaths in the study. • The number of participants experiencing laboratory abnormalities in specific liver tests.

Trial name: RELATIVITY-047	NCT number: NCT03470922
	• The number of participants experiencing laboratory abnormalities in specific thyroid tests.
Method of analysis	OS was compared between the randomized groups at final analysis by using a two-sided log-rank test stratified according to LAG-3 expression, American Joint Committee on Cancer metastasis stage, and BRAF mutation status. An O'Brien–Fleming a-spending function determined the nominal significance level for the final analysis to be P<0.043 (two-sided), with a cumulative design power of 69% for a target OS hazard ratio of 0.75. The Kaplan–Meier method was used to estimate OS and PFS curves, as well as both medians and rates for OS and PFS, within each treatment group along with corresponding 95% CI values. Two-sided 95% CIs were computed via the log-log transformation method, and OS rate estimate CIs were derived based on the Greenwood formula for variance derivation and on log-log transformation applied on the survivor function. For OS and PFS, hazard ratios and corresponding two-sided 95% CIs were estimated by using a Cox proportional-hazards model, with the treatment group as a single covariate, stratified according to the aforementioned stratification factors.
Subgroup analyses	The relevant patient population for this application is the prespecified patient subgroup of patients with PD-L1 expression <1%. In the relatlimab + nivolumab treatment arm, 209 patients had PD-L1 expression <1%. In the nivolumab treatment arm, 212 patients had PD-L1 expression <1%. The prespecified PFS, OS, and ORR subgroup analyses were exploratory and descriptive in nature.
Other relevant information	Not applicable.

Table 65 Main characteristic of studies included (CheckMate 067)

Trial name: CheckMate 067	NCT number: NCT01844505
Objective	The purpose of this study was to show that Nivolumab and/or Nivolumab in combination with Ipilimumab will extend progression free survival and overall survival compared to Ipilimumab alone.
Publications – title, author, journal, year	Wolchok, J.D., et al., Long-Term Outcomes With Nivolumab Plus Ipilimumab or Nivolumab Alone Versus Ipilimumab in Patients With Advanced Melanoma. J Clin Oncol, 2022. 40(2): p. 127-137.

Trial name: CheckMate 067	NCT number: NCT01844505
	Schadendorf, D., et al., Health-related quality of life results from the phase III CheckMate 067 study. Eur J Cancer, 2017. 82: p. 80-91.
Study type and design	Randomised (1:1:1), parallel assignment, quadruple masked, phase 3 trial.
Sample size (n)	Nivo (n=316). Nivo+ipi (n=314). Ipi (n=315).
Main inclusion criteria	• Histologically confirmed stage III (unresectable) or stage IV melanoma. • Treatment naïve patients. • Measurable disease by computed tomography (CT) or Magnetic Resonance Imaging (MRI) per RECIST 1.1 criteria. • Tumor tissue from an unresectable or metastatic site of disease for biomarker analyses. • Eastern Cooperative Oncology Group (ECOG) performance status (PS) 0 or 1.
Main exclusion criteria	• Active brain metastases or leptomeningeal metastases. • Ocular melanoma. • Subjects with active, known or suspected autoimmune disease. • Subjects with a condition requiring systemic treatment with either corticosteroids (>10 mg daily prednisone equivalents) or other immunosuppressive medications within 14 days of treatment. • Prior treatment with an anti-Programmed Death receptor-1 (PD-1), anti-Programmed Death-1 ligand-1 (PD-L1), anti-PD-L2, or anti-cytotoxic T lymphocyte associated antigen-4 (anti-CTLA-4) antibody.
Intervention	Nivolumab 1 mg/kg plus ipilimumab 3 mg/kg once every 3 weeks (four doses) followed by nivolumab 3 mg/kg once every 2 weeks.
Comparator(s)	Nivolumab 3 mg/kg once every 2 weeks, or Ipilimumab 3 mg/kg once every 3 weeks (four doses).
Follow-up time	6.5 years. Minimum follow-up for the study was 77 months.
Is the study used in the health economic model?	No, a cost-minimization analysis was conducted.

Trial name: CheckMate 067	NCT number: NCT01844505
Primary, secondary and exploratory endpoints	**Endpoints included in this application:** The primary endpoint progression-free survival (PFS). PFS was defined as the time between the date of randomization and the first date of documented progression, as determined by the Investigator, or death due to any cause, whichever occurred first. The primary endpoint overall survival (OS). OS was defined as the time between the date of randomization and the date of death. For participants without documentation of death, OS was censored on the last date the participant was known to be alive. The primary endpoint rate of overall survival. The overall survival rate at time T was defined as the probability that a participant was alive at time T following randomization. The primary endpoint rate of progression-free survival. Melanoma-specific survival (MSS), defined as death caused by melanoma, with deaths resulting from other causes censored. The rate of MSS. **Other endpoints (not included in the application):** The secondary endpoint objective response rate (ORR) per investigator assessment. The ORR was defined as the number of participants with a best overall response (BOR) of a complete response (CR) or partial response (PR) divided by the number of randomized participants for each arm. The secondary endpoint progression-free survival based on PD-L1 expression level. PD-L1 expression was defined as the percent of tumor cells demonstrating plasma membrane PD-L1 staining of any intensity using an IHC assay. The secondary endpoint overall survival based on PD-L1 expression level. The secondary endpoints mean change from baseline in European Organization for Research and Treatment of Cancer Quality of Life Questionnaire (EORTC QLQ-C30) Global Health Status, Social Functioning, Cognitive Functioning, Emotional Functioning, Role Functioning and Physical Functioning.
Method of analysis	Time-to-event distributions (i.e., progression-free survival and overall survival) and values at fixed timepoints were estimated using Kaplan-Meier methods. Hazard ratios and corresponding two-sided 95% Cis were estimated with a stratified Cox proportional hazards model, with descriptive p values also provided.
Subgroup analyses	The relevant patient population for this application is the prespecified patient subgroup of patients with PD-L1 expression <1%.

Trial name: CheckMate 067	NCT number: NCT01844505
	In the nivolumab+ipilimumab treatment arm, 123 patients had PD-L1 expression <1%. In the nivolumab treatment arm, 117 patients had PD-L1 expression <1%. The prespecified PFS, OS, and ORR subgroup analyses were exploratory and descriptive in nature.
Other relevant information	Not applicable.

Appendix B. Efficacy results per study

Results per study REALATIVITY-047

The results presented below are from the 3-year database lock update of the RELATIVITY-047 trial, for the relevant PD-L1 <1% population.

Table 66 Results per study, RELATIVITY-047, 3-year database lock, PD-L1 <1%

Results of [RELATIVITY-047 (NCT03470922)]											
				Estimated absolute difference in effect			Estimated relative difference in effect			Description of methods used for estimation	References
Outcome	Study arm	N	Result (CI)	Difference	95% CI	*P* value	Difference	95% CI	*P* value		
Median OS months	Nivo+rela	209	[redacted]	[redacted]	NA.	NA.	[redacted]	[redacted]	NA.	The Kaplan–Meier method was used to estimate OS and PFS curves, medians and rates for OS and PFS, with corresponding 95% CI values. The Cox proportional-hazards model was used for OS and PFS.	Data on file, [42]
	Nivo	212	[redacted]								Data on file [47]
Median BIRC assessed PFS	Nivo+rela	209	[redacted]	[redacted]	NA.	NA.	[redacted]	[redacted]	NA.		
	Nivo	212	[redacted]								

Results per study CheckMate 067

In Table 67 results are presented from the CheckMate 067 trial with a minimum of 90 months (7.5 years) for the relevant PD-L1 <1% population. Please note that the used in the ITC by Long et al [4] truncated the data to match the follow up between the trials. Results for the PD-L1 <1% subgroup (n=353) are presented Table 67.

Violations to the proportional hazards assumption were assessed and dismissed using the Schoenfeld residual test, as indicated by a *P* value of <.05 (resulting p-values for OS and PFS were p = 0.1829 for OS and p = 0.6350 for PFS) (data on file).

Table 67 Results per study CheckMate 067

Results of [CheckMate 067 (NCT01844505)]											
				Estimated absolute difference in effect			Estimated relative difference in effect			Description of methods used for estimation	References
Outcome	**Study arm**	**N**	**Result (CI)**	**Difference**	**95% CI**	***P* value**	**Difference**	**95% CI**	***P* value**		
Median OS, months	Nivo+ipi	123	[redacted]	[redacted]	NA.	NA.	[redacted]	[redacted]		The Kaplan–Meier method was used to estimate OS and PFS curves, medians and rates for OS and PFS, with corresponding 95% CI values. The Cox proportional-hazards	Data on file
	Nivo	117	[redacted]								
Median INV	Nivo+ipi	123	[redacted]	[redacted]	NA.	NA.	[redacted]	[redacted]			

Results of [CheckMate 067 (NCT01844505)]												
				Estimated absolute difference in effect			Estimated relative difference in effect			Description of methods used for estimation	References
Outcome	**Study arm**	**N**	**Result (CI)**	**Difference**	**95% CI**	***P* value**	**Difference**	**95% CI**	***P* value**		
assessed PFS, months	Nivo	117	[redacted]							model was used for OS and PFS.	

NA: not available, NR: not reached, HR: hazard ratio

Appendix C. Comparative analysis of efficacy

Table 68 Comparative analysis of studies comparing relatlimab and nivolumab to nivolumab and ipilimumab for patients with advanced (unresectable or metastatic) melanoma in with tumour cell PD-L1 expression < 1% [44]

Outcome		Absolute difference in effect			Relative difference in effect			Method used for quantitative synthesis	Result used in the health economic analysis?
	Studies included in the analysis	Difference	CI	P value	Difference	CI	P value		
Median OS, (months) unweighted	RELATIVITY-047 CheckMate 067	Not reached	NA.	NA.	HR: 1.04	0.77 – 1.41	NA.	A propensity score model was used to generate inverse probability of treatment weighting, which adjusted for any imbalances in the	NA.
Median OS, (months) weighted	RELATIVITY-047 CheckMate 067	Not reached	NA.	NA.	HR: 1.01	0.74 – 1.37	NA.		

Outcome		Absolute difference in effect			Relative difference in effect			Method used for quantitative synthesis	Result used in the health economic analysis?
	Studies included in the analysis	Difference	CI	P value	Difference	CI	P value		
Median PFS per INV, (months) unweighted	RELATIVITY-047 CheckMate 067	-4.1 months	NA.	NA.	HR: 1.20	0.92 1.56)	NA.	distribution of baseline characteristics between the two trials. The distribution of baseline characteristics was compared between the weighted cohorts using a standardized mean difference (SMD) of <0.2 to indicate balance between treatments [4]	
Median PFS per INV, (months) weighted	RELATIVITY-047 CheckMate 067	-3.4 months	NA.	NA.	HR: 1.16	0.89 – 1.51	NA.		
ORR per INV % unweighted	RELATIVITY-047 CheckMate 067	-3.6 %	NA.	NA.	OR: 0.86	0.64 - 1.17	NA.		
ORR per INV % weighted	RELATIVITY-047 CheckMate 067	[redacted]	NA.	NA.	[redacted]	[redacted]	NA.		

Abbreviations: HR, hazard ratio; NA,not available; INV, investigator

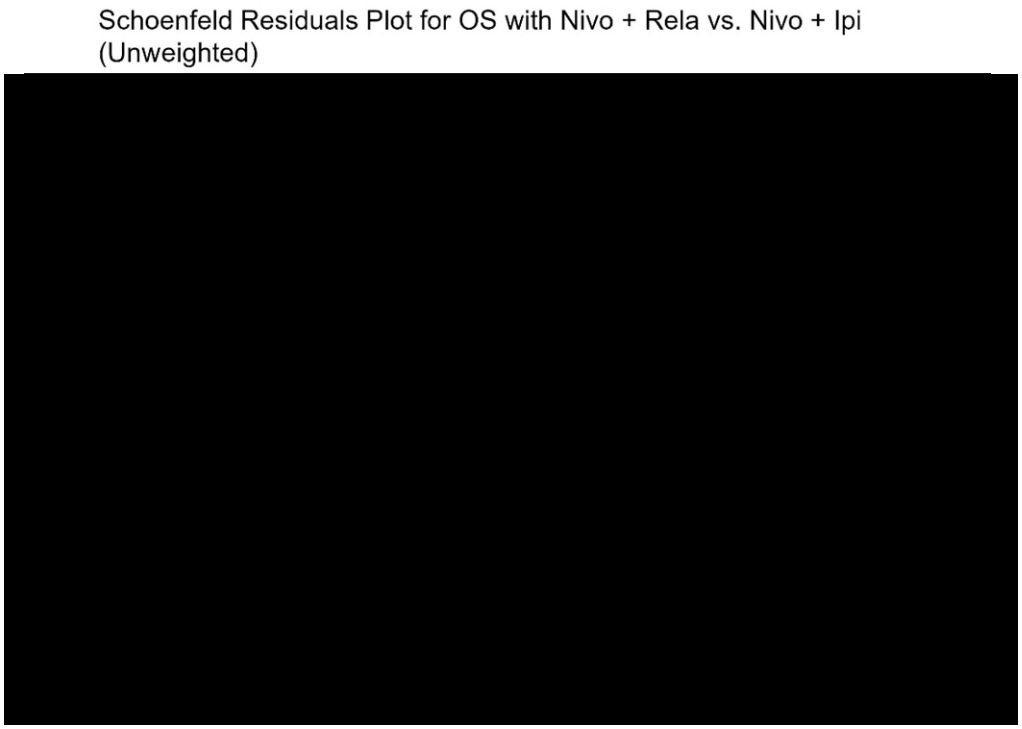


Figure 14 Schoenfeld Residuals plot for OS, unweighted

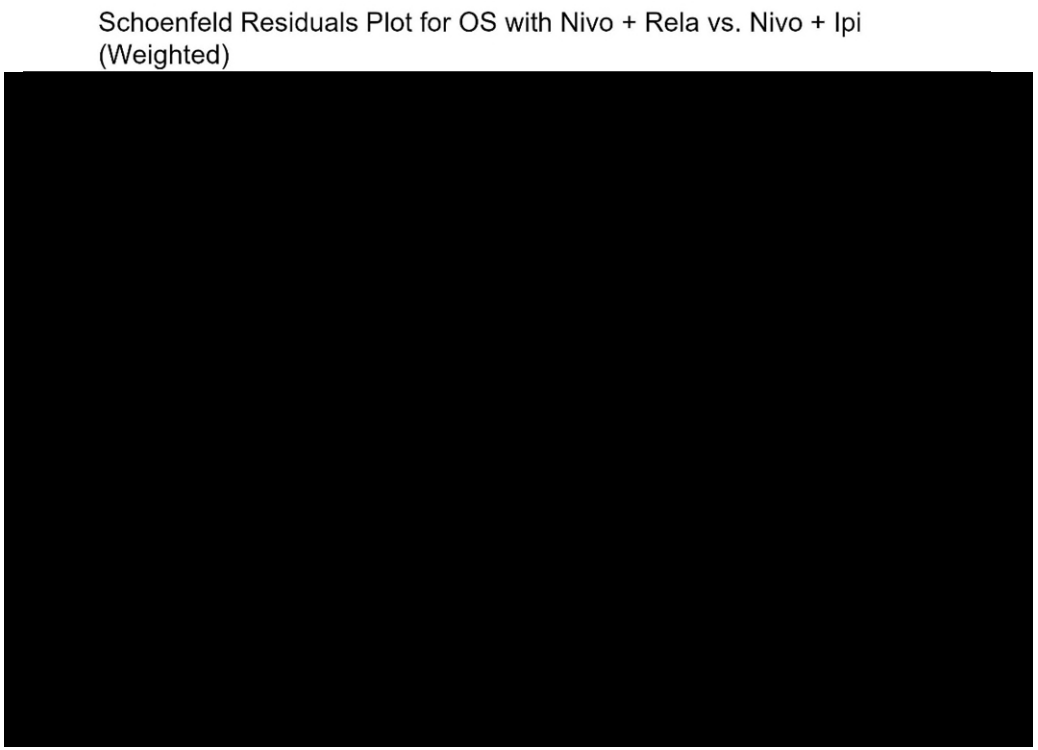


Figure 15 Schoenfeld Residuals plot for OS, weighted

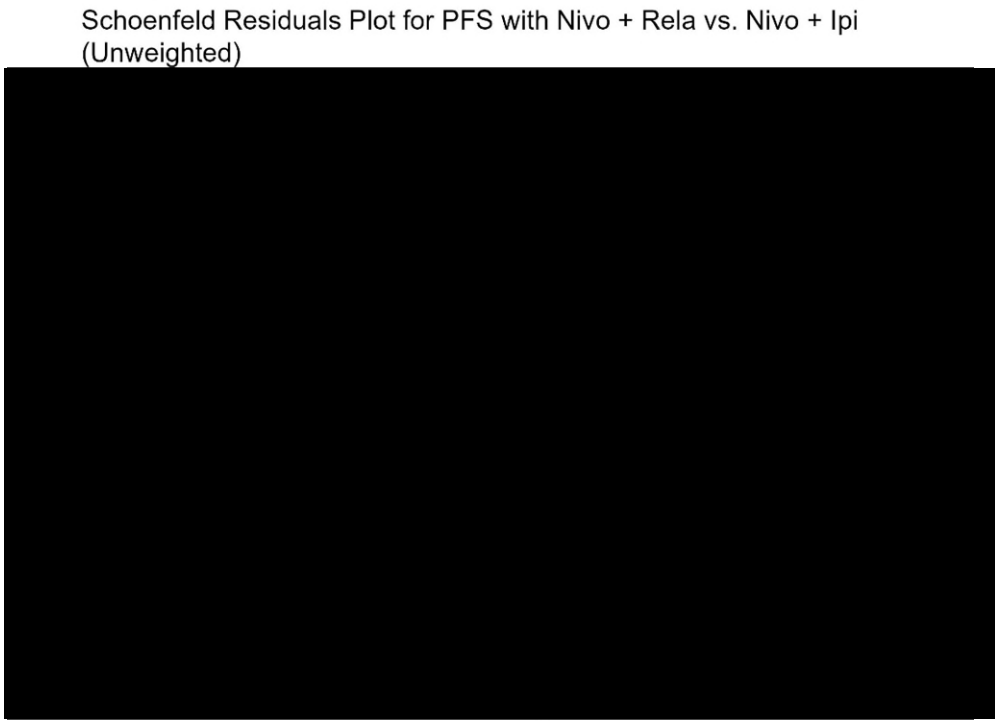


Figure 16 Schoenfeld Residuals plot for PFS, unweighted

Schoenfeld Residuals Plot for PFS with Nivo + Rela vs. Nivo + Ipi (Weighted)

Figure 17 Schoenfeld Residuals plot for PFS, weighted

Appendix D. Extrapolation N/A

[Describe in detail how extrapolation is performed in accordance with sections 6.4.2 and 6.4.3 of the methods guide and the online appendix "Anvendelse af forløbsdata i sundhedsøkonomiske analyser".

- Specify which parametric function was selected for the intervention and comparator, respectively. All standard parametric models (exponential, Weibull, Gompertz, gamma, log normal, log logistic and generalized gamma) and other considered extrapolations must be available in the Excel model.
- Specify if the extrapolation models for the intervention and comparator are fitted in a joint model or independently.
- The section must include a discussion about using the same or different parametric function to extrapolate data for the intervention and comparator.
- A graphical representation of the time-to-event data curves where both the Kaplan-Meier (KM) estimate and the parametric distributions are shown in the same figure must be presented in this section (for both intervention and comparator). The figure must include a graph with the general population's mortality rate and must display the entire time horizon of the model.
- Describe whether (and how) adjustments have been made for treatment switching/cross-over (intervention and/or comparator).
- Describe and explain how the extrapolations have been validated and present the results. When relevant, present a graphical representation of the validation.]

D.1 Extrapolation of [effect measure 1]

D.1.1 Data input

D.1.2 Model

D.1.3 Proportional hazards

[If the extrapolation model relies on proportional hazards, provide a plot with Schoenfeld residuals and a log-cumulative hazard plot.]

D.1.4 Evaluation of statistical fit (AIC and BIC)

[Provide a table with the AIC and BIC and discuss the statistical fit.]

D.1.5 Evaluation of visual fit

D.1.6 Evaluation of hazard functions

[Provide a plot of the hazard function of the effect measure. The plots must be presented in separate figures for the intervention and comparator, respectively, and must include the estimated hazard for the observed data (if applicable). The plot must be discussed in the context of chosen the distribution for extrapolating the data of the effect measure.]

D.1.7 Validation and discussion of extrapolated curves

D.1.8 Adjustment of background mortality

D.1.9 Adjustment for treatment switching/cross-over

D.1.10 Waning effect

D.1.11 Cure-point

D.2 Extrapolation of [effect measure 2]

[For each effect measure please, fill in this section using the same template as stated in section D.1]

Appendix E. Serious adverse events

E.1 Summary of SAE - RELATIVITY-047

Table 69 RELATIVITY-047 - Summary of all grade serious adverse events all grade, all treated subjects [56]

	Nivo+rela (N=355)	Nivo mono (N=359)
Total subject with an event	121 (34.1)	105 (29.2)
Infections and infestations	23 (6.5)	19 (5.3)
COVID-19	3 (0.8)	1 (0.3)
Pneumonia	3 (0.8)	3 (0.8)
Diverticulitis	2 (0.6)	0
Encephalitis	2 (0.6)	1 (0.3)
Sepsis	2 (0.6)	2 (0.6)
Urinary tract infection	2 (0.6)	3 (0.8)
Abscess soft tissue	1 (0.3)	0
Atypical pneumonia	1 (0.3)	1 (0.3)
Cellulitis	1 (0.3)	2 (0.6)
COVID-19 pneumonia	1 (0.3)	1 (0.3)
Device related infection	1 (0.3)	1 (0.3)
Erysipelas	1 (0.3)	2 (0.6)
Febrile infection	1 (0.3)	0
Infection	1 (0.3)	0
Influenza	1 (0.3)	0
Postoperative wound infection	1 (0.3)	0

Septic shock	1 (0.3)	0
Asymptomatic COVID-19	0	1 (0.3)
Gastroenteritis	0	1 (0.3)
Infected seroma	0	1 (0.3)
Lower respiratory tract infection	0	1 (0.3)
Pyelonephritis	0	1 (0.3)
Streptococcal sepsis	0	1 (0.3)
Tooth abscess	0	1 (0.3)
Upper respiratory tract infection	0	1 (0.3)
Urosepsis	0	1 (0.3)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	23 (6.5)	30 (8.4)
Malignant neoplasm progression	13 (3.7)	19 (5.3)
Basal cell carcinoma	2 (0.6)	3 (0.8)
Metastases to central nervous system	2 (0.6)	3 (0.8)
Breast cancer	1 (0.3)	0
Cancer pain	1 (0.3)	0
Infected neoplasm	1 (0.3)	1 (0.3)
Metastases to spine	1 (0.3)	0
Squamous cell carcinoma	1 (0.3)	2 (0.6)
Transitional cell carcinoma	1 (0.3)	0
Tumour associated fever	1 (0.3)	0
Tumour haemorrhage	1 (0.3)	1 (0.3)
Tumour pain	1 (0.3)	1 (0.3)

Bowen's disease	0	1 (0.3)
Metastases to adrenals	0	1 (0.3)
Metastasis	0	1 (0.3)
Gastrointestinal disorders	22 (6.2)	13 (3.7)
Colitis	4 (1.1)	1 (0.3)
Diarrhoea	4 (1.1)	2 (0.6)
Abdominal pain	3 (0.8)	0
Gastrointestinal disorders		
Constipation	2 (0.6)	0
Gastritis	2 (0.6)	1 (0.3)
Vomiting	2 (0.6)	1 (0.3)
Autoimmune colitis	1 (0.3)	0
Gastric volvulus	1 (0.3)	0
Intestinal obstruction	1 (0.3)	1 (0.3)
Melaena	1 (0.3)	0
Nausea	1 (0.3)	0
Oesophagitis	1 (0.3)	0
Rectal haemorrhage	1 (0.3)	0
Small intestinal obstruction	1 (0.3)	0
Abdominal pain upper	0	1 (0.3)
Ascites	0	1 (0.3)
Inguinal hernia	0	1 (0.3)
Pancreatitis	0	1 (0.3)
Proctalgia	0	1 (0.3)
Upper gastrointestinal haemorrhage	0	1 (0.3)

Musculoskeletal and connective tissue disorders	17 (4.8)	7 (1.9)
Back pain	4 (1.1)	2 (0.6)
Arthralgia	3 (0.8)	0
Myalgia	3 (0.8)	0
Arthritis	1 (0.3)	1 (0.3)
Autoimmune arthritis	1 (0.3)	1 (0.3)
Bursitis	1 (0.3)	0
Muscular weakness	1 (0.3)	1 (0.3)
Myositis	1 (0.3)	0
Osteoarthritis	1 (0.3)	0
Osteochondrosis	1 (0.3)	0
Pathological fracture	1 (0.3)	0
Polymyalgia rheumatica	1 (0.3)	0
Pain in extremity	1 (0.3)	2 (0.6)
Cardiac disorders	13 (3.7)	10 (2.8)
Myocarditis	4 (1.1)	1 (0.3)
Acute myocardial infarction	3 (0.8)	1 (0.3)
Arrhythmia	1 (0.3)	0
Atrial fibrillation	1 (0.3)	1 (0.3)
Bradycardia	1 (0.3)	0
Cardiac disorder	1 (0.3)	0
Myocardial infarction	1 (0.3)	1 (0.3)
Palpitations	1 (0.3)	0
Ventricular extrasystoles	1 (0.3)	0
Cardiac failure	0	1 (0.3)

Cardiac failure congestive	0	1 (0.3)
Coronary artery disease	0	1 (0.3)
Heart valve incompetence	0	1 (0.3)
Myocardial ischaemia	0	1 (0.3)
Sinus tachycardia	0	1 (0.3)
Respiratory, thoracic and mediastinal disorders	10 (2.8)	11 (3.1)
Dyspnoea	3 (0.8)	1 (0.3)
Pneumonitis	3 (0.8)	1 (0.3)
Acute respiratory failure	1 (0.3)	0
Chronic obstructive pulmonary disease	1 (0.3)	1 (0.3)
Pleural effusion	1 (0.3)	1 (0.3)
Pulmonary embolism	1 (0.3)	0
Pulmonary oedema	1 (0.3)	0
Respiratory failure	1 (0.3)	1 (0.3)
Dysphonia	0	1 (0.3)
Hypoxia	0	1 (0.3)
Lung disorder	0	1 (0.3)
Organising pneumonia	0	1 (0.3)
Pulmonary sarcoidosis	0	1 (0.3)
Tachypnoea	0	1 (0.3)
General disorders and administration site conditions	9 (2.5)	12 (3.3)
Pyrexia	3 (0.8)	3 (0.8)
General physical health deterioration	2 (0.6)	2 (0.6)
Asthenia	1 (0.3)	0

Death	1 (0.3)	1 (0.3)
Fatigue	1 (0.3)	1 (0.3)
Vascular stent stenosis	1 (0.3)	0
Chest pain	0	1 (0.3)
Inflammation	0	1 (0.3)
Pain	0	1 (0.3)
Sudden death	0	2 (0.6)
Nervous system disorders	9 (2.5)	5 (1.4)
Syncope	2 (0.6)	2 (0.6)
Dysdiadochokinesis	1 (0.3)	0
Guillain-Barre syndrome	1 (0.3)	0
Optic neuritis	1 (0.3)	1 (0.3)
Paraesthesia	1 (0.3)	0
Paraplegia	1 (0.3)	0
Radiculopathy	1 (0.3)	0
Spinal cord compression	1 (0.3)	0
Basilar artery thrombosis	0	1 (0.3)
Cerebrovascular accident	0	1 (0.3)
Headache	0	1 (0.3)
Endocrine disorders	8 (2.3)	1 (0.3)
Adrenal insufficiency	4 (1.1)	0
Adrenocortical insufficiency acute	1 (0.3)	0
Hypophysitis	1 (0.3)	0
Hypothyroidism	1 (0.3)	0
Lymphocytic hypophysitis	1 (0.3)	0

Endocrine disorders		
Hyperthyroidism	0	1 (0.3)
Metabolism and nutrition disorders	8 (2.3)	7 (1.9)
Dehydration	2 (0.6)	1 (0.3)
Hypokalaemia	2 (0.6)	0
Hyperglycaemia	1 (0.3)	0
Hyponatraemia	1 (0.3)	2 (0.6)
Metabolic acidosis	1 (0.3)	0
Type 1 diabetes mellitus	1 (0.3)	1 (0.3)
Diabetic ketoacidosis	0	1 (0.3)
Hypoglycaemia	0	1 (0.3)
Type 2 diabetes mellitus	0	2 (0.6)
Renal and urinary disorders	7 (2.0)	1 (0.3)
Acute kidney injury	2 (0.6)	1 (0.3)
Renal failure	2 (0.6)	0
Immune-mediated nephritis	1 (0.3)	0
Nephrolithiasis	1 (0.3)	0
Tubulointerstitial nephritis	1 (0.3)	0
Blood and lymphatic system disorders	4 (1.1)	2 (0.6)
Anaemia	3 (0.8)	1 (0.3)
Haemolytic anaemia	1 (0.3)	0
Acquired haemophilia	0	1 (0.3)
Hepatobiliary disorders	4 (1.1)	4 (1.1)
Autoimmune hepatitis	1 (0.3)	0
Bile duct stone	1 (0.3)	0

Hepatitis	1 (0.3)	0
Immune-mediated cholangitis	1 (0.3)	0
Cholecystitis	0	1 (0.3)
Cholestasis	0	1 (0.3)
Hepatitis toxic	0	1 (0.3)
Immune-mediated hepatitis	0	1 (0.3)
Injury, poisoning and procedural complications	4 (1.1)	8 (2.2)
Fall	1 (0.3)	1 (0.3)
Postoperative thrombosis	1 (0.3)	0
Spinal fracture	1 (0.3)	1 (0.3)
Thoracic vertebral fracture	1 (0.3)	0
Humerus fracture	0	1 (0.3)
Infusion related reaction	0	2 (0.6)
Jaw fracture	0	1 (0.3)
Lower limb fracture	0	1 (0.3)
Post procedural discomfort	0	1 (0.3)
Post procedural haemorrhage	0	1 (0.3)
Investigations	4 (1.1)	2 (0.6)
Lipase increased	1 (0.3)	0
Liver function test increased	1 (0.3)	0
Respiratory syncytial virus test positive	1 (0.3)	0
Troponin increased	1 (0.3)	1 (0.3)
Blood creatine phosphokinase MB increased	0	1 (0.3)

Troponin T increased	0	1 (0.3)
Vascular disorders	4 (1.1)	1 (0.3)
Aortic aneurysm	1 (0.3)	0
Aortic thrombosis	1 (0.3)	0
Embolism	1 (0.3)	0
Hypovolaemic shock	1 (0.3)	0
Iliac artery stenosis	1 (0.3)	0
Shock	1 (0.3)	0
Hypertensive crisis	0	1 (0.3)
Eye disorders	2 (0.6)	2 (0.6)
Ulcerative keratitis	1 (0.3)	0
Vogt-Koyanagi-Harada disease	1 (0.3)	0
Autoimmune uveitis	0	1 (0.3)
Papilloedema	0	1 (0.3)
Vision blurred	0	1 (0.3)
Psychiatric disorders	2 (0.6)	0
Confusional state	1 (0.3)	0
Suicide attempt	1 (0.3)	1 (0.3)
Ear and labyrinth disorders	1 (0.3)	0
Vertigo	1 (0.3)	0
Pregnancy, puerperium and perinatal conditions	1 (0.3)	0
Pregnancy	1 (0.3)	0
Skin and subcutaneous tissue disorders	1 (0.3)	5 (1.4)
Rash macular	1 (0.3)	0
Dermatitis	0	1 (0.3)

Dermatitis bullous	0	1 (0.3)
Lichen planus	0	1 (0.3)
Pemphigoid	0	1 (0.3)
Rash	0	1 (0.3)
Surgical and medical procedures	1 (0.3)	0
Tumour excision	1 (0.3)	0
Immune system disorders	0	1 (0.3)
Infusion related hypersensitivity reaction	0	1 (0.3)

[1]Includes events reported between first dose and 30 days after last dose of study therapy.

The terms from vocabulary for the adverse events correspond to MedDRA Version 23.1. and CTC Version 5.0.

Sources: [56]

E.2 Summary of SAE – CheckMate 067

Table 70 CheckMate 067 - Summary of all grade serious adverse events all grade, all treated subjects [58]

	Nivo mono (N=313)	Nivo+ipi (N = 313)
Total subjects with an event	133 (42.5)	233 (71.2)
Neoplasms benign, malignant and unspecified	48 (15.3)	24 (7.7)
Squamous cell carcinoma	8 (2.6)	1 (0.3)
Basal cell carcinoma	7 (2.2)	2 (0.6)
Malignant melanoma	4 (1.3)	0
Malignant neoplasm progression	25 (8.0)	16 (5.1)
Metastases to central nervous system	2 (0.6)	0
Prostate cancer	2 (0.6)	0
Adenoid cystic carcinoma of salivary gland	1 (0.3)	0

Bowen’s disease	0	1 (0.3)
Infected neoplasm	0	1 (0.3)
Metastases to bone	0	1 (0.3)
Metastases to meninges	0	1 (0.3)
Tumour pain	0	2 (0.6)
Gastrointestinal disorders	33 (10.5)	85 (27.2)
Diarrhoea	6 (1.9)	33 (10.6)
Abdominal pain	4 (1.3)	5 (1.6)
Colitis	3 (1.0)	31 (9.9)
Gastrointestinal haemorrhage	3 (1.0)	1 (0.3)
Vomiting	3 (1.0)	10 (3.2)
Ascites	2 (0.6)	2 (0.6)
Constipation	2 (0.6)	2 (0.6)
Dysphagia	2 (0.6)	0
Nausea	2 (0.6)	9 (2.9)
Small intestinal obstruction	2 (0.6)	2 (0.6)
Autoimmune colitis	1 (0.3)	1 (0.3)
Autoimmune pancreatitis	1 (0.3)	0
Diverticular perforation	1 (0.3)	0
Enteritis	1 (0.3)	0
Gastric haemorrhage	1 (0.3)	1 (0.3)
Gastrointestinal disorder	1 (0.3)	0
Lymphangiectasia intestinal	1 (0.3)	0
Pancreatitis	1 (0.3)	0
Retroperitoneal haemorrhage	1 (0.3)	0

Upper gastrointestinal haemorrhage	1 (0.3)	0
Chronic gastritis	0	1 (0.3)
Enterocolitis	0	1 (0.3)
Gastritis	0	1 (0.3)
Ileus paralytic	0	1 (0.3)
Intestinal perforation	0	1 (0.3)
Large intestine perforation	0	1 (0.3)
Rectal haemorrhage	0	1 (0.3)
Small intestinal perforation	0	1 (0.3)
Volvulus	0	1 (0.3)
General disorders and administration site conditions	14 (4.5)	47 (15.0)
Chest pain	3 (1.0)	0
General physical health deterioration	3 (1.0)	8 (2.6)
Fatigue	2 (0.6)	5 (1.6)
Pyrexia	2 (0.6)	26 (8.3)
Death	1 (0.3)	0
Hyperthermia	1 (0.3)	0
Malaise	1 (0.3)	0
Mucosal inflammation	1 (0.3)	0
Non-cardiac chest pain	1 (0.3)	0
Pain	1 (0.3)	4 (1.3)
Asthenia	0	1 (0.3)
Catheter site discharge	0	1 (0.3)
Influenza like illness	0	1 (0.3)

Performance status decreased	0	1 (0.3)
Sudden cardiac death	0	1 (0.3)
Sudden death	0	4 (1.3)
Respiratory, thoracic and mediastinal disorders	14 (4.5)	27 (8.6)
Dyspnoea	3 (1.0)	8 (2.6)
Pleural effusion	3 (1.0)	6 (1.9)
Pneumonitis	2 (0.6)	6 (1.9)
Pulmonary embolism	2 (0.6)	8 (2.6)
Atelectasis	1 (0.3)	0
Cough	1 (0.3)	2 (0.6)
Haemoptysis	1 (0.3)	1 (0.3)
Hepatic hydrothorax	1 (0.3)	0
Hypoxia	1 (0.3)	0
Pneumothorax	1 (0.3)	1 (0.3)
Pulmonary oedema	1 (0.3)	0
Respiratory failure	1 (0.3)	3 (1.0)
Asthma	0	2 (0.6)
Interstitial lung disease	0	3 (1.0)
Lung infiltration	0	1 (0.3)
Infections and infestations	11 (3.5)	29 (9.3)
Bronchitis	0	2 (0.6)
Gastroenteritis	0	3 (1.0)
Gastroenteritis viral	0	2 (0.6)
Groin abscess	0	1 (0.3)
Herpes zoster	0	1 (0.3)

Infective exacerbation of chronic obstructive airways disease	0	1 (0.3)
Lower respiratory tract infection	0	2 (0.6)
Lower respiratory tract infection	0	1 (0.3)
Pneumonia	0	6 (1.9)
Respiratory tract infection	0	1 (0.3)
Septic shock	0	1 (0.3)
Viral infection	0	1 (0.3)
Wound infection	0	1 (0.3)
Appendicitis	1 (0.3)	0
Clostridium bacteraemia	1 (0.3)	0
Clostridium difficile colitis	1 (0.3)	2 (0.6)
Peritonitis bacterial	1 (0.3)	1 (0.3)
Pneumocystis jirovecii pneumonia	1 (0.3)	0
Urinary tract infection	1 (0.3)	2 (0.6)
Cellulitis	2 (0.6)	2 (0.6)
Erysipelas	2 (0.6)	0
Lung infection	2 (0.6)	1 (0.3)
Sepsis	3 (1.0)	3 (1.0)
Musculoskeletal and connective tissue disorders	11 (3.5)	11 (3.5)
Nervous system disorders	7 (2.2)	0
Intraventricular haemorrhage	3 (1.0)	0
Back pain	2 (0.6)	2 (0.6)
Osteoarthritis	2 (0.6)	0

Groin pain	1 (0.3)	0
Intervertebral disc protrusion	1 (0.3)	0
Musculoskeletal chest pain	1 (0.3)	0
Musculoskeletal stiffness	1 (0.3)	0
Myalgia	1 (0.3)	0
Nerve compression	1 (0.3)	0
Pain in extremity	1 (0.3)	1 (0.3)
Pathological fracture	1 (0.3)	0
Polymyositis	1 (0.3)	0
Rotator cuff syndrome	1 (0.3)	0
Arthralgia	0	1 (0.3)
Arthritis	0	1 (0.3)
Arthropathy	0	1 (0.3)
Bone pain	0	1 (0.3)
Chondrocalcinosis pyrophosphate	0	2 (0.6)
Intervertebral disc disorder	0	1 (0.3)
Spinal pain	0	1 (0.3)
Nervous system disorder	1 (0.3)	15 (4.8)
Neuropathy peripheral	1 (0.3)	0
Peripheral motor neuropathy	1 (0.3)	0
Spinal claudication	1 (0.3)	0
Subarachnoid haemorrhage	1 (0.3)	0
Syncope	1 (0.3)	1 (0.3)
Diabetic coma	0	1 (0.3)
Epilepsy	0	1 (0.3)

Facial paralysis	0	1 (0.3)
Guillain-barre syndrome	0	1 (0.3)
Haemorrhagic stroke	0	1 (0.3)
Headache	0	2 (0.6)
Ischaemic stroke	0	1 (0.3)
Lethargy	0	1 (0.3)
Neuralgia	0	1 (0.3)
Paraparesis	0	1 (0.3)
Polynuropathy	0	1 (0.3)
Somnolence	0	1 (0.3)
Spinal cord compression	0	1 (0.3)
Transient ischaemic attack	0	2 (0.6)
Blood and lymphatic system disorders	6 (1.9)	9 (2.9)
Anaemia	4 (1.3)	3 (1.0)
Neutropenia	1 (0.3)	0
Thrombocytopenia	1 (0.3)	1 (0.3)
Febrile neutropenia	0	1 (0.3)
Hemolytic anemia	0	1 (0.3)
Lymphadenitis	0	1 (0.3)
Microcytic anemia	0	1 (0.3)
Normochromic normocytic anemia	0	1 (0.3)
Endocrine disorders	6 (1.9)	29 (9.3)
Adrenal insufficiency	2 (0.6)	0
Hypogonadism	2 (0.6)	0
Hyperparathyroidism	1 (0.3)	0

Hypopituitarism	1 (0.3)	2 (0.6)
Adrenal insufficiency	0	7 (2.2)
Adrenocortical insufficiency acute	0	1 (0.3)
Goitre	0	1 (0.3)
Hyperthyroidism	0	6 (1.9)
Hypophysitis	0	8 (2.6)
Hypothyroidism	0	2 (0.6)
Lymphocytic hypophysitis	0	1 (0.3)
Thyroiditis	0	2 (0.6)
Injury, poisoning and procedual complications	6 (1.9)	6 (1.9)
Multiple fractures	1 (0.3)	0
Osteoradionecrosis	1 (0.3)	0
Post procedural complication	1 (0.3)	0
Radius fracture	1 (0.3)	0
Spinal fracture	1 (0.3)	0
Tibia fracture	1 (0.3)	0
Urinary retention postoperative	1 (0.3)	0
Concussion	0	1 (0.3)
Femoral neck fracture	0	1 (0.3)
Hip fracture	0	1 (0.3)
Humerus fracture	0	1 (0.3)
Laceration	0	1 (0.3)
Procedural pneumothorax	0	1 (0.3)
Hepatobiliary disorders	5 (1.6)	20 (6.4)

Autoimmune hepatitis	2 (0.6)	6 (1.9)
Cholelithiasis	1 (0.3)	0
Hepatotoxicity	1 (0.3)	5 (1.6)
Portal hypertension	1 (0.3)	0
Cholecystitis acute	0	1 (0.3)
Hepatitis	0	4 (1.3)
Hepatitis acute	0	1 (0.3)
Hepatocellular injury	0	1 (0.3)
Hepatorenal failure	0	1 (0.3)
Hypertransaminasaemia	0	1 (0.3)
Skin and subcutaneous tissue disorder	5 (1.6)	4 (1.3)
Dermatitis exfoliative	1 (0.3)	0
Rash	1 (0.3)	0
Rash maculo-papular	1 (0.3)	0
Rash pruritic	1 (0.3)	0
Toxic skin eruption	1 (0.3)	0
Pemphigoid	0	1 (0.3)
Pruritus	0	1 (0.3)
Rash generalised	0	2 (0.6)
Metabolism and nutrition disorders	4 (1.3)	0
Diabetes mellitus	1 (0.3)	0
Diabetes mellitus inadequate control	1 (0.3)	0
Hyperglycaemia	1 (0.3)	0
Hypocalcaemia	1 (0.3)	0

Renal and urinary disorders	4 (1.3)	17 (5.4)
Renal failure	2 (0.6)	3 (1.0)
Acute kidney injury	1 (0.3)	7 (2.2)
Nephrolithiasis	1 (0.3)	0
Renal colic	1 (0.3)	0
Autoimmune nephritis	0	1 (0.3)
Dysuria	0	1 (0.3)
Glomerulonephritis	0	1 (0.3)
Nephropathy toxic	0	1 (0.3)
Perennial failure	0	1 (0.3)
Renal impairment	0	1 (0.3)
Tubulointerstitial nephritis	0	1 (0.3)
Vascular disorder	4 (1.3)	7 (2.2)
Embolism	1 (0.3)	0
Haematoma	1 (0.3)	0
Hypotension	1 (0.3)	0
Lymphorrhoea	1 (0.3)	0
Deep vein thrombosis	0	1 (0.3)
Hypertension	0	1 (0.3)
Hypotension	0	2 (0.6)
Inferior vena caval occlusion	0	1 (0.3)
Orthostatic hypotension	0	1 (0.3)
Superior vena cava syndrome	0	1 (0.3)
Investigations	3 (1.0)	17 (5.4)
Blood creatine phosphokinase increased	1 (0.3)	0

Liver function test increased	1 (0.3)	1 (0.3)
Transaminases increased	1 (0.3)	8 (2.6)
Alanine aminotransferase increased	0	3 (1.0)
Aspartate aminotransferase increased	0	2 (0.6)
Hepatic enzyme increased	0	3 (1.0)
Lipase increased	0	2 (0.6)
Cardiac disorder	2 (0.6)	10 (3.2)
Acute coronary syndrome	1 (0.3)	0
Atrial flutter	1 (0.3)	1 (0.3)
Atrial fibrillation	0	4 (1.3)
Atrioventricular block	0	1 (0.3)
Cardiac failure	0	1 (0.3)
Cardiac tamponade	0	1 (0.3)
Myocardial infarction	0	1 (0.3)
Sinus tachycardia	0	1 (0.3)
Eye disorder	1 (0.3)	2 (0.6)
Diplopia	1 (0.3)	1 (0.3)
Uveitis	0	1 (0.3)
Product issue	1 (0.3)	2 (0.6)
Device breakage	1 (0.3)	0
Device loosening	0	1 (0.3)
Device malfunction	0	1 (0.3)
Unassigned	1 (0.3)	0
Unassigned	1 (0.3)	0

Reproductive system and breast disorders	0	1 (0.3)
Ejaculation failure	0	1 (0.3)

[1]Includes events reported between first dose and 30 days after last dose of study therapy.

The terms from vocabulary for the adverse events correspond to MedDRA Version: 19.0 and CTC Version 4.0

Sources: [58]

Appendix F. Health-related quality of life N/A

Not applicable

Appendix G. Probabilistic sensitivity analyses

In Table 71 all the parameters included in the cost minimisation model are shown

Table 71. Overview of parameters in the PSA

Input parameter	Point estimate	Lower bound	Upper bound	Probability distribution
Baseline settings				
Weight	79.7			Normal
Duration of treatment (number of doses) - Opdualag (nivolumab + relatlimab)	11.4			Lognormal
Duration number of doses - Combination phase nivo+ipi	3.1			Lognormal
Duration number of doses - Nivolumab montheraphy phase	6.25			Lognormal
Proportion of caregivers	100%			Beta
Propotion of patients	50%			Beta
Time (hours) per administration - Opdualag	0.5			Lognormal
Time (hours) per administration - Nivolumab + Ipilimumab (combination phase)	1			Lognormal

Time (hours) per administration - Nivolumab monotherapy phase	0.5	Lognormal
Number of roundtrips - Opdualag	11.4	Lognormal
Number of roundtrips - Nivolumab + Ipilimumab (combination phase) AND Nivolumab monotherapy phase	9.35	Lognormal
AES rates - Opdualag		
Abdominal pain		Beta
Arthralgia	0.0%	Beta
Asthenia	0.8%	Beta
Colitis	0.3%	Beta
Cough	0.0%	Beta
Decreased appetite	0.0%	Beta
Decreased weight	0.0%	Beta
Diarrhoea	0.0%	Beta
Dyspnea	1.4%	Beta
Fatigue	0.0%	Beta
Headache	1.4%	Beta
Hyperthyroidism	0.0%	Beta
Hypophysitis	0.0%	Beta

Hypothyroidism	0.0%	Beta
Increased ALT	0.0%	Beta
Increased amylase	1.4%	Beta
Increased AST	0.0%	Beta
Increased lipase	1.4%	Beta
Myalgia	0.0%	Beta
Nausea	0.3%	Beta
Pneumonitis	0.0%	Beta
Pruritus	0.0%	Beta
Pyrexia	0.0%	Beta
Rash	0.0%	Beta
Vomiting	0.8%	Beta
AEs rates - Nivolumab + Ipilimumab		
Abdominal pain	0.3%	Beta
Arthralgia	0.6%	Beta
Asthenia	0.3%	Beta
Colitis	8.6%	Beta
Cough	0.3%	Beta
Decreased appetite	1.3%	Beta
Decreased weight	0.3%	Beta
Diarrhoea	11.2%	Beta
Dyspnea	1.0%	Beta

Fatigue	4.2%	Beta
Headache	0.6%	Beta
Hyperthyroidism	1.0%	Beta
Hypophysitis	1.6%	Beta
Hypothyroidism	0.3%	Beta
Increased ALT	9.9%	Beta
Increased amylase	2.9%	Beta
Increased AST	6.7%	Beta
Increased lipase	0.6%	Beta
Myalgia	0.3%	Beta
Nausea	2.2%	Beta
Pneumonitis	1.9%	Beta
Pruritus	1.9%	Beta
Pyrexia	0.6%	Beta
Rash	3.8%	Beta
Vomiting	2.2%	Beta
Costs		
Abdominal pain	5,103.00 kr	Gamma
Arthralgia	2,058.00 kr	Gamma
Asthenia	5,103.00 kr	Gamma
Colitis	1,561.00 kr	Gamma
Cough	5,103.00 kr	Gamma
Decreased appetite	5,103.00 kr	Gamma

Decreased weight	5,103.00 kr	Gamma
Diarrhoea	1,561.00 kr	Gamma
Dyspnea	5,103.00 kr	Gamma
Fatigue	5,103.00 kr	Gamma
Headache	5,103.00 kr	Gamma
Hyperthyroidism	3,000.00 kr	Gamma
Hypophysitis	3,000.00 kr	Gamma
Hypothyroidism	3,000.00 kr	Gamma
Increased ALT	1,947.00 kr	Gamma
Increased amylase	5,103.00 kr	Gamma
Increased AST	1,947.00 kr	Gamma
Increased lipase	5,103.00 kr	Gamma
Myalgia	5,103.00 kr	Gamma
Nausea	5,103.00 kr	Gamma
Pneumonitis	1,311.00 kr	Gamma
Pruritus	5,103.00 kr	Gamma
Pyrexia	5,103.00 kr	Gamma
Rash	2,322.00 kr	Gamma
Vomiting	5,103.00 kr	Gamma
Patients (hourly rate)	188	Gamma
Caregivers (hourly rate)	188	Gamma
Transportation (round trip)	140	Gamma

Administration cost	1,625 kr	Gamma
Average treatment duration	4.85	Lognormal
Share Subs Opdualag	0.435	Beta
Share Subs Nivo+Ipi	0.478	Beta
Ipilumab monotherapy	19.0%	Beta
Nivolumab monotherapy	20.6%	Beta
Pembrolizumab	9.5%	Beta
Tafinlar/mekinist	50.8%	Beta
Ipilumab monotherapy	10.0%	Beta
Nivolumab monotherapy	5.0%	Beta
Pembrolizumab	23.3%	Beta
Tafinlar/mekinist	61.7%	Beta
Pembrolizumab doses	27.6	Gamma
Tafinlar doses	1461.0	Gamma
Mekinist doses	730.4	Gamma

Appendix H. Literature searches for the clinical assessment N/A

H.1 Efficacy and safety of the intervention and comparator(s)

[Follow section 3 of the methods guide. Describe how the literature search was performed. Explain the selection of the search criteria and terms used, search filters, and the inclusion and exclusion criteria. Sufficient details should be provided so that the results may be reproduced.
Literature searches that are more than one year old are generally not accepted. If this is the case, a new search (e.g. in PubMed) should be carried out for more recent literature on the intervention and chosen comparator(s).

If an existing/global systematic literature review (SLR) is (re)used the appendix must be filled out with data/information from such SLR and it must be clear how the SLR has been adapted to the current application. The inclusion and exclusion criteria, PRISMA flowchart, and list of excluded full text references should reflect the purpose of the application. Thus, unedited technical reports or SLRs will not be accepted in/as the appendix. Please find an editable PRISMA flowchart at the end of this document. This diagram is to be used when existing SLRs are (re)used, so it is clear how it has been locally adapted, i.e. how many references are included and excluded from the original SLR. As mentioned above, if the literature search is more than a year old, a new search (e.g. in PubMed) should be carried out for more recent literature on the intervention and chosen comparator(s).

Objective of the literature search: What questions is the literature search expected to answer?

Databases/other sources: Fill in the databases and other sources, e.g. conference material used in the literature search.]

Table 72 Bibliographic databases included in the literature search

Database	Platform/source	Relevant period for the search	Date of search completion
Embase	e.g. Embase.com	E.g. 1970 until today	dd.mm.yyyy
Medline			dd.mm.yyyy
CENTRAL	Wiley platform		dd.mm.yyyy

Abbreviations:

Table 73 Other sources included in the literature search

Source name	Location/source	Search strategy	Date of search
e.g. NICE	www.nice.org.uk		dd.mm.yyyy
e.g. EMA website			dd.mm.yyyy

Abbreviations:

Table 74 Conference material included in the literature search

Conference	Source of abstracts	Search strategy	Words/terms searched	Date of search
Conference name	e.g. conference website	Manual search	List individual terms used to search in the conference material:	dd.mm.yyyy
	Journal supplement [insert reference]	Skimming through abstract collection		dd.mm.yyyy

H.1.1 Search strategies

[Describe the development of the search strategy and search string. Specify the inclusion and exclusion criteria for the search and justify (e.g. patient population, intervention, comparator, outcomes, study design, language, time limits, etc.).]

[The search must be documented with exact search strings line by line as run, incl. results, for each database.]

Table 75 of search strategy table for [name of database]

No.	Query	Results
#1		88244
#2		85778
#3		115048
#4		7011
#5		10053
#6		12332
#7		206348

No.	Query	Results
#8		211070
#9	#7 OR #8	272517
#10	#3 AND #6 AND #9	37

H.1.2 Systematic selection of studies

[Describe the selection process, incl. number of reviewers and how conflicts were resolved. Provide a table with criteria for inclusion or exclusion. If the table relates to an existing SLR broader in scope, please indicate which criteria are relevant for the current application.]

Table 76 Inclusion and exclusion criteria used for assessment of studies

Clinical effectiveness	Inclusion criteria	Exclusion criteria	Changes, local adaption
Population			
Intervention			
Comparators			
Outcomes			
Study design/publication type			
Language restrictions			

[Insert the PRISMA flow diagram(s) here (see example here) or use the editable diagram at the end of this document. If an existing SLR is used, the editable diagram is to be used, so it is clear how many references have been included and excluded from the original SLR.]

Table 77 Overview of study design for studies included in the analyses

Study/ID	Aim	Study design	Patient population	Interven-tion and compara-tor (sample size (n))	Primary outcome and follow-up period	Secondary outcome and follow-up period
Study 1						
Study 2						

H.1.3 Excluded fulltext references

[Please provide in a list or table the references that were excluded during fulltext screening along with a short reason. If using an existing, locally adapted SLR, please fill in the references originally included in the SLR but excluded in the current application.]

H.1.4 Quality assessment

[Describe strengths and weaknesses of the literature search performed.]

H.1.5 Unpublished data

[The quality of any unpublished data must be specifically addressed and a publication plan for unpublished data must be submitted].

Appendix I. Literature searches for health-related quality of life N/A

I.1 Health-related quality-of-life search

A literature search was not conducted as the applicant is data owner of the relevant publications presenting HRQoL.

Table 78 Bibliographic databases included in the literature search

Database	Platform	Relevant period for the search	Date of search completion
Embase	Embase.com		dd.mm.yyyy
Medline	Ovid		dd.mm.yyyy
Specific health economics databases[1]			dd.mm.yyyy

Abbreviations:

Table 79 Other sources included in the literature search

Source name	Location/source	Search strategy	Date of search
e.g. NICE	www.nice.org.uk		dd.mm.yyyy
ScHARRHUD	www.scharrhud.org		dd.mm.yyyy

Table 80 Conference material included in the literature search

Conference	Source of abstracts	Search strategy	Words/terms searched	Date of search
Conference name	e.g. conference website	Electronic search	List individual terms used to search in the	dd.mm.yyyy

[1] Papaioannou D, Brazier J, Paisley S. Systematic searching and selection of health state utility values from the literature. Value Health. 2013;16(4):686-95.

Conference	Source of abstracts	Search strategy	Words/terms searched	Date of search
			congress material:	
	Journal supplement [insert reference]	Skimming through abstract collection		dd.mm.yyyy

I.1.1 Search strategies

[Describe the development of the search strategy and search string. Enter the inclusion and exclusion criteria for the search and justify (e.g. patient population, outcomes, study design, language, time frame, etc.).

The search must be documented for each database or resource incl. terms and syntax used, number of results retrieved in the table below.

Describe which criteria have been used to reject irrelevant studies (for example of a table to record exclusions, see Table 5 in NICE DSU Technical Support Document 9) and how the final selection has been made. Use PRISMA charts if appropriate (see example here) or use the editable table at the end of this document].

Table 81 Search strategy for [name of database]

No.	Query	Results
#1		88244
#2		85778
#3		115048
#4		7011
#5		10053
#6		12332
#7		206348
#8		211070
#9	#7 OR #8	272517
#10	#3 AND #6 AND #9	37

Literature search results included in the model/analysis:

[Insert results in a table]

I.1.2 Quality assessment and generalizability of estimates

[Provide a complete quality assessment for each relevant study identified. When non-Danish estimates are used, generalizability must be addressed.]

I.1.3 Unpublished data

[The quality of any unpublished data must be specifically addressed and a publication plan for unpublished data must be submitted.]

Appendix J. Literature searches for input to the health economic model N/A

J.1 External literature for input to the health economic model

[Describe and document how the literature for the model was identified and selected. This may be a combination of systematic database searches, targeted searches etc. Explain in separate sections (for each type of search) the sources used, the selection of the search criteria and terms used, and explain the process for inclusion and exclusion. Sufficient details should be provided so that the results may be reproduced where possible.]

J.1.1 Example: Systematic search for […]

[Objective of the literature search: What questions is the literature search expected to answer?]

Table 51 Sources included in the search

Database	Platform/source	Relevant period for the search	Date of search completion
Embase	e.g. Embase.com	e.g. 1970 until today	dd.mm.yyyy
Medline			dd.mm. yyyy
CENTRAL	Wiley platform		dd.mm. yyyy

Abbreviations:

[Describe the selection process and criteria for inclusion or exclusion. For systematic searches, the requirements from the literature search for clinical evidence apply, see Appendix H].

J.1.2 Example: Targeted literature search for [estimates]

[Objective of the literature search: What questions is the literature search expected to answer?]

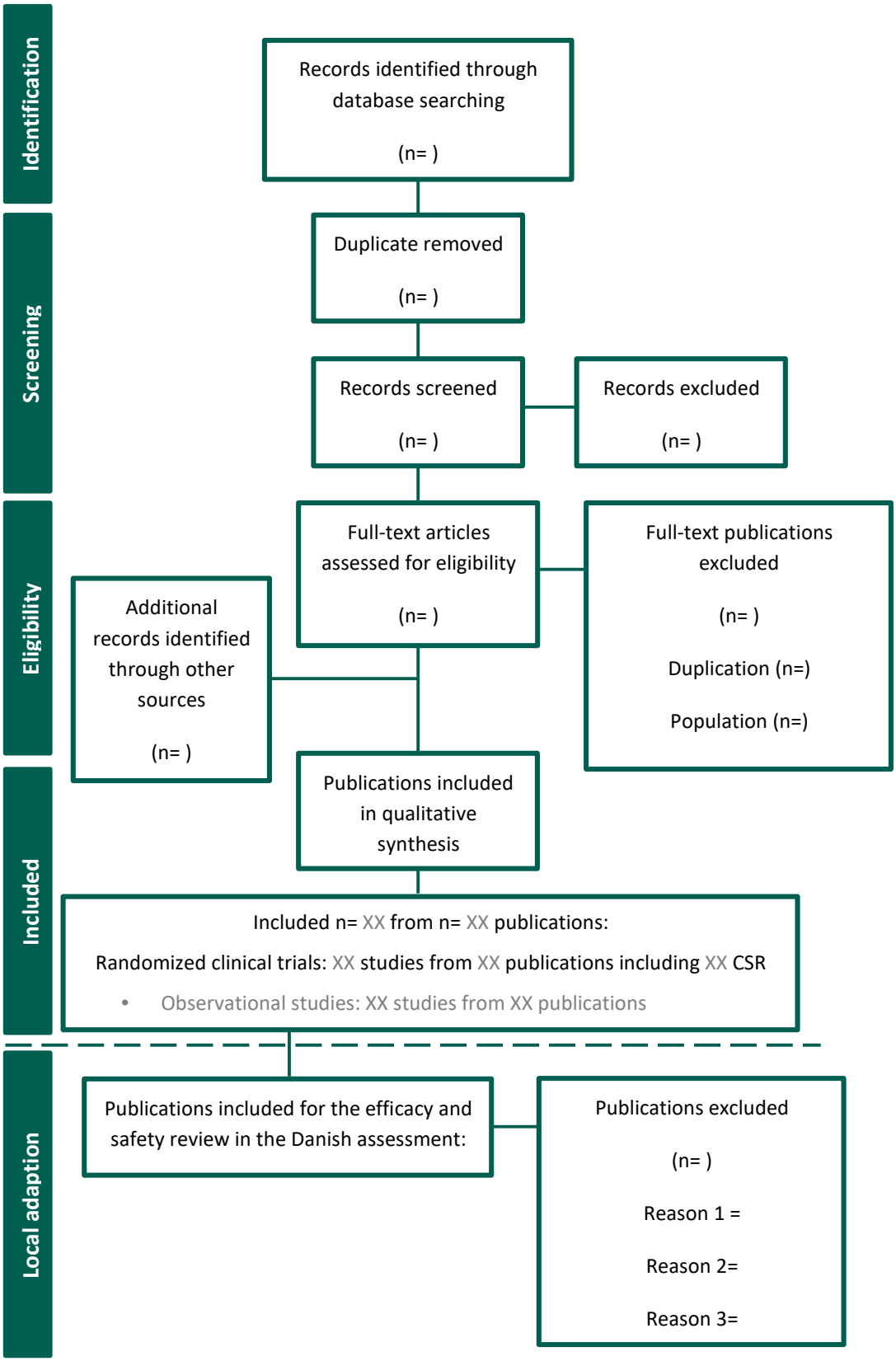
Table 52 Sources included in the targeted literature search

Source name/ database	Location/source	Search strategy	Date of search
e.g. NICE	www.nice.org.uk		dd.mm.yyyy
			dd.mm.yyyy

Abbreviations:

[Describe the selection process and criteria for inclusion or exclusion.]

Example of PRISMA diagram. The diagram is editable and may be used for recording the records flow for the literature searches and for the adaptation of existing SLRs.



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