Medicinrådet

Bilag til Medicinrådets anbefaling vedr. nivolumab til adjuverende behandling af muskelinvasivt urotelialt karcinom

Patienter med PD-L1-tumorcelle-ekspression ≥ 1 % og høj risiko for recidiv efter radikal operation

Vers. 1.0

Bilagsoversigt

1. Ansøgers notat til Rådet vedr. nivolumab til adjuverende behandling af muskelinvasivt urotelialt karcinom
2. Forhandlingsnotat fra Amgros vedr. nivolumab til adjuverende behandling af muskelinvasivt urotelialt karcinom
3. Ansøgers endelige ansøgning vedr. nivolumab til adjuverende behandling af muskelinvasivt urotelialt karcinom

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Virum, 16.12.2022.

Til Medicinrådet

Bristol Myers Squibbs tilbagemelding på udkast til vurderingsrapport for nivolumab til adjuverende behandling af muskelinvasivt urotelialt karcinom (adj. MIUC).

Bristol Myers Squibb (BMS) imødeser Medicinrådets (Rådet) anbefaling vedr. behandling med nivolumab til adj. MIUC og vil gerne takke for en rigtig god vurderingsrapport, som det er tydeligt af se bygger på et solidt fagligt arbejde med velbegrundede argumenter. BMS vil også gerne takke for et rigtig godt samarbejde på trods af den lange ventetid fra indsendelse af ansøgning (29.4.2022) til sagen blev taget op til validering (valideringsspørgsmål 23.8.2022).

BMS har kun enkelte kommentarer til vurderingsrapporten:

For det første undrer BMS sig over, at Rådet endnu engang undlader at vise ansøgers resultat. Rådet ændrer funktionen til ekstrapolering af kurverne for disease free survival fra Gompertz(BMS) til Gen. Gamma uden at vise resultatet fra ansøgningen.

Selvom Rådet begrunder ændringen med, at Gompertz er for optimistisk på baggrund af placeboarmen samt at Gen.Gamma har bedre statistisk fit, så er det en udfordring at ansøgers resultat ikke vises. Usikkerhed er et vilkår og selvom ændringen af funktion har minimal betydning i denne sag, er det vigtigt, at Rådet præsenteres for relevante scenarier så Rådet informeres tilstrækkeligt om usikkerheden forbundet med Medicinrådssekretariatets analyse. Dette kunne ske ved at Gompertz tilføjes som en følsomhedsanalyse i tillæg til Rådets følsomhedsanalyse med log-normal funktionen, som har et ringere fit til data end Gompertz.

For det andet kan den estimerede andel af PD-L1 positive patienter forventes at være lidt større end de 33 % (ca. 1/3) som Rådet beskriver i afsnit 1.2. I CheckMate274 havde ~40% PD-L1 ≥ 1% bestemt på tumorceller (hhv 39,7 % i nivolumabgruppen og 39,9 i placebogruppen). Diskrepansen mellem de 33 % og 40 %, kan skyldes, at PD-L1 markøren i CheckMate274 blev bestemt alene på tumorceller (TPS) og altså en anderledes metode end den scoringsnøgle, der f.eks. er benyttet i Keynote-052 i 1L/lokal avanceret blærekræft (Balar AV et al., The lancet 2017), hvor ca 30% havde en combined positive score (CPS) CPS≥10.

Med venlig hilsen,

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21. december 2022
DBS/CAF

Forhandlingsnotat

Dato for behandling i Medicinrådet	25. januar 2023
Leverandør	BMS
Lægemiddel	Opdivo (nivolumab)
Ansøgt indikation	Opdivo (nivolumab) til adjuverende behandling af muskelinvasivt urotelialt karcinom (patienter med PD-L1-tumorcelleekspression > 1% og høj risiko for recidiv efter radikal operation)

Forhandlingsresultat

Amgros har følgende pris på Opdivo (nivolumab).

Tabel 1: Forhandlingsresultat Opdivo (nivolumab)

Lægemiddel	Styrke	Pakningsstørrelse	AIP (DKK)	Forhandlet SAIP (DKK)	Rabatprocent ift. AIP
Opdivo (nivolumab)	240 mg/24 ml	1 stk.	21.453,65	[redacted]	[redacted]
Opdivo (nivolumab)	100 mg/10 ml	1 stk.	8.939,02	[redacted]	[redacted]
Opdivo (nivolumab)	40 mg/4 ml	1 stk.	3.598,42	[redacted]	[redacted]

Prisen vil være gældende indtil 31.12.2023.

[redacted]

Konkurrencesituationen

Der er på nuværende tidspunkt ingen konkurrence på Opdivo (nivolumab) til denne indikation.

[redacted]

Status fra andre lande

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

Konklusion

[redacted]

[1] https://nyemetoder.no/metoder/nivolumab-opdivo-indikasjon-xvi
[2] https://janusinfo.se/download/18.5e669ac418069c4cb9a2a41c/1651136553008/Opdivo-adjuvant-vid-urotelcellscancer-220428.pdf
[3] https://www.nice.org.uk/guidance/ta817/chapter/1-Recommendations

Application for the assessment of nivolumab (OPDIVO®) monotherapy for the adjuvant treatment of muscle-invasive urothelial carcinoma with tumour cell PD-L1 expression ≥ 1% at high risk of recurrence after radical resection

Contains confidential information (marked in yellow)

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1 Basic information

Contact information	
Name	Lasse Gundtoft
Title	Market Access Manager
Phone number	+45 20 45 47 97
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Overview of the pharmaceutical	
Proprietary name	OPDIVO®
Generic name	Nivolumab
Marketing authorisation holder in Denmark	Bristol Myers Squibb AB Hummeltoftevej 49 2830 Virum Denmark
ATC code	L01FF01
Pharmacotherapeutic group	Antineoplastic agents, monoclonal antibodies and antibody drug conjugates, PD-1/PD-L1 inhibitors.
Active substance(s)	Nivolumab
Pharmaceutical form(s)	IV infusion Concentrate for solution for infusion, sterile concentrate. Clear to opalescent, colourless to pale yellow liquid that may contain few light particles. The solution has a pH of approximately 6.0 and an osmolality of approximately 340 mg/kg.
Mechanism of action	Nivolumab is a human, monoclonal immunoglobulin G4 antibody that acts as a PD-1 inhibitor, blocking the interaction of PD-1 with PD-L1 and PD-L2. Binding of PD-L1 and PD-L2 to the PD-1 receptor found on T cells, inhibits T-cell proliferation and cytokine production. Nivolumab binds to the PD-1 receptor and blocks its interaction with PD-L1 and PD-L2, releasing PD-1 pathway-mediated inhibition of the immune response including the antitumour immune response, and helps to restore antitumour immune response.
Dosage regimen	240 mg every 2 weeks (30-minute IV infusion) or 480 mg every 4 weeks (60-minute IV infusion) for a maximum of 1 year
Therapeutic indication relevant for assessment (as defined by the European Medicines Agency [EMA])	**OPDIVO as monotherapy is indicated for the adjuvant treatment of adults with muscle-invasive urothelial carcinoma (MIUC) with tumour cell PD-L1 expression ≥ 1%, who are at high risk of recurrence after undergoing radical resection of MIUC**
Other approved therapeutic indications	**Melanoma** OPDIVO as monotherapy or in combination with ipilimumab is indicated for the treatment of advanced (unresectable or metastatic) melanoma in adults. Relative to nivolumab monotherapy, an increase in progression-free survival and overall survival for the combination of nivolumab with ipilimumab is established only in patients with low tumour PD-L1 expression. **Adjuvant treatment of melanoma** OPDIVO as monotherapy is indicated for the adjuvant treatment of adults with melanoma with involvement of lymph nodes or metastatic disease who have undergone complete resection. **Non–small cell lung cancer** OPDIVO in combination with ipilimumab and 2 cycles of platinum-based chemotherapy is indicated for the first-line treatment of metastatic non–small cell

Overview of the pharmaceutical	
	lung cancer in adults whose tumours have no sensitising EGFR mutation or ALK translocation. OPDIVO as monotherapy is indicated for the treatment of locally advanced or metastatic non–small cell lung cancer after prior chemotherapy in adults. **Malignant pleural mesothelioma** OPDIVO in combination with ipilimumab is indicated for the first-line treatment of adult patients with unresectable malignant pleural mesothelioma. **Renal cell carcinoma** OPDIVO as monotherapy is indicated for the treatment of advanced renal cell carcinoma after prior therapy in adults. OPDIVO in combination with ipilimumab is indicated for the first-line treatment of adult patients with intermediate/poor-risk advanced renal cell carcinoma. OPDIVO in combination with cabozantinib is indicated for the first-line treatment of adult patients with advanced renal cell carcinoma. **Classical Hodgkin lymphoma** OPDIVO as monotherapy is indicated for the treatment of adult patients with relapsed or refractory classical Hodgkin lymphoma after autologous stem cell transplant and treatment with brentuximab vedotin. **Squamous cell cancer of the head and neck** OPDIVO as monotherapy is indicated for the treatment of recurrent or metastatic squamous cell cancer of the head and neck in adults progressing on or after platinum-based therapy. **Urothelial carcinoma** OPDIVO as monotherapy is indicated for the treatment of locally advanced unresectable or metastatic urothelial carcinoma in adults after failure of prior platinum-containing therapy. **Adjuvant treatment of urothelial carcinoma** OPDIVO as monotherapy is indicated for the adjuvant treatment of adults with MIUC with tumour cell PD-L1 expression ≥ 1%, who are at high risk of recurrence after undergoing radical resection of MIUC. **Mismatch repair deficient or microsatellite instability-high colorectal cancer** OPDIVO in combination with ipilimumab is indicated for the treatment of adult patients with mismatch repair deficient or microsatellite instability-high metastatic colorectal cancer after prior fluoropyrimidine-based combination chemotherapy. **Oesophageal squamous cell carcinoma** OPDIVO as monotherapy is indicated for the treatment of adult patients with unresectable advanced, recurrent, or metastatic oesophageal squamous cell carcinoma after prior fluoropyrimidine- and platinum-based combination chemotherapy. OPDIVO in combination with fluoropyrimidine- and platinum-based combination chemotherapy is indicated for the first-line treatment of adult patients with unresectable advanced, recurrent, or metastatic oesophageal squamous cell carcinoma with tumour cell PD-L1 expression ≥ 1%. OPDIVO in combination with ipilimumab is indicated for the first-line treatment of adult patients with unresectable advanced, recurrent, or metastatic oesophageal squamous cell carcinoma with tumour cell PD-L1 expression ≥ 1%. **Adjuvant treatment of oesophageal or gastro-oesophageal junction cancer** OPDIVO as monotherapy is indicated for the adjuvant treatment of adult patients with oesophageal or gastro-oesophageal junction cancer who have residual pathologic disease following prior neoadjuvant chemoradiotherapy.

Overview of the pharmaceutical	
	Gastric, gastro-oesophageal junction or oesophageal adenocarcinoma OPDIVO in combination with fluoropyrimidine- and platinum-based combination chemotherapy is indicated for the first-line treatment of adult patients with HER2-negative advanced or metastatic gastric, gastro-oesophageal junction, or oesophageal adenocarcinoma whose tumours express PD-L1 with a combined positive score ≥ 5.
Will dispensing be restricted to hospitals?	Yes
Combination therapy and/or co-medication	No
Packaging – types, sizes/number of units, and concentrations	Each millilitre of concentrate for solution for infusion contains 10 mg of nivolumab. One vial of 4 mL contains 40 mg of nivolumab. One vial of 10 mL contains 100 mg of nivolumab. One vial of 12 mL contains 120 mg of nivolumab. One vial of 24 mL contains 240 mg of nivolumab.
Orphan drug designation	No

ALK = anaplastic lymphoma kinase; ATC = Anatomical Therapeutic Chemical Classification System; BMS = Bristol Myers Squibb; EGFR = epidermal growth factor receptor; HER2 = human epidermal growth factor receptor 2; IV = intravenous; MIUC = muscle-invasive urothelial carcinoma; PD-1 = programmed cell death protein 1; PD-L1 = programmed death-ligand 1; PD-L2 = programmed death-ligand 2.

2 Abbreviations

Abbreviation/term	Definition
AE	adverse event
AIC	Akaike information criterion
ALK	anaplastic lymphoma kinase
ATC	Anatomical Therapeutic Chemical Classification System
BIC	Bayesian information criterion
BMS	Bristol Myers Squibb
CBC	complete blood count
CEM	cost-effectiveness model
CI	confidence interval
CM	CheckMate
CSR	clinical study report
CT	computed tomography
DBL	database lock
DC	discontinuation
DF	Disease Free
DFS	disease-free survival
DMC	Danish Medicines Council
DMFS	distant metastasis-free survival
DR	Distant Recurrence
DRG	diagnosis-related group
DSA	deterministic sensitivity analysis

Abbreviation/term	Definition
DSS	disease-specific survival
DSU	Decision Support Unit
EC	European Commission
ECOG	Eastern Cooperative Oncology Group
EGFR	epidermal growth factor receptor
EMA	European Medicines Agency
EORTC	European Organisation for Research and Treatment of Cancer
EORTC QLQ-C30	European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire–Core Module
FDA	Food and Drug Administration
FU	follow-up
G-CSF	granulocyte colony-stimulating factor
GP	general practitioner
HBV	hepatitis B virus
HCV	hepatitis C virus
HD-MVAC	high-dose mitoxantrone, vinblastine, and CCNU (lomustine)
HER2	human epidermal growth factor receptor 2
HR	hazard ratio
HRQOL	health-related quality of life
HSUV	health-state utility value
HTA	health technology assessment
ICER	incremental cost-effectiveness ratio
ICUR	incremental cost-utility ratio
IHC	immunohistochemistry
IMAE	immune-mediated adverse event
IQR	interquartile range
ITT	intention to treat
IUC	(muscle) invasive urothelial carcinoma
IV	intravenous
KM	Kaplan-Meier
LCI	lower confidence interval
LR	Local Recurrence
LS	least squares
LY	life-year
LYG	life-year gained
mDFS	median disease-free survival
MedDRA	Medical Dictionary for Regulatory Activities
MIBC	muscle-invasive bladder cancer
MIUC	muscle-invasive urothelial carcinoma
MMRM	mixed model repeated measures

Abbreviation/term	Definition
mUC	metastatic urothelial carcinoma
MVAC	mitoxantrone, vinblastine, and CCNU (lomustine)
NA	not applicable or not available
NCI-CTCAE	National Cancer Institute Common Terminology Criteria for Adverse Events
NCT	National Clinical Trial
NE	not estimable
NICE	National Institute for Health and Care Excellence
NIVO	nivolumab
NoMA	Norwegian Medicines Agency
NR	not reached
NUTRFS	non–urothelial-tract recurrence-free survival
OESI	other event of special interest
OS	overall survival
PBO	placebo
PD-1	programmed cell death protein 1
PD-L1	programmed death-ligand 1
PD-L2	programmed death-ligand 2
PFS	progression-free survival
PRS	postrecurrence survival
PS	performance status
PSA	probabilistic sensitivity analysis
Q2W	every 2 weeks
Q3W	every 3 weeks
Q4W	every 4 weeks
QALY	quality-adjusted life-year
QOL	quality of life
RD	Recurred Disease
RMST	restricted mean survival time
SAE	serious adverse event
SD	standard deviation
SE	standard error
SG	standard gamble
SMC	Scottish Medicines Consortium
SmPC	summary of product characteristics
TBC	to be confirmed
TLV	Swedish Dental and Pharmaceutical Benefits Agency
TNM	tumour-node-metastasis
TRAE	treatment-related adverse event
TTO	time–trade-off
UCI	upper confidence interval

Abbreviation/term	Definition
US	United States
VAB	virtual advisory board
VAS	visual analogue scale
WTP	willingness to pay

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3 Tables and Figures

4 Summary

4.1 Indication

Nivolumab monotherapy is indicated for the adjuvant treatment of adults with muscle-invasive urothelial carcinoma (MIUC) with tumour cell programmed death-ligand 1 (PD-L1) expression ≥ 1%, who are at high risk of recurrence after undergoing radical resection of MIUC. High risk of recurrence is defined as[1]:

- ypT2-ypT4a or ypN+[1] who received neoadjuvant cisplatin chemotherapy, or
- pT3-pT4a or pN+[1] who had not received neoadjuvant cisplatin chemotherapy and were not eligible for or refused adjuvant cisplatin chemotherapy.

This indication received a positive opinion by The Committee for Medicinal Products for Human Use on 24 February 2022 and was granted European Commission (EC) approval on 1 April 2022 based on the efficacy, safety, and health-related quality-of-life (HRQOL) outcomes demonstrated in the pivotal phase 3 study CheckMate-274.[2-5]

4.2 Disease overview

Urothelial carcinoma (also known as *transitional cell carcinoma*) begins in the urothelial cells lining the mucosal surfaces of the lower urinary tract (including the urethra and bladder) and the upper urinary tract (including the ureter and renal pelvis) (see Figure 1).[6] In 90% to 95% of cases, urothelial carcinoma develops in the bladder; in approximately 5% to 10% of cases, urothelial carcinoma develops in the upper urinary tract.[7,8] It has been reported that 20% to 40% of urothelial carcinoma cells express PD-L1.[1,9]

Urothelial carcinoma is considered to be muscle invasive when it invades the muscularis propria and beyond and is classified as T2-T4a (see Figure 3) using the tumour-node-metastasis (TNM) staging system.[10,11]

The availability of epidemiological data relating specifically to urothelial carcinoma is limited. Instead, most data focus either on all types of cancer in the urinary tract (not just urothelial carcinoma) or only bladder cancer (where most urothelial carcinomas originate). In Denmark, 21,637 people (15,919 males and 5,718 females) were living with a diagnosis of urinary tract cancer at the end of 2019 and approximately 1,695 and 617 new cases are diagnosed in males and females, respectively, each year.[12] Age-standardised relative survival for urinary tract cancer in Denmark at 1 year is 91.0% (male) and 86.0% (female) and at 5 years is 80.0% (male) and 72.9% (female) (see Table 4)[12] but varies greatly according to stage of disease. Data about this from Denmark are not available, but data from other countries show that survival for late-stage disease may be as low as 10% to 12%.[13,14]

4.3 Current management of muscle-invasive urothelial carcinoma and unmet medical need

The Danish Multidisciplinary Cancer Group (Danske Multidisciplinære Cancer Grupper) recommends that the primary treatment of patients with muscle-invasive bladder cancer (T2-T4a, N0-NX, M0) is radical cystectomy with lymph node excision preceded by neoadjuvant chemotherapy (if patients are eligible for chemotherapy). Routine use of adjuvant chemotherapy is not recommended.[15]

For patients with MIUC in the upper urinary tract, the primary treatment is radical nephroureterectomy. Neoadjuvant chemotherapy and adjuvant chemotherapy are not routinely recommended.[16] Therefore, the

[1] See Section 5.1.1.2 for an explanation of cancer staging in MIUC.

standard of care in Denmark for patients with MIUC who have undergone radical resection is observation/ no adjuvant therapy, with follow-up at 4, 12, and 24 months after surgery.[15] However, it is estimated that half of all patients who have undergone radical resection will experience disease recurrence.[14,17] Maintenance treatments, such as avelumab, may be offered to some patients to delay disease progression,[18] but once disease has recurred, the median survival for patients with metastatic disease is approximately 3 to 6 months if untreated or 12 to 20 months if the patient is eligible to be treated with combination chemotherapy.[19]

Therefore, there is an unmet need for adjuvant treatments for people who are at high risk of recurrence after undergoing radical resection of MIUC to reduce the risk of disease recurrence.

4.4 Nivolumab

Nivolumab is a human, monoclonal immunoglobulin G4 antibody that acts as a programmed cell death protein 1 (PD-1) inhibitor, blocking the interaction of PD-1 with PD-L1 and programmed death-ligand 2 (PD-L2). Binding of PD-L1 and PD-L2, to the PD-1 receptor found on T cells inhibits T-cell proliferation and cytokine production. Nivolumab binds to the PD-1 receptor and blocks its interaction with PD-L1 and PD-L2, releasing PD-1 pathway-mediated inhibition of the immune response, including the antitumour immune response, and helps to restore antitumour immune response.[5]

4.5 The comparator

In Denmark, the standard of care for patients with MIUC is radical resection (preceded by preoperative neoadjuvant chemotherapy for those with MIUC in the bladder only).[15,16] Adjuvant treatments are not recommended[15,16]; therefore, the standard of care is observation/no adjuvant therapy. This is represented by placebo in the CheckMate-247 trial; therefore, no comparator is provided in this assessment.

4.6 Efficacy and safety

The efficacy and safety of nivolumab have been demonstrated in the ongoing phase 3 placebo-controlled trial, CheckMate-274.[1] The trial was designed to assess the efficacy and safety of nivolumab in all randomised patients and in patients with tumour cell PD-L1 expression ≥ 1%. The clinical results included in this dossier relate to different subgroups and interim analyses depending on the outcome. Table 1 summarises these results, and Section 7 presents a detailed explanation.

Table 1. Summary of the available efficacy and safety data from CheckMate-274 included in this dossier

Data	Study population	Analysis
Efficacy	Tumour cell PD-L1 expression ≥ 1% subgroup	Interim analysis 2 (based on February 2021 database lock)
Patient-reported outcomes (HRQOL)	Tumour cell PD-L1 expression ≥ 1% subgroup	Interim analysis 1 (based on August 2020 database lock)
Safety	All-randomised population	Interim analysis 1 (based on August 2020 database lock)

HRQOL = health-related quality of life; PD-L1 = programmed death-ligand 1.

The CheckMate-274 trial demonstrated that, for the tumour cell PD-L1 expression ≥ 1% subgroup and after a median follow-up of 25.5 months for the nivolumab arm and 22.4 months for the placebo arm (minimum, 11.4 months):

- Treatment with nivolumab led to a statistically significant and clinically meaningful improvement in disease-free survival (DFS) compared with placebo (hazard ratio [HR], 0.53; 95% confidence interval [CI], 0.38-0.75).[20]
  - DFS at 12 months was 67.6% for nivolumab versus 46.3% for placebo.[20]
  - DFS favoured nivolumab regardless of pathologic lymph node status or prior use of neoadjuvant chemotherapy.[21]
- Treatment with nivolumab led to a statistically significant and clinically meaningful improvement in non–urothelial-tract recurrence-free survival (NUTRFS) compared with placebo (HR, 0.54; 95% CI, 0.39-0.77).[20]
- Treatment with nivolumab led to a statistically significant and clinically meaningful improvement in distant metastasis-free survival (DMFS) compared with placebo (HR, 0.60; 95% CI, 0.41-0.88).[20]

In addition, CheckMate-274 demonstrated that, for the all-randomised patient population and after a median follow-up of 20.9 months (minimum, 5.9 months), nivolumab had a manageable and tolerable safety profile consistent with previous studies and no new safety signals were observed in high-risk patients who underwent radical resection of MIUC.[1]

4.7 Health economics

The base-case analysis is based on a 3-health-state Markov model because this was determined to be the most suitable approach accounting for data availability and disease. However, alternative options for model structure and data were investigated through the model development process and are presented as part of the submission for transparency and to minimise decision uncertainty. The current analysis of adjuvant nivolumab in MIUC compared with the current standard of care, observation, is expected to result in 1,78 additional quality-adjusted life-years (QALYs) at an additional cost of DKK 327,805. Thus, the resulting incremental cost-effectiveness ratio (ICER) for introducing adjuvant nivolumab in MIUC in Denmark is DKK 184,626.

4.8 Conclusion

Nivolumab is estimated to be a life-extending and cost-effective adjuvant treatment option for adults with MIUC in Denmark.

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

5.1 The medical condition and patient population

This dossier focuses on MIUC that has developed in the bladder, ureter, or renal pelvis. Often, the published literature that is available does not focus on this specific group and may instead refer to the following:

- **Urinary tract cancer** includes cancer in the bladder, ureter, renal pelvis, and urethra. It includes urothelial carcinoma as well as other types of cancer and may be muscle invasive or non–muscle invasive.
  - 90% of urinary tract cancers are urothelial carcinoma, and 90% to 95% of them develop in the bladder.[7,22]
- **Upper urinary tract cancer** includes the renal pelvis and ureter.

  - At diagnosis, approximately 60% of urothelial carcinoma in the upper urinary tract is muscle invasive.[14,16]

- **Bladder cancer** includes both urothelial carcinoma and other types of bladder cancer and may be muscle invasive or non–muscle invasive.
  - 90% of bladder cancers are urothelial carcinoma; at diagnosis, up to 25% are muscle invasive.[14,15,23]

5.1.1 Disease background

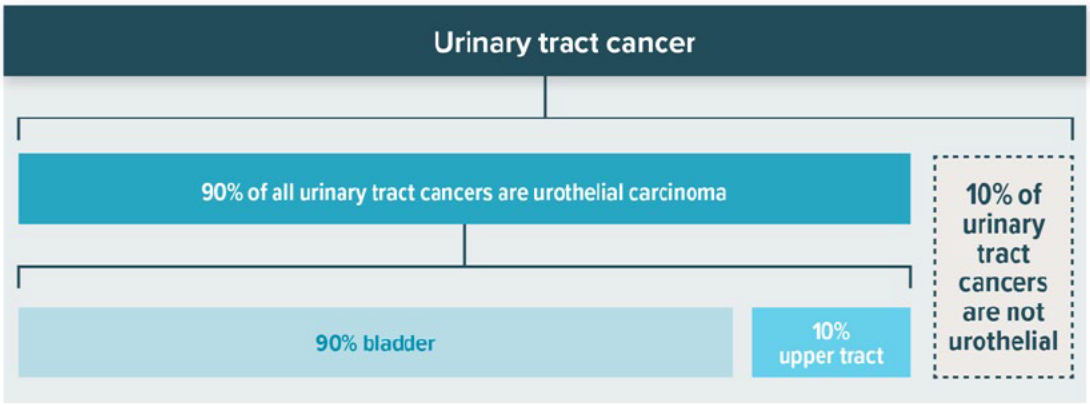
Section 5.1.4 presents information regarding the patient populations relevant for this application.

Urothelial carcinoma (also known as *transitional cell carcinoma*) is a type of urinary tract cancer that begins in the urothelium that lines the lower urinary tract (including the urethra and bladder) and the upper urinary tract (including the ureter and renal pelvis) (Figure 1).[6]

Urothelial carcinoma is the most common type of urinary tract cancer. Approximately 90% of urinary tract cancers are urothelial carcinoma, with the remaining 10% being squamous cell carcinoma, small cell carcinoma, and adenocarcinoma.[22]

In 90% to 95% of cases, urothelial carcinoma develops in the bladder; in approximately 5% to 10% of cases, urothelial carcinoma develops in the upper urinary tract (Figure 2).[7,8,25]

Figure 2. **Types of urinary tract cancer**



5.1.1.1 Presentation and diagnosis

The symptoms of urothelial carcinoma vary depending on its location. Individuals with bladder cancer typically present with painless gross haematuria (visible blood in the urine),[7,26] increased urinary frequency, urgency, nocturia, and dysuria.[7,11] If bladder cancer reaches an advanced stage, individuals may present with an inability to urinate, lower back pain on one side, pelvic or bone pain, reduced appetite and weight loss, weakness and fatigue, or pedal oedema.[26] The similarity of these symptoms to those of benign disorders (e.g., urinary tract infection, cystitis, prostatitis) and the potentially intermittent nature of symptoms may delay diagnosis of bladder cancer, which can lead to worse outcomes.[27,28] The main risk factors for bladder cancer are cigarette smoking, exposure to benzene derivatives and aromatic amines, and chronic irritative conditions of the bladder.[15]

People with cancer in the upper urinary tract (renal pelvis and ureter) often have no symptoms and the cancer is identified incidentally.[14] Individuals who do have symptoms may present with macroscopic haematuria.[14] If the tumour causes an obstruction, it may cause hydronephrosis and kidney infections.[7] Most of the risk factors identified with cancer in the upper urinary tract are identical to the risk factors for bladder cancer. In addition, exposure to plants containing aristolochic acid is another specific risk factor for cancer in the upper urinary tract.[16]

5.1.1.2 Disease staging and progression

Once diagnosed, urothelial carcinomas are most often staged using the TNM staging system,[11,23,29,30] which characterises cancers from stages I to IV according to the size of the primary tumour (T, or Tis if the tumour is in situ), the degree of involvement of regional lymph nodes (N), and the presence of distant metastases (M)[14,17,31] (Table 2). Figure 3 presents the TNM stages for muscle-invasive disease that are relevant to this submission.

Table 2. Clinical classification and TNM staging of bladder cancer

Clinical classification	T	N	M	Description
Non–muscle invasive	Ta	0	0	Non-invasive papillary carcinoma, no regional lymph node metastases
	Tis	0	0	Carcinoma in situ, no regional lymph node metastases
	T1	0	0	Invades lamina propria, no regional lymph node metastases
Muscle invasive, resectable	T2a	0-1[a]	0	Invades superficial muscularis propria, no regional lymph node metastases (0) or single regional lymph node metastasis in true pelvis (1)
	T2b	0-1[a]	0	Invades deep muscularis propria, no regional lymph node metastases (0) or single regional lymph node metastasis in true pelvis (1)
	T3a	0-1[a]	0	Invades perivesical tissue (microscopically) no regional lymph node metastases (0) or single regional lymph node metastasis in true pelvis (1)
	T3b	0-1[a]	0	Invades perivesical tissue (macroscopically) no regional lymph node metastases (0) or single regional lymph node metastasis in true pelvis (1)
	T4a	0-1[a]	0	Invades prostate, uterus or vagina no regional lymph node metastases (0) or single regional lymph node metastasis in true pelvis (1)
Locally advanced, unresectable	T4b	0	0	Invades pelvis or abdominal wall, no regional lymph node metastases
Metastatic	Any	Any	1	Distant metastases

TNM = tumour-node-metastasis.

Note: The staging of muscle-invasive urothelial carcinoma in the upper urinary tract is broadly similar to staging of bladder cancer, whereby T2 indicates the tumour is invading the muscularis propria, T3 indicates the tumour is invading the periureteric or peripelvic fat, and T4 indicates the tumour is invading adjacent organs or into perinephric fat.[32]

[a] In some cases, patients with ≥ 2 lymph nodes in the true pelvis (N2) or lymph node metastasis to common iliac lymph nodes (N3) may also have resectable disease.

Sources: AJCC (2018)[10]; Cancer Research UK (2019)[33]

In addition, the TNM stage may also include 1 or more prefixes to indicate when the stage is assigned, for example:

- p to indicate the staging was based on pathologic examination (e.g., pT1)[30]
- yp to indicate the staging was assigned after neoadjuvant therapy (e.g., ypT3)[30]

For people with bladder cancer, it is estimated that 25% of cancers are muscle invasive at diagnosis.[14,15,23] For people with urothelial carcinoma in the upper urinary tract, approximately 60% are muscle invasive at diagnosis.[14,16] In addition, some people diagnosed with non–muscle invasive disease will progress to invasive disease.

[redacted]

5.1.2 Epidemiology

Epidemiology data specifically related to urothelial carcinomas with tumour cell PD-L1 expression ≥ 1% are limited. Instead, most data presented in this section focus either on all types of cancer in the urinary tract (not just urothelial carcinoma) or only on bladder cancer (where most urothelial carcinomas originate), depending on the availability of data. It is has been reported that 20% to 30% of all urothelial carcinomas express PD-L1[9]; in the CheckMate-274 trial, approximately 40% of patients with MIUC had tumour cell PD-L1 expression ≥ 1%.[1]

5.1.2.1 Incidence and prevalence in Denmark

Data on the incidence and prevalence of urothelial carcinoma in Denmark are limited, but data are available for urinary tract cancer, approximately 90% of which are urothelial carcinoma in origin.

In Denmark, the average age at the time of diagnosis is approximately 68 years.[35] At the end of 2019, 21,637 people (15,919 males and 5,718 females) were living with a diagnosis of urinary tract cancer, with approximately 1,695 new cases diagnosed in males and 617 in females each year[12]; of these, approximately 500 people are diagnosed with muscle-invasive disease.[36]

Table 3. Incidence and prevalence of urinary tract cancer in Denmark (2015-2019)

	Male	Female
Number of new cases per year (incidence 2015-2019)	1,695	617
Age-standardised incidence rate per 100,000 persons per year (Nordic)	56.0	17.4
Persons living with the diagnosis at the end of 2019 (prevalence)	15,919	5,718
Number of persons living with the diagnosis per 100,000 per year	549.7	195.5

Source: NORDCAN (2021)[12]

5.1.2.2 Survival in Denmark

Survival data specific to urothelial carcinoma in Denmark are limited, but data are available for urinary tract cancer. Between 2015 and 2019, an average of 562 people per year have died as a result of urinary tract cancer. Age-standardised relative survival for urinary tract cancer in Denmark at 1 year is 91.0% (male) and 86.0% (female) and at 5 years is 80.0% (male) and 72.9% (female) (Table 4).[12] However, prognosis varies depending on the extent of disease, and one of the most important prognostic factors is T stage, determined either histologically or clinically.[23]

Table 4. Urinary tract cancer survival in Denmark (2015-2019), all stages

	Male	Female
Number of deaths per year (2015-2019)	386	176
Age-standardised death rate per 100,000 persons per year (Nordic)	13.9	4.9
Relative survival (2015-2019), % (95% CI)		
1 year	91.0 (90.2-91.7)	86.0 (84.5-87.4)
5 years	80.0 (78.7-81.2)	72.9 (70.7-74.9)

Source: NORDCAN (2021)[12]

Data specific to Denmark are not available, but data from Sweden show that 5-year relative survival ranges from less than 40% for patients with T2 disease to less than 25% for patients with T3-T4 disease[37] (Figure 5). Data from the United States show that 5-year survival for late-stage bladder cancer is approximately 12%.[13] For urothelial carcinoma in the upper urinary tract, European guidelines state that prognosis is poor, with 5-year survival ranging from less than 50% for patients with stage pT2/pT3 disease to less than 10% for patients with stage pT4 disease.[14] Therefore, there is a need for life-extending therapies for patients diagnosed with high-risk or late-stage disease.

Global data also show variation in survival with patients with more invasive disease having poorer 5-year survival (Table 5). Therefore, a key goal of treatment is preventing development of later-stage disease, which drives the need for effective therapies at earlier lines including in the adjuvant setting.

Table 5. 5-year overall survival rates in later-stage bladder cancer after radical cystectomy (global data)

Pathologic stage	5-year overall survival
pT2,N0 Overall population	56%-77%
pT3-4a,N0 Overall population	44%-64%
pT3-4a,N+ Overall population	24%-40%
Node-positive Overall population	25%-31%
pT2-4 or N+ Received neoadjuvant cisplatin	~20%-45%
pT3-4 or N+ Deferred cisplatin at recurrence	15%-50%

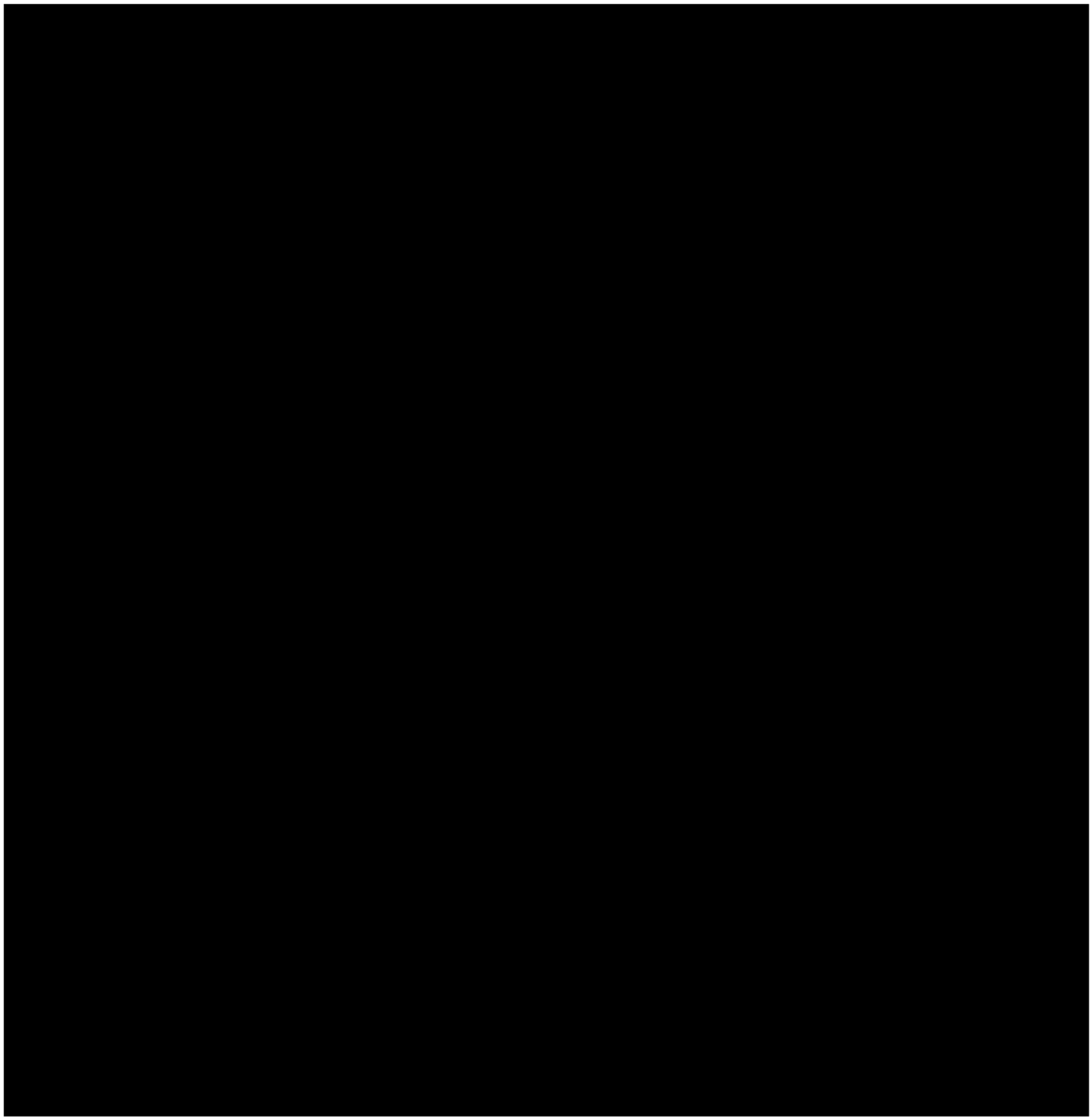
Note: "Overall population" indicates that the population is not subdivided by therapies received.
Sources: Dalbagni et al. (1999)[38]; Stein et al. (2001)[39]; Meeks et al. (2012)[40]; Mitra et al. (2014)[41]; Sternberg et al. (2015)[42]

5.1.3 Disease recurrence

Radical resection is the treatment of choice for MIUC and has curative intent, but more than 50% of patients with MIUC in the bladder and 22% to 50% of patients with MIUC in the upper urinary tract who have undergone radical resection experience disease recurrence.[14,16,17]

The pathological stage of the tumour and the nodal status are predictors of disease recurrence.[17] Among patients with MIUC in the bladder who have received neoadjuvant chemotherapy, pathologic stage ≥ ypT2 or

ypN+ is associated with poor survival[43] (Figure 6); among those who have not received neoadjuvant chemotherapy,[2] pathologic stage ≥ pT3 or pN+ is associated with high risk of recurrence, irrespective of nodal involvement[39] (Figure 7). Among patients with MIUC in the upper urinary tract, pathologic stage ≥ T2 is associated with a shorter time to urinary bladder recurrence and distant organ metastasis.[44]



In the absence of care options, adjuvant cisplatin-based chemotherapy may be considered even though it is not recommended. However, approximately 60% of patients at high risk of recurrence are not eligible to receive it because of their Eastern Cooperative Oncology Group performance status, comorbidities, or prior treatment with neoadjuvant chemotherapy.[45,46] Therefore, there is an unmet need for adjuvant treatments for people with MIUC who are at high risk of recurrence after undergoing radical resection.

[2] A small proportion of patients (48 of 1,054) received neoadjuvant chemotherapy.

In Denmark, maintenance treatments, such as the immunotherapy avelumab, may be offered to a limited number of patients to delay disease progression[18] (see Section 5.2.1). However, once disease has recurred, the median survival for patients with metastatic disease is approximately 3 to 6 months if untreated or 12 to 20 months if the patient is eligible to be treated with combination chemotherapy.[19]

5.1.4 Patient populations relevant for this application

Approximately 52 patients per year with tumour cell PD-L1 expression ≥ 1% who are at high risk of recurrence after radical resection of MIUC in the bladder would be eligible to receive adjuvant nivolumab (Table 6). In Denmark, the average age at the time of diagnosis is approximately 68 years.[35] The CheckMate-274 trial had a mean age of 65.3 years (range, 30-92 years) for the nivolumab group and 65.9 years (range, 42-88 years) for the placebo group.[1] Therefore, CheckMate-274 reflects the MIUC population in Denmark.

Table 6. Eligible patient calculations (bladder cancer only)

Population	Proportion	No. of patients	Source	Calculation
Overall number of patients with bladder cancer undergoing cystectomy		380	Table A in DaBlaCa (2021)[36]	380 is an estimate based on data from 2019-2017
Number of patients at high risk of recurrence	34%	130	DaBlaCa (2021)[36]	Out of 380 patients, 60 will receive neoadjuvant chemotherapy; of those, 50% will have ≥ ypT2 and/or N+ disease. Of the remaining 320 patients, approximately 35% will have ≥ ypT3 and/or N+ disease.
Number of patients with tumour cell PD-L1 expression ≥ 1%	40%	52	Bajorin et al. (2021)[1]	130 × 0.4

PD-L1 = programmed death-ligand 1.

5.2 Current treatment options and choice of comparator(s)

5.2.1 Current treatment options

In Denmark, the Danish Multidisciplinary Cancer Group (Danske Multidisciplinære Cancer Grupper) provides national guidelines for the treatment and follow-up of muscle-invasive bladder cancer[15] (90% of which is urothelial carcinoma[22]) and urothelial cancer in the upper urinary tract.[16] The recommendations from these guidelines apply to the patient's care irrespective of their PD-L1 status:

- For patients with muscle-invasive bladder cancer (T2-T4a, N0-NX, M0), the primary treatment is radical cystectomy with lymph node excision preceded by neoadjuvant chemotherapy. Routine use of adjuvant chemotherapy is not recommended.[15]
- For patients with MIUC in the upper urinary tract, the primary treatment is radical nephroureterectomy. Neoadjuvant chemotherapy and adjuvant chemotherapy are not routinely recommended.[16]

In addition, it is recommended that all patients are followed up with computed tomography (CT) scans of the thorax and the abdomen at 4, 12, and 24 months (and at 36 months for those with MIUC in the upper urinary tract).[15,16] Table 7 presents key recommendations from the Danish Multidisciplinary Cancer Group guidelines.

Table 7. Key recommendations for the treatment of bladder and urothelial cancer in Denmark

Vigtigste anbefalinger	Key recommendations	Level of evidence[a]
Blære	**Bladder**	
Præoperativ neoadjuverende kemoterapi tilbydes egnede patienter (alder < 75 år, PS 0-1, normal nyrefunktion).	Preoperative neoadjuvant chemotherapy is offered to suitable patients (aged < 75 years, PS 0-1, normal renal function).	A
Rutinemæssig anvendelse af adjuverende kemoterapi anbefales ikke.	Routine use of adjuvant chemotherapy is not recommended.	B
Radikal cystektomi evt. Forudgået af neoadjuverende kemoterapi er førstevalgsbehandling hos patienter med muskelinvasiv blærekræft (T2-T4a, N0-1, M0).	Radical cystectomy preceded by neoadjuvant chemotherapy is first-line treatment in patients with muscle-invasive bladder cancer (T2-T4a, N0-1, M0).	B
Strålebehandling kan tilbydes til patienter med T2 til T4a-tumorer med N0-N1, og uden tegn på fjernmetastaser (M0) med PS 0-2. Patienter skal klinisk og billeddiagnostisk udredes som patienter til cystektomi.	Radiation therapy may be offered to patients with T2-T4a tumours with N0-N1, and without signs of distant metastases (M0) with PS 0-2. Patients should be examined clinically and via imaging as patients for cystectomy.	C
Til patienter i god almentilstand (performancestatus 0-1, under 75 år i biologisk alder) kan konkomitant kemoterapi med mitomycin og 5-floururacil overvejes.	For patients in good general condition (PS 0-1, under 75 years in biological age) concomitant chemotherapy with mitomycin and 5-fluorouracil may be considered.	A
Trimodal terapi med maksimal TUR-B, kemobehandling/radiosensitizer samt ekstern strålebehandling kan tilbydes selekterede patienter.	Trimodal therapy with maximum transurethral resection of bladder tumours, chemotherapy/radiosensitiser as well as external radiation therapy can be offered to selected patients.	C
Efter cystektomi med urinafledning, alle patienter undersøges efter ca. 4 mdr., 12 mdr. Og 24 mdr. Med CT-scanning af thorax og abdomen.	After cystectomy with urine diversion, all patients are examined after approximately 4, 12, and 24 months with CT scan of the thorax and abdomen.	D
Øvre urinveje	**Upper urinary tract**	
Radikal nefroureterektomi bør tilbydes til patienter med high grade tumor, multifokal tumor, mistanke om invasion på billeddiagnostik og eller tumor der er for stor til lokalbehandling.	Radical nephroureterectomy should be offered to patients with high-grade tumour, multifocal tumour, suspected invasion of imaging and/or tumour that is too large for local treatment.	B
Patienter skal tilbydes perioperativ Mitomycin C efter nefroureterektomi.	Patients should be offered perioperative Mitomycin C after nephroureterectomy.	A
Strålebehandling: Kan overvejes som palliation ved betydende hæmaturi eller smerter.	Radiation therapy: may be considered as palliative care in case of significant haematuria or pain.	D
Neoadjuverende kemoterapi anbefales ikke rutinemæssigt.	Neoadjuvant chemotherapy is not routinely recommended.	D
Adjuverende kemoterapi anbefales ikke rutinemæssigt.	Adjuvant chemotherapy is not routinely recommended.	D

Vigtigste anbefalinger	Key recommendations	Level of evidence[a]
Patienter med lokalavanceret sygdom kan overvejes nefroureterektomi i tilfælde af operabel resttumor.	In patients with locally advanced disease, nephroureterectomy may be considered in case of operable residual tumour	D
Ved invasive tumorer skal suppleres med CT af thorax og abdomen i op til 3 år (4, 12, 24 og 36 måneder)	In the case of invasive tumours, CT of the thorax and abdomen should be undertaken for up to 3 years (4, 12, 24, and 36 months).	D

CT = computed tomography; PS = performance status.

[a] Recommendations marked A are strongest, and recommendations marked D are weakest. Further information on the strength and evidence assessment can be found at oxford-levels-of-evidence-2009_dansk-v.1.1.pdf (dmcg.dk).

Sources: Danske Multidisciplinære Cancer Grupper (2020)[15]; Danske Multidisciplinære Cancer Grupper (2020)[16]

After recurrence to metastatic disease, patients with bladder cancer and upper urinary tract cancer are managed according to the guideline on the treatment and follow-up of T4b and metastatic bladder cancer,[16,47] which recommends the following:

- First line: gemcitabine plus cisplatin chemotherapy. Patients for whom gemcitabine plus cisplatin chemotherapy is not suitable can be offered PD-1/PD-L1 targeted immunotherapy if they express the biomarker PD-L1 at the required level or chemotherapy with carboplatin plus gemcitabine or gemcitabine alone.
- Second-line: reinduction gemcitabine plus cisplatin chemotherapy (for patients who received it as first line) or PD-1/PD-L1 targeted immunotherapy irrespective of PD-L1 biomarker expression. Vinflunine may be offered for patients who are not suitable for immunotherapy.
- Third line: immunotherapy for those who have not previously received it, treatment with vinflunine or reinduction with carboplatin plus gemcitabine or gemcitabine alone.

The Danish Medicines Council (DMC; Medicinrådet) has approved the following PD-1/PD-L1 targeted immunotherapies:

- Avelumab can be used as a maintenance treatment in patients with advanced (locally advanced or metastatic) urothelial carcinoma that has not progressed after receiving platinum-based chemotherapy.[18]
- Atezolizumab can be used as a first-line treatment of those patients with performance status 0-2 with PD-L1 > 5% who are not candidates for cisplatin-based chemotherapy, and as a second-line treatment of those with performance status 0-1 with disease progression after platinum-based chemotherapy.[48]
- Pembrolizumab can be used as a first-line treatment of patients with performance status 0-2 and combined positive PD-L1 score > 10 who are not candidates for cisplatin-based chemotherapy, and as a second-line treatment of those with performance status 0-1 with disease progression after platinum-based chemotherapy.[49]

No immune PD-1/PD-L1 targeted immunotherapies are currently recommended for the treatment of MIUC in the adjuvant setting.

5.2.2 Choice of comparator(s)

In Denmark, the standard of care for patients with MIUC after radical resection (cystectomy or nephroureterectomy) is observation/no adjuvant therapy.

5.2.3 Description of the comparator(s)

Observation/no adjuvant therapy is represented by placebo in the CheckMate-247 trial; therefore, no comparator description is provided.

5.3 The intervention

Nivolumab is a fully human, IgG4 monoclonal antibody that acts as a PD-1 inhibitor, blocking the interaction of PD-1 with PD-L1 and PD-L2. Binding of PD-L1 and PD-L2 to the PD-1 receptor found on T cells inhibits T-cell proliferation and cytokine production. Nivolumab binds to the PD-1 receptor and blocks its interaction with PD-L1 and PD-L2, releasing PD-1 pathway-mediated inhibition of the immune response, including the antitumour immune response, and helps to restore antitumour immune response.[5]

Nivolumab monotherapy is indicated for the adjuvant treatment of adults with tumour cell PD-L1 expression ≥ 1% who are at high risk of recurrence after undergoing radical resection of MIUC. Table 8 summarises the use of nivolumab in this indication. The summary of product characteristics[5] provides full details of the prescribing information.

Table 8. Description of nivolumab

Dosage regimen	240 mg every 2 weeks (30-minute IV infusion) or 480 mg every 4 weeks (60-minute IV infusion)
Method of administration	IV infusion
Treatment duration/criteria for treatment discontinuation	Up to 1 year or until disease recurrence or discontinuation
Should the pharmaceutical be administered with other medicines?	No
Necessary monitoring, both during administration and during the treatment period	Patients should be monitored continuously (at least up to 5 months after the last dose)
Need for diagnostic or other test	PD-L1 expression status of the tumour cells should be confirmed by a validated test

IV = intravenous; PD-L1 = programmed death-ligand 1; SmPC = summary of product characteristics.

5.3.1 Position in the care pathway

Nivolumab is positioned as an adjuvant treatment option for patients at high risk of recurrence who would otherwise receive observation/no adjuvant treatment (Figure 8).

6 Literature search and identification of efficacy and safety studies

6.1 Identification and selection of relevant studies

The indication for nivolumab included in this submission received EC approval on 1 April 2022 based on the pivotal trial CheckMate-274. Therefore, at the time of submission, CheckMate-274 is the only study relevant to this indication. CheckMate-274 has been reported in 4 publications: Bajorin et al. (2021)[50], Bajorin et al. (2021)[1], Galsky et al. (2021)[20], and Galsky et al. (2021)[51].

6.2 List of relevant studies

CheckMate-274 is the only study that is relevant to the scope of this assessment and is summarised in Section 7.1.1. Appendix B presents detailed information on CheckMate-274.

Table 9. Relevant study included in the assessment: CheckMate-274

Reference (title, journal)	NCT number	Dates of study (start and expected completion date)	Publications relating to this study
Bajorin et al. (2021)[1] Adjuvant nivolumab versus placebo in muscle-invasive urothelial carcinoma. N Engl J Med.	NCT02632409	22 March 2016 to 3 April 2026	▪ Bajorin et al. (2021)[50] ▪ Galsky et al. (2021)[51] ▪ Galsky et al. (2021)[20]

NCT = National Clinical Trial.

7 Efficacy and safety

7.1 Efficacy and safety of nivolumab compared with placebo for adults with high-risk muscle-invasive urothelial carcinoma

7.1.1 Relevant study: CheckMate-274

CheckMate-274 (NCT02632409) is an ongoing double-blind, multicentre, randomised phase 3 trial evaluating nivolumab compared with placebo as adjuvant therapy in adults with high-risk MIUC.[1] The coprimary objectives were to compare DFS for nivolumab versus placebo in patients with tumour cell PD-L1 expression ≥ 1% and in all randomised patients. The secondary objectives were to compare overall survival (OS), evaluate NUTRFS, and evaluate disease-specific survival for nivolumab versus placebo in patients with tumour cell PD-L1 expression ≥ 1% and in all randomised patients.

A coprimary approach was used to assess the potential enrichment of nivolumab treatment effects in patients with tumour cell PD-L1 expression < 1% and in patients with tumour cell PD-L1 expression ≥ 1%. Although patients with tumour cell PD-L1 expression ≥ 1% were hypothesised to derive the greatest benefit from nivolumab, enrichment of nivolumab treatment effect has never been studied in the adjuvant setting in which patients have no evidence of disease. If enrichment based on PD-L1 expression was not observed, the coprimary approach allowed outcomes in all-comers to be adequately assessed. The results presented in Section 7.1.2 relate to the tumour cell PD-L1 expression ≥ 1% subgroup only because this aligns with the European Medicines Agency (EMA) label. For completeness, Appendix I.1 presents results for the all-randomised population.

Table 10 summarises details of the study, and Figure 9 presents the study design.

Table 10. CheckMate-274 (CA209274): summary of trial methodology

Aspect of trial	CheckMate-274 (CA209274); Bajorin et al. (2021)[1]
Sample size (n)	709 patients were randomised into 2 treatment groups in a 1:1 ratio
Study design	Double-blind, multicentre, randomised phase 3 trial
Location	170 sites in 30 countries (Argentina, Australia, Austria, Belgium, Brazil, Canada, Chile, China, Colombia, **3 sites in Denmark**, France, Germany, Greece, Ireland, Israel, Italy, Japan, South Korea, Mexico, Netherlands, Peru, Poland, Romania, Russia, Spain, Sweden, Switzerland, Taiwan, United Kingdom, and United States)

<table>
<tr><th>Aspect of trial</th><th>CheckMate-274 (CA209274); Bajorin et al. (2021)[1]</th></tr>
<tr><td>Patient population</td><td>Adults with high-risk MIUC at radical resection:
Patients who received neoadjuvant cisplatin: ypT2-pT4a or ypN+
Patients who have not received neoadjuvant cisplatin: pT3-pT4a or pN+ and who were not eligible for, or refused, adjuvant cisplatin chemotherapy</td></tr>
<tr><td>Assessment of PD-L1 status</td><td>PD-L1 expression was determined by the percentage of positive tumour cell membrane staining in a minimum of 100 evaluable tumour cells using the PD-L1 IHC 28-8 PharmDx immunohistochemistry assay. Tumour tissue used was from the most recently resected site of disease or from the transurethral resection that yielded the initial MIUC diagnosis.</td></tr>
<tr><td>Intervention(s)</td><td>Nivolumab 240 mg IV over 30 minutes every 2 weeks for up to 1 year or until disease recurrence or discontinuation from the trial</td></tr>
<tr><td>Comparator(s)</td><td>Placebo administered IV over 30 minutes every 2 weeks for up to 1 year or until disease recurrence or discontinuation from the trial</td></tr>
<tr><td>Follow-up period</td><td>Study duration: 60 months
Planned follow-up: 17 months
<table><tr><th></th><th>All randomised population</th><th>Tumour cell PD-L1 expression ≥ 1%</th></tr><tr><td>27 August 2020 database lock</td><td></td><td></td></tr><tr><td>Median follow-up, months</td><td>20.9 (NIVO), 19.5 (PBO)</td><td>22.11 (NIVO), 18.69 (PBO)</td></tr><tr><td>Minimum follow-up, months</td><td>5.9</td><td>6.3</td></tr><tr><td>1 February 2021 database lock</td><td></td><td></td></tr><tr><td>Median follow-up, months</td><td>24.4 (NIVO), 22.5 (PBO)</td><td>25.5 (NIVO), 22.4 (PBO)</td></tr><tr><td>Minimum follow-up, months</td><td>11.0</td><td>11.4</td></tr></table></td></tr>
<tr><td>Is the study used in the health economic model?</td><td>Yes</td></tr>
<tr><td>Reasons for use/non-use of the study in model</td><td>CheckMate-274 provides the best evidence for the efficacy of nivolumab in this patient population vs. current standard of care and therefore is used in the model</td></tr>
<tr><td>Primary endpoints reported</td><td>Coprimary endpoint assessed in all patients who underwent randomisation (intention-to-treat population) and among those with a tumour cell PD-L1 expression ≥ 1%:
Disease-free survival (time from randomisation until death from any cause or first recurrence whichever occurred first)</td></tr>
</table>

Aspect of trial	CheckMate-274 (CA209274); Bajorin et al. (2021)[1]
Other outcomes reported	Secondary endpoints assessed in all patients who underwent randomisation (intention-to-treat population) and among those with a tumour cell PD-L1 expression ≥ 1%: ▪ Overall survival: time from randomisation until death of any cause ▪ Non–urothelial-tract recurrence-free survival: time from randomisation until the first recurrence (local non–urothelial tract or distant) or death from any cause, whichever occurs first ▪ Disease-specific survival: time from randomisation until death due to urothelial carcinoma Key exploratory endpoints: ▪ Incidence rates of adverse events, serious adverse events, deaths, and laboratory abnormalities ▪ Time to recurrence: time from randomisation until the first recurrence (local urothelial tract, local non–urothelial tract, or distant) or death due to disease, whichever occurs first ▪ Distant metastasis-free survival: time from randomisation until first distant recurrence (non-local) or death from any cause, whichever occurs first ▪ Second progression-free survival: time from randomisation to the date of investigator-defined disease progression after the subsequent next-line systemic anticancer therapy, or the start of second subsequent next-line systemic anticancer therapy, or death from any cause, whichever comes first ▪ General health status using the EQ-5D-3L ▪ Cancer-specific health-related quality of life using EORTC QLQ-C30

EORTC QLQ-C30 = European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire–Core Module; IV = intravenous; MIUC = muscle-invasive urothelial carcinoma; NIVO = nivolumab; PBO = placebo; PD-L1 = programmed death-ligand 1.

[redacted]

7.1.1.1 Statistical analysis

In total, 709 patients were randomised into 2 treatment groups in a 1:1 ratio.[1] The sample size was based on the comparison of the DFS distribution between treatment groups. Demographics and baseline laboratory results were summarised by treatment arm as randomised using descriptive statistics. Analyses were conducted on all randomised patients and in patients with tumour cell PD-L1 expression ≥ 1%.

Interim analyses of the primary, secondary, and exploratory endpoints

Two database locks (DBLs) have taken place:

- The first DBL was a planned, event-driven interim analysis for DFS, that was triggered after the number of DFS events exceeded the prespecified number required in the study protocol and statistical analysis plan The boundary for statistical significance for DFS was crossed, and the interim analysis became the final analysis for DFS. The DBL for this final analysis had a data cut off of 27 August 2020, and the results were published in in the New England Journal of Medicine.[1]
- The second DBL was the first interim analysis for OS, which was triggered based on the final DFS analysis, with data cut off on 1 February 2021. The interim analysis for OS did not cross the prespecified boundary for declaring statistical significance, and the study continues to remain blinded. As part of the first interim analysis for OS, efficacy endpoints including DFS, NUTRFS, and DMFS were included as part of the DBL and the results were disclosed at the Society of Urologic Oncology (SUO) congress in December 2021.[20] This analysis supersedes the previous DFS analysis and provides a minimum follow-up of 11 months for the ITT population and a minimum follow-up of 11.4 months for the PD L1 ≥ 1% population. Safety and HRQOL endpoints were not analysed in the second DBL because 85% of events of disease recurrence or death in each trial population had been observed (348 events in the intention-to-treat [ITT] population and 137 in the group of patients with tumour cell PD-L1 expression ≥ 1%), representing a significant portion of the overall study population. The first DBL demonstrated that the overall safety profile of nivolumab monotherapy was manageable, no new safety signals were observed, and the HRQOL of patients was sustained.
- Therefore, Section 7.1.2 of this dossier reports efficacy data from the second DBL, and safety and HRQOL data are from the first DBL.

In addition, the results presented in this dossier vary depending on the patient subgroup:

- Efficacy data (see Sections 7.1.2.1, 7.1.2.2, and 7.1.2.3) relate to the tumour cell PD-L1 expression ≥ 1% subgroup only. This is to maintain consistency with the label approved by the EMA. Data are from an interim analysis based on a DBL that occurred in February 2021. For completeness, Appendix I.1 presents efficacy results relating to the all-randomised population.
- Patient-reported outcomes (see Section 7.1.2.4) relate to the tumour cell PD-L1 expression ≥ 1% subgroup only. This is to maintain consistency with the EMA-approved label. Data are from an interim analysis based on a DBL that occurred in August 2020 because these outcomes were not updated at the February 2021 DBL.
- Safety data (see Section 7.1.2.5) relate to the all-randomised population because these outcomes are not expected to vary according to PD-L1 status, and the most comprehensive data analysis is of the all-randomised population. Data are from the first interim analysis (based on the DBL that occurred in August 2020) because these outcomes were not updated at the February 2021 DBL.

Table 11 summarises the interim analyses.

Table 11. Summary of the interim analyses

	All-randomised population	Tumour cell PD-L1 expression ≥ 1%
First DBL (August 2020)		
Minimum follow-up (months)	5.9	6.3
Median follow-up (months)	20.9 (NIVO), 19.5 (PBO)	22.11 (NIVO), 18.69 (PBO)
Efficacy data	Reported	Reported
HRQOL data	Reported	Reported
Safety data	Reported*	Reported*
Second DBL (February 2021)		
Minimum follow-up (months)	11.0	11.4
Median follow-up (months)	24.4 (NIVO), 22.5 (PBO)	25.5 (NIVO), 22.4 (PBO)
Efficacy data	Reported and supersede data from August 2020	Reported and supersede data from August 2020
HRQOL data	Not provided	Not provided
Safety data	Not provided	Not provided

DBL = database lock; HRQOL = health-related quality of life; NIVO = nivolumab; PBO = placebo; PD-L1 = programmed death-ligand 1.

* Based on the all treated population

Sources: Bajorin et al. (2021)[1]; Galsky et al. (2021)[20]

7.1.1.2 Baseline demographic and disease characteristics

Baseline demographic and disease characteristics for all randomised patients and all randomised patients with tumour cell PD-L1 expression ≥ 1% were generally well-balanced across the treatment groups and representative of the target patient population—those who have undergone radical resection of MIUC originating in the bladder or upper urinary tract and are at high risk of recurrence.[1] Most patients had bladder as the tumour location, and 40% to 43% of patients had received prior cisplatin-based neoadjuvant therapy.[1]

Appendix B presents detailed study characteristics. Appendix C presents baseline characteristics of patients included in each study.

7.1.2 Efficacy and safety—results per study

The results presented in this section focus on the tumour cell PD-L1 expression ≥ 1% population that aligns with the label. For completeness, Appendix I.1 presents results for the all-randomised population.

7.1.2.1 Primary endpoint: DFS for all randomised patients with tumour cell PD-L1 expression ≥ 1%

At the first interim analysis (based on the August 2020 DBL and a minimum follow-up of 6.3 months), CheckMate-274 met its primary endpoint of statistically significant and clinically relevant improved DFS with nivolumab compared with placebo in patients with tumour cell PD-L1 expression ≥ 1%, (HR, 0.55; 98.72% CI,

0.35-0.85; $P < 0.001$)[1] (see Appendix I.1.1 for further details of the first interim analysis). These results continued to be statistically significant and clinically relevant at the second interim analysis (based on the February 2021 DBL with a minimum follow-up of 11.4 months) (HR, 0.53; 95% CI, 0.38-0.75) (Figure 10).[20] By the first disease assessment (at 3 months), the Kaplan-Meier curves for DFS had separated, favouring nivolumab. At 6 months, DFS rates were 74.5% versus 55.7% for nivolumab and placebo, respectively, and this separation was maintained at 12 months.[20]

Subgroup analysis of DFS for all randomised patients with tumour cell PD-L1 expression ≥ 1%

In CheckMate-274, patients were stratified according to prior neoadjuvant cisplatin-based therapy use and nodal status.[1] At the first interim analysis (based on the August 2020 DBL and 6.3 months of follow-up), the DFS benefit of nivolumab versus placebo was observed in each of these subgroups (HR < 1)[1] (see Appendix I.1.2 for further details of the first interim analysis). This benefit continued at the second interim analysis (based on the February 2021 DBL and a minimum follow-up of 11.4 months) (Figure 11).[21] Even among the relatively lower-risk node-negative patients with 10 or more nodes removed, a treatment benefit with nivolumab was noted.[21]

A subgroup analysis also favoured nivolumab over placebo in nearly all other subgroups analysed (Figure 11).[21] Two of the initial tumour origin subgroups (renal pelvis and ureter) were not estimable or demonstrated an HR > 1. However, these analyses were not robust because of the small sample sizes and low number of events, which limited the reliability of these particular results.[21] Overall, CheckMate-274 was not designed to detect statistically significant differences in the treatment effect in these subgroups; therefore, subgroup results should be interpreted with caution.[20]

[redacted]

7.1.2.2 Secondary endpoint: NUTRFS survival for all randomised patients with tumour cell PD-L1 expression ≥ 1%

At the first interim analysis (based on the August 2020 DBL) and after a minimum follow-up of 6.3 months, nivolumab treatment resulted in a clinically meaningful improvement in NUTRFS compared with placebo in patients with tumour cell PD-L1 expression ≥ 1% (HR, 0.55; 95% CI, 0.39-0.79)[1] (see Appendix I.1.3 for further details of the first interim analysis). This benefit continued at the second interim analysis (based on the February 2021 DBL and a minimum follow-up of 11.4 months) (HR, 0.54; 95% CI, 0.39-0.77) (Figure 12).[20] By the first disease assessment (at 3 months), the Kaplan-Meier curves for NUTRFS had separated, favouring nivolumab. At 6 months, NUTRFS rates were 75.3% in the nivolumab arm and 56.7% in the placebo arm.[20]

7.1.2.3 Exploratory endpoints in all randomised patients with tumour cell PD-L1 expression ≥ 1%: DMFS

At the first interim analysis (based on the August 2020 DBL) and after a minimum follow-up of 6.3 months, nivolumab treatment resulted in a clinically meaningful improvement in DMFS compared with placebo in patients with tumour cell PD-L1 expression ≥ 1% (HR, 0.61; 95% CI, 0.42-0.90)[1] (see Appendix I.1.4 for further details of the first interim analysis). This benefit continued at the second interim analysis (based on the February 2021 DBL and a minimum follow-up of 11.4 months) (HR, 0.60; 95% CI, 0.41-0.88) (Figure 13).[20] At 6 months, DMFS rates were higher in the nivolumab arm than in the placebo arm.[20]

7.1.2.4 Patient-reported outcomes

Patients who have undergone radical surgery for MIUC often have impaired HRQOL.[52] During the CheckMate-274 study, HRQOL was assessed using the European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire–Core Module (EORTC QLQ-C30) and EQ-5D-3L questionnaires. Health-related QOL assessments were completed on cycle 1 day 1 (baseline), then every second cycle (4 weeks) for the first 6 months of treatment, and every third cycle (6 weeks) thereafter until discontinuation of study treatment. Health-related QOL endpoints were not analysed as part of the latest interim analysis (see Section 7.1.1.1 for further details). Therefore, the results presented below are from the first interim analysis (based on the August 2020 DBL).

The first interim analysis on the HRQOL-evaluable population[3] with tumour cell PD-L1 expression ≥ 1% showed that, compared with placebo, adjuvant nivolumab monotherapy did not compromise the HRQOL of patients with MIUC[1,53] (Figure 14 and Figure 15).

[3] The evaluable population included 123 patients in the nivolumab arm and 128 in the placebo arm for EORTC QLQ-C30; and 126 in the nivolumab arm and 129 in the placebo arm for EQ-5D VAS.

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A post hoc analysis of HRQOL using data from CheckMate-274 is available[51] but is not summarised here because it focuses on the all-randomised population, not the tumour cell PD-L1 expression ≥ 1% subgroup, which is the focus of this dossier. For completeness, Appendix I.1.5 summarises these results.

7.1.2.5 Safety

Summary of safety data from CheckMate-274

Safety endpoints were not analysed as part of the latest interim analysis based on the February 2021 DBL (see Section 7.1.1.1 for details). Safety data from the August 2020 DBL are presented in Appendix E for both the all treated population and the PD-L1 expression ≥ 1% population. Although no formal comparison of data have been made, the safety profile of nivolumab in all treated patients with tumour cell PD-L1 expression ≥ 1% was considered consistent with that reported in all treated patients.[1] Therefore, the summary of safety data from CheckMate-274 is based on the all-treated population and the first interim analysis based on the August 2020 DBL.

After a minimum follow-up of 5.9 months, 3 treatment-related deaths occurred in the nivolumab group (further details are included below).

Table 12 shows adverse events (AEs) that occurred in at least 5% of patients in either treatment arm. In the context of the observed clinical efficacy, treatment with adjuvant nivolumab demonstrated a favourable overall safety profile in all patients treated and among patients with tumour cell PD-L1 expression ≥ 1%, consistent with the known safety profile of nivolumab monotherapy.[1] Overall, no new safety signals or toxicities were identified for nivolumab monotherapy in the adjuvant treatment of high-risk patients who underwent radical resection of MIUC.[1]

In all treated patients, the median duration of exposure was 8.2 months (range, 0.0-12.6 months) for placebo and 8.8 months (range, 0.0-12.5 months) for nivolumab.[1]

Table 12. CheckMate-274: adverse events that occurred in at least 5% of patients in either trial group

	Number of patients (%)			
	Nivolumab (n = 351)		Placebo (n = 348)	
Adverse event	Any grade	Grade ≥ 3	Any grade	Grade ≥ 3
Adverse event of any cause	347 (98.9)	150 (42.7)	332 (95.4)	128 (36.8)
Adverse event related to nivolumab or placebo[a]	272 (77.5)	63 (17.9)	193 (55.5)	25 (7.2)
Pruritus	81 (23.1)	0	40 (11.5)	0
Fatigue	61 (17.4)	1 (0.3)	42 (12.1)	0
Diarrhoea	59 (16.8)	3 (0.9)	38 (10.9)	1 (0.3)
Rash	53 (15.1)	2 (0.6)	19 (5.5)	0
Increased lipase level	34 (9.7)	18 (5.1)	20 (5.7)	9 (2.6)
Hypothyroidism	34 (9.7)	0	5 (1.4)	0
Increased amylase level	33 (9.4)	13 (3.7)	20 (5.7)	5 (1.4)
Hyperthyroidism	33 (9.4)	0	3 (0.9)	0
Asthenia	24 (6.8)	2 (0.6)	17 (4.9)	0
Nausea	24 (6.8)	0	13 (3.7)	0
Decreased appetite	20 (5.7)	2 (0.6)	11 (3.2)	0
Increased blood creatinine level	20 (5.7)	1 (0.3)	11 (3.2)	0
Maculopapular rash	19 (5.4)	2 (0.6)	4 (1.1)	0

Note: the events shown are those that were reported between the first dose and 30 days after the last dose of nivolumab or placebo.

[a] The events shown are those that occurred in at least 5% of patients in either trial group.

Source: Bajorin et al. (2021)[1]

Treatment-related adverse events

There were 3 treatment-related deaths in the nivolumab arm and none in the placebo arm (Table 13). Two deaths reported in [1] were caused by pneumonitis. Glucocorticoid treatment was started at the onset of pneumonitis; 1 patient began 3 days after the last dose of trial therapy, and the other began 16 days after the last dose of trial therapy. A third death was due to bowel perforation, and the patient started glucocorticoid treatment 5 days after the last dose of trial therapy.

Table 13. CheckMate-274: safety summary of treatment-related adverse events—all treated patients

	Nivolumab (n = 351)		Placebo (n = 348)	
TRAE, %	Any grade	Grade 3-4	Any grade	Grade 3-4
Any TRAE[a]	77.5	17.9	55.5	7.2
TRAEs leading to discontinuation	12.8	—	2.0	—
Treatment-related deaths	3		0	

TRAE = treatment-related adverse event.

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

Source: Bajorin et al. (2021)[1]

The most common treatment-related AEs (TRAEs) were pruritus, fatigue, and diarrhoea across both treatment arms (Table 14).[1] Although the incidence of any grade TRAEs and grade 3-4 TRAEs was numerically greater in the patients treated with nivolumab compared with placebo, nivolumab demonstrated a manageable safety profile with most TRAEs being grade 1 or 2 (see Table 13). In total, 12.8% of patients discontinued therapy as a result of a TRAE, further demonstrating nivolumab's overall tolerability (see Table 13).

Table 14. CheckMate-274: treatment-related adverse events in ≥ 15% of patients in any treatment arm

		Nivolumab (n = 351)		Placebo (n = 348)	
		Any grade	Grade 3-4	Any grade	Grade 3-4
General	Fatigue	17.4%	0.3%	12.1%	0%
Gastrointestinal	Diarrhoea	16.8%	0.9%	10.9%	0.3%
Skin and subcutaneous tissue	Rash	15.1%	0.6%	5.5%	0%
	Pruritus	23.1%	0%	11.5%	0%

Note: includes events reported between first dose and 30 days after last dose of study therapy.

Source: Bajorin et al. (2021)[1]

7.1.3 Comparative analyses of efficacy and safety

The most relevant comparator in this indication is observation/no adjuvant therapy. This comparator is represented by the placebo arm in the CheckMate-274 trial. Therefore, the head-to-head trial data summarised in Section 7.1.2 are used to compare nivolumab with current standard of care for this assessment.

7.1.3.1 Method of synthesis

Head-to-head trial data are used; therefore, no synthesis has been included in this submission.

7.1.3.2 Results from the comparative analysis

Head-to-head trial data are used; therefore, no comparative analysis has been undertaken.

8 Health economic analysis

8.1 Model

8.1.1 Type of economic evaluation

A cost-utility analysis was conducted that was informed by the tumour cell PD-L1 expression ≥ 1% subgroups of the clinical trial CheckMate-274. Outcomes were expressed as incremental costs per QALY gained as recommended by the DMC guidelines. Cost-effectiveness results were also reported as incremental costs per life-year (LY) gained.

8.1.2 Target population

The analysis population is aligned with the EMA regulatory approval for patients with MIUC who are at high risk of recurrence after radical resection with tumour cell PD-L1 expression ≥ 1%. The patient characteristics of the model population have been informed by tumour cell PD-L1 expression ≥ 1% subgroups of the clinical trial CheckMate-274. High-risk patients in CheckMate-274 were defined as:

- Patients with pathological state of ypT2-ypT4a or ypN+[4] MIUC who had neoadjuvant cisplatin chemotherapy
- Patients with pathological stage of pT3-pT4a or pN+[4] MIUC without prior neoadjuvant cisplatin chemotherapy and not eligible for or refused adjuvant cisplatin chemotherapy

The model assumes a starting age of 65.2 years for the cohort and a male-to-female ratio of 75.5% to 24.5% based on the patient population observed in CheckMate-274.[54] For the population affected by MIUC at high risk of recurrence after radical resection, the average body weight is assumed to be 73.9 kg based on the average body weight reported in the CheckMate-274 clinical study report.[54] The average body surface area is assumed to be 1.89 m^2 based on the previously reported body surface area for the Danish population.[55]

8.1.3 Comparators

To assess the cost-effectiveness of nivolumab as adjuvant treatment of MIUC in patients with tumour cell PD-L1 expression ≥ 1%, observation/no adjuvant therapy was chosen as the comparator for the analysis. This represents the standard of care in Danish clinical practice because there are currently no reimbursed therapies indicated for the adjuvant treatment of MIUC in Denmark. This comparison is also well aligned with the placebo comparator arm in the CheckMate-274 clinical trial.

8.1.4 Perspective

The analysis was conducted from the Danish limited societal perspective as per DMC guidelines.[56]

8.1.5 Time horizon

According to DMC guidelines, the model time horizon should be of sufficient length to capture all costs and outcomes relevant to the treatments being compared and should match the natural course of the disease.[56]

The base-case time horizon was set to 20 years because the interventions were expected to have differential effects on mortality. Given that the mean age of the CheckMate-274 tumour cell PD-L1 expression ≥ 1%

[4] Please see Section 5.1.1.2 for explanation of cancer staging in MIUC.

patient population was 65.2 years (64.4 and 65.9 years for nivolumab and placebo, respectively), a 20-year time horizon was deemed sufficient to capture the lifetime of the average patient. A scenario analysis was performed to estimate the effect of different time horizons on the incremental cost-utility ratio (ICUR).

8.1.6 Discount rate

A 3.5% annual discount rate for costs and effects was used, as per the DMC guidelines.[56]

8.1.7 Cycle length and half-cycle correction

The cycle length selected for the model was 1 week (7 days) to align with treatment cycles and to adequately capture events. A half-cycle correction was applied to the calculation of LYs and QALYs to account for the transition of patients from one health state to another happening in a continuous process, representing an average transition halfway through a cycle (i.e., not at the beginning or end of a cycle).

8.1.8 Modelling considerations

8.1.8.1 Model structure and health states

For the base case, a Markov model with 3 health states was used.

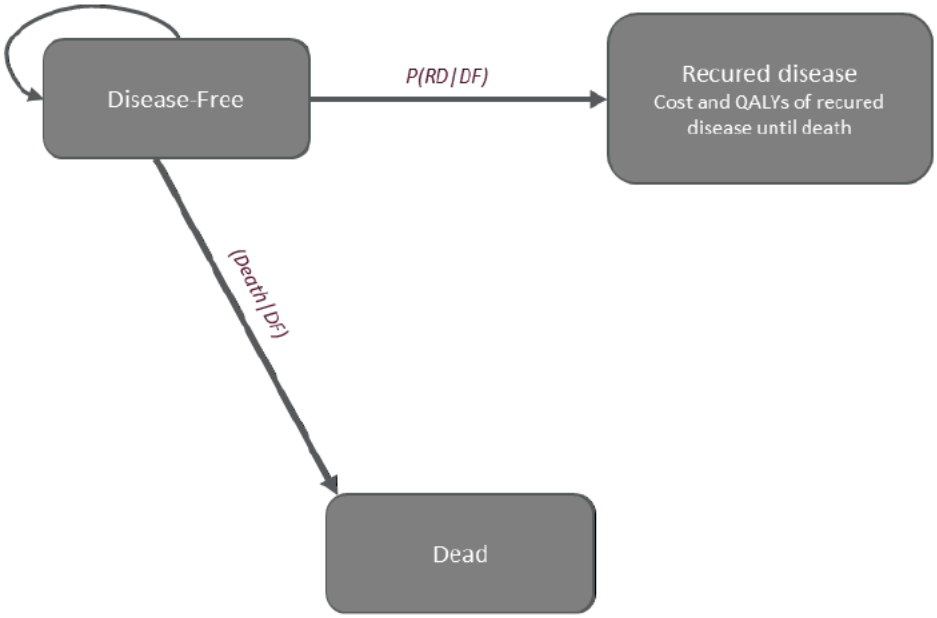
The 3-health-state Markov model is composed of the following key health states (Figure 16):

- **DF**: Disease free
- **RD**: Recurred disease; comprising patients who have either had a Local Recurrence (LR) or a Distant Recurrence (DR)
- **Death**

The Markov model structure in this analysis was chosen for the following reasons:

- The absence of OS data from CheckMate-274 presents challenges in generating a valid OS curve required for a traditional 3-health-state partitioned survival model. A Markov model allows for combining the DFS observed in the trial with external data to estimate costs and outcomes associated with disease recurrence.
- A partitioned survival model approach requires strong assumptions being made about the relationship between DFS or DMFS and OS, whereas the Markov approach is more explicit and transparent about the assumptions, hence providing greater flexibility for sensitivity analysis.

Figure 16. Overview of 3-health-state model



DF = Disease Free; P(RD|DF) = probability of moving from DF to RD; P(Death|DF) = probability of death from DF; QALY = quality-adjusted life-year; RD = Recurred Disease.

Note: Arrows represent possible transition probabilities in the semi-Markov model; Dead and RD are absorbing states.

Patients begin in the DF health state, in which they receive adjuvant nivolumab treatment or observation, which is the only comparator in the model. At each subsequent cycle, patients can experience a recurrence (either LR or DR) and therefore move to RD, die, or remain in the DF health state. The transition probabilities for the proportion of patients moving to RD and Death are based on CheckMate-274 DFS data, whereas outcomes for the RD health state are based on estimates from the literature. For patients in the DF health state, the costs and QALYs are based on the health-state utility observed in CheckMate-274. For patients in the RD health state, total cost and QALY are applied when entering the RD health state; therefore, no explicit transition is modelled from RD health state to Death.

Sections 8.1.8.2 and 8.3 present information on the data and methods used to model state occupancy and transitions from DFS, and Sections 8.1.8.3, 8.5.5, and 8.6.6 present methods used to estimate outcomes of RD.

In addition to the 3-health-state model used for the base-case analysis, the Excel model includes the functionality to expand into a 4-health-state model in which the RD state is separated into 2 states for local and distant recurrence (Appendix J). The 3-health-state model was chosen over the 4-health-state model because of limited data to inform the more complex 4-health-state model and to avoid complicating the model and model assumptions unnecessarily. The complexity of the 4-health-state model was especially considered unnecessary given the few local recurrence events observed in CheckMate-274 (see Table 15). Further, evidence of the low probability of true local recurrence events is also presented in Appendix J.1.2, showing that, of the 151 patients identified in the ITT population with a recorded true local recurrence event, only around a third of these (59 patients) did not have an earlier or coinciding distant recurrence event.

8.1.8.2 Probability of transitioning from disease-free health state

Disease-free survival curves from CheckMate-274 inform the probability of patients staying in the DF health state (see Section 8.3), while all other patients move out of DF to either RD or Death health states. The

transition probabilities for the proportion of patients moving to RD and Death are based on CheckMate-274 DFS data, and the proportion of patients transitioning to either health state is based on the first recurrence of events observed in CheckMate-274. Table 15 shows the number of first events (recurrences and deaths) from DFS as observed in CheckMate-274 across both the nivolumab and placebo arms for patients with tumour cell PD-L1 expression ≥ 1%, which is used in the base-case analysis to align with the EMA approval and target population for the analysis. The distribution of first events for each treatment and both treatments pooled together is further calculated using the following methodology:

- **Proportion of RD recurrence** (*% of patients with* $DR_{CM\text{-}274}$): this is calculated as the total recurrence of events as a proportion of total events from DFS

  $= \frac{Recurrence\ (LR\ or\ DR)\ from\ DFS\ events}{Total\ DFS\ events}$ = 92.2% (Table 15)

- **Proportion of death** (*% of patients with* $Death_{CM\text{-}274}$): this is calculated as death events from DFS as a proportion of the total events from DFS

  $= \frac{Death\ from\ DFS\ events}{Total\ DFS\ events}$ = 7.8% (Table 15)

The distribution of the first events (pooled data from both arms) is used when estimating the transitions from the DF state in the base case. The distribution of first recurrence events is assumed to be constant until the DFS risk is equal to the general population mortality, after which point patients are no longer at risk of recurrence and only at risk of dying.

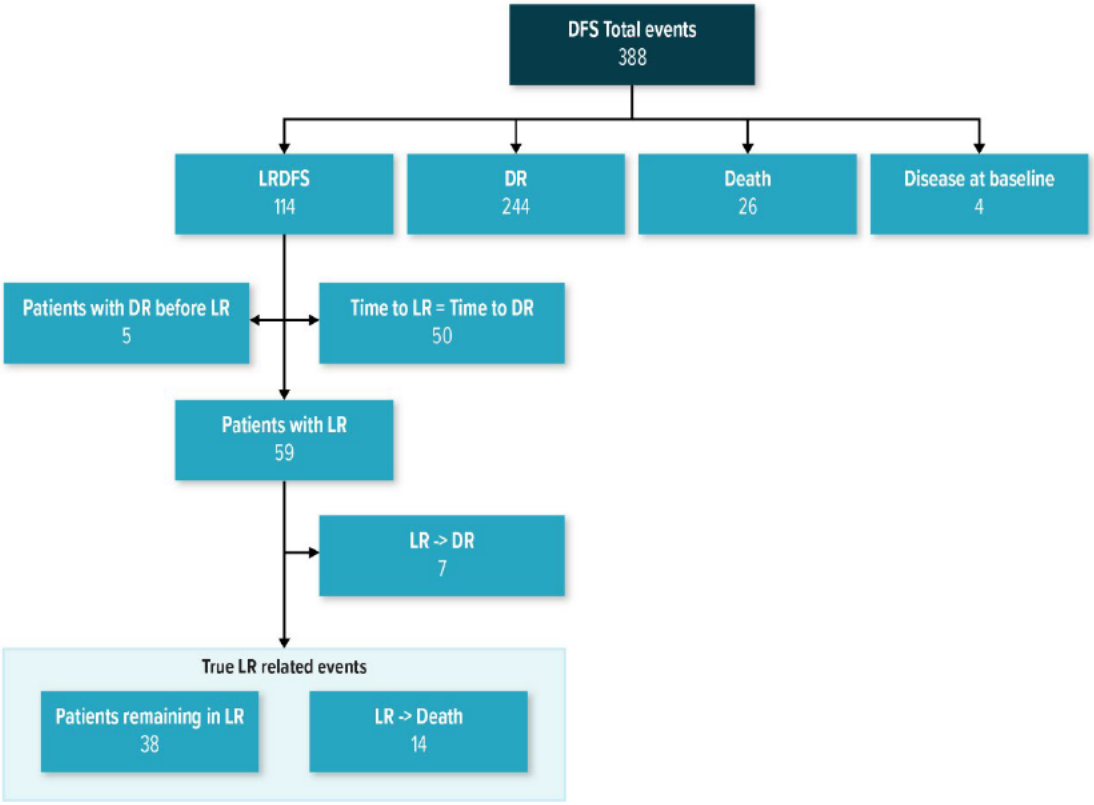
The assumption of constant distribution over time is further supported by the first recurrence events from the trial data when split into 6-month periods as shown in Table 16, pooled across the 2 trial arms to increase the sample size and power of the data. The data beyond 2 years are too scarce with few DFS events, which is not deemed suitable or appropriate to inform the acceptability of the constant weight between recurrence or death as DFS events over time. The impact of the constant weight assumption is furthermore diminished with time because most DFS events have taken place in the first 2 years, as can be seen from the DFS Kaplan-Meier curves from CheckMate-274. The 6-month rates presented in Table 16 are for the ITT population, as these data are too scarce when broken down for the tumour cell PD-L1 expression ≥ 1% subgroup.

[redacted]

8.1.8.3 Estimating cost and QALYs for the recurred disease health state

Once patients experience a recurrence and move to the RD state, they are assumed to experience events conditional on having experienced a recurrence. In the 3-health-state model, all recurrences are assumed to be metastatic in nature; thus, evidence on the outcomes and efficacy of first-line metastatic urothelial carcinoma (mUC) treatments was needed to inform the RD health state. This is supported by the data from CheckMate-274 showing that most recurrence events are DRs. Figure 17 presents a summary of events experienced in the trail. From Table J-1 a total of 388 DFS events were observed in the ITT CheckMate 274 population within the trial follow-up time (minimum follow-up 11.0 months). 4 of these events were removed from further analysis as they had disease at baseline.[1] Of those, 244 were DR and 26 death as first events in the trial, thus 114 events were recorded as LR. Looking at local recurrence disease free survival (LRDFS) as a stand-alone outcome there were 151 LRDFS events observed (Appendix J.1.2). However 37 of these were reported with a DR event at the same time (so 151-37=114). As further reported in Appendix J.1.2 50 had a LR event and were censored for DR at the same time and 5 were censored for DR before havening an LR event. This resulted in 59 LR events. Of the remaining 59 patient 7 had a subsequent DR (see Table J-2). Therefore, of the 388 DFS events observed in the trial only 52 events, or 13% of all DFS evnets, were patients remaining in LR or died while in LR.

Figure 17. Proportion of local recurrence events (CheckMate-274, ITT population)



DFS = Disease Free Survival; LR = Local Recurrence; DR = Distant Recurrence.

Because of the severity of mUC (median survival, approximately 12 months),[58] patients are expected to die from metastatic disease. Because OS data from the CheckMate-274 trial are not available to inform survival from mUC, data identified from the literature were used to inform the estimated total cost and QALYs for recurred mUC under the assumption that first-line mUC is equivalent to recurrent disease from the adjuvant setting. Therefore, in the base-case analysis, the outcome of RD was modelled based on estimated one-off total costs and QALYs of experiencing an RD event (see Sections 8.5.5 and 8.6.6 for estimates used in the base-case analysis). However, alternative approaches were also explored as part of the model development process with one alternative method retained within the submitted file for transparency. The alternative approaches explored and rationale for modelling the RD health state using estimated total costs and QALYs are outlined below. Section 8.4 presents further information on data explored for the alternative modelling approaches.

- Approach 1: Fully model time-dependent RD survival with accompanied cost and QALYs based on published survival data for each mUC treatment
- Approach 2: Model outcome of RD based on one-off total costs and QALYs applied when entering RD
  - Based on modelling RD survival with accompanied cost and QALYs based on published survival data for each mUC treatment (data sources aligned with approach 1 but not accounting for the time dependence of entering RD health state)
  - Based on total cost and QALYs estimated from the literature

To model the RD health state in full, with transitions to death dependent on time of transitioning into the RD health state (approach 1), would have resulted in a significantly more complex model than one-off total costs and QALYs (approach 2). For such an approach, time-dependent transition probabilities would need to be

applied to each subsequent treatment to fully capture the estimated costs and QALYs associated with each treatment. Further, submodels tracking patients dependent on time of transitioning into RD would need to be implemented for each cycle. Not only would this have required a significantly more complex model, but it would also have required a large array of scenarios to be run and presented so that alternative assumptions regarding survival extrapolations for each treatment in combination with other parameters could be explored. The need for scenarios is especially pertinent because BMS would not have access to patient-level data for these analyses; thus, uncertainty around potential extrapolations would be more pronounced than in normal circumstances (see below for further limitations on data availability). Therefore, modelling of subsequent therapy in full with transitions to death dependent on time of transitioning into the RD health state (approach 1) was not deemed sufficiently transparent and suitable to adequately reflect the best evidence for this submission. Further, most QALY gains are acquired in the DF health state because survival in those with disease recurrence, i.e. mUC, is poor and therefore unlikely to be the key driver of differences between treatment strategies. Similarly, as there are not any anticipated differences in subsequent lines of therapy between the intervention arms, modelling of subsequent therapy in detail is not anticipated to be a key driver of overall results.

To improve transparency and avoid unnecessary complexity of the model, estimating RD outcomes based on one-off total costs and QALYs was explored using 2 different approaches. The first option (approach 2a) reviewed the literature to identify data on survival and duration of therapy for each of the subsequent therapies. Extrapolation of digitised survival data was then used to model the total cost and QALYs of each treatment which were subsequently applied to patients' transition to the RD health state. The data needed for this approach would be aligned with those needed for approach 1 but would be incorporated into the model as one-off outcomes instead of time-dependent events and thus reduce the complexity of the model. However, because of lack of data availability for several of the metastatic treatment options, this approach was deemed to be unreliable. In particular, there was a lack of data pertaining to atezolizumab, pembrolizumab, and avelumab. Although some clinical data are presented and available for these treatments, much of the data used for previous health economic models submitted to DMC and other health technology assessment (HTA) agencies are lacking because of, for example, confidentiality (Table 17). Therefore, modelling of RD using external clinical data was not deemed the most appropriate method. However, this method has been implemented into the model so that scenario analyses could be conducted based on this approach. Section 8.4 further describes the data and methods used for such modelling. Of note, the same limitations in data would have been an issue for approach 1 in addition to the much more complex model structure. In addition, for methods for both approaches 1 and 2a, fully implementing these methods (even if BMS had full access to clinical data) would de facto require BMS to develop full cost-effectiveness models (CEMs) of all subsequent treatments.

Table 17. Summary of evidence for first-line treatments of metastatic urothelial carcinoma

Treatment	HTA agency	Findings regarding data availability	Reference
Avelumab (maintenance)	DMC	Data on key modelling assumptions, such as survival and cost-effectiveness results, are confidential.	Medicinrådet (2021)[59]
	NoMA	Data on key assumptions such as survival analysis and cost-effectiveness results at list price are available but not possible to assess the impact of confidential pricing.	Statens legemiddelverk (2021)[60]
	NICE	Information pertaining to costs and QALYs redacted.	
Pembrolizumab	DMC	Cost-effectiveness not assessed.	Medicinrådet (2018)[49]

Treatment	HTA agency	Findings regarding data availability	Reference
	TLV	Modelled cost-effectiveness based on early data cut and as observed from the NICE appraisal (see below), results of analyses with more mature data were not aligned with initial data cuts.	TLV (2017)[61]
	NICE	Manufacturer did not submit evidence for appraisal following availability of data from the phase 3 KEYNOTE-361 study and exit from Cancer Drugs Fund.	NICE (2021)[62]
Atezolizumab	NICE	Information pertaining to modelling assumptions, costs, and QALYs redacted.	NICE (2021)[63]
	TLV	Data on key modelling assumptions, such as survival analysis and duration of therapy are confidential.	TLV (2017)[64]

HTA = health technology assessment; NICE = National Institute for Health and Care Excellence; NoMA = Norwegian Medicines Agency; QALY = quality-adjusted life-year; TLV = Swedish Dental and Pharmaceutical Benefits Agency.

Given the limitations with both approaches 1 and 2a, approach 2b was deemed the most appropriate and thus used in the base-case analysis. For this approach, a combination of modelling based on almost fully mature trial data for chemotherapies, information from HTAs on cost and QALYs per treatment, and assumptions was used. Sections 8.5.4 and 8.6.6 present the methods used to estimate cost and QALYs for each treatment, respectively. A significant advantage with using approach 2b over approaches 1 and 2a is that it helps the DMC conduct scenario analyses to investigate the impact of alternative estimates on costs and outcomes for each subsequent treatment based on their potential information regarding the cost-effectiveness for first-line mUC treatments in Denmark.

8.1.8.4 Model validation

The model underwent internal validation, with a thorough review of all calculations and data inputs. The model approach and inputs were also validated by international clinical and health economic experts. This included a review of the model face validity in terms of DFS/RD curve extrapolation (see Section 8.3), appropriateness of data sources, and key clinical assumptions.

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

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

Table 18 presents an overview of the input data used in the model and where in this dossier further information about how the input values were obtained/estimated can be found.

Table 18. Summary of input data used in the model

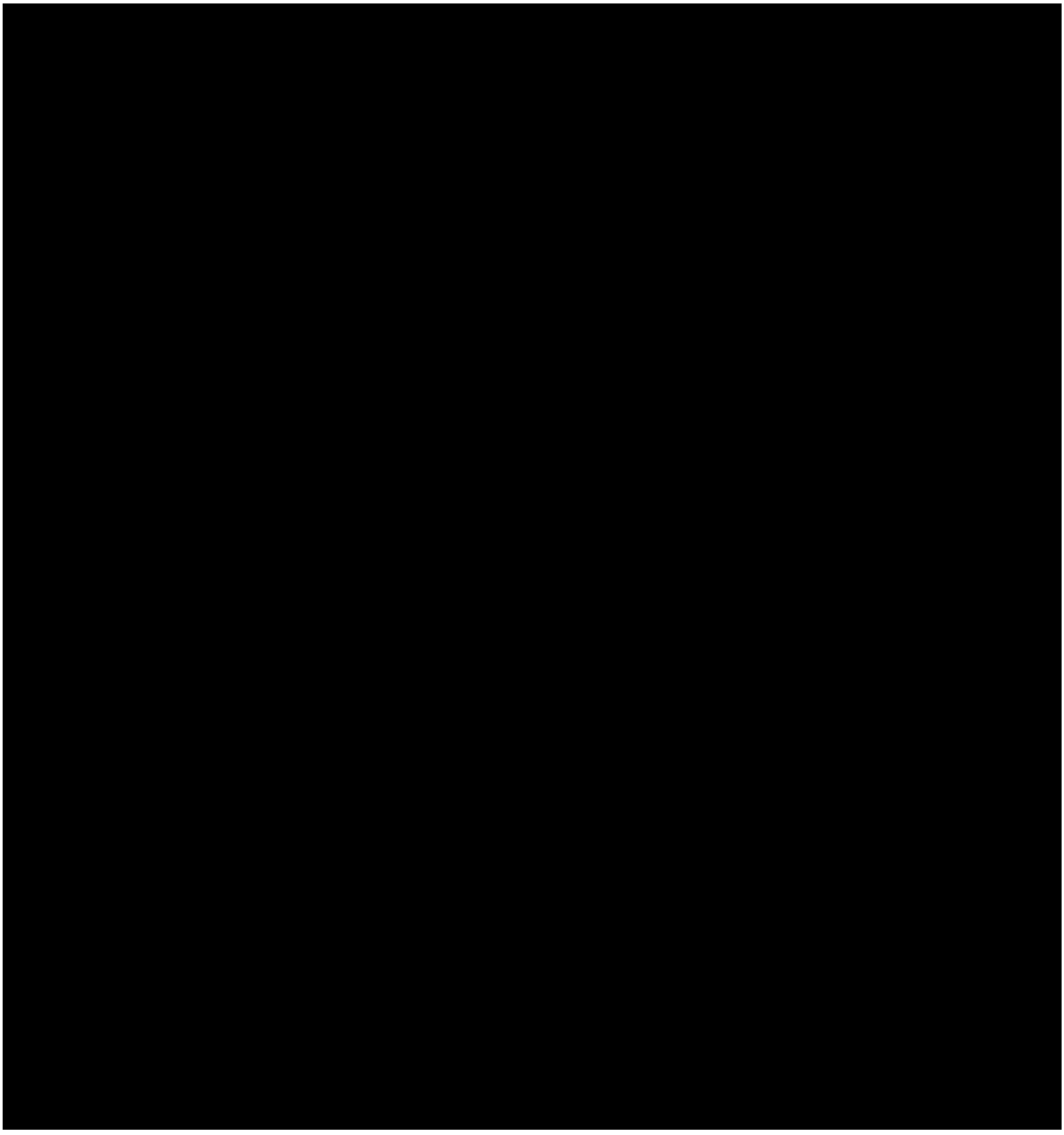
Estimate	Results from study or external data	Input value used in the model	How is the input value obtained/estimated
Primary outcome: DFS in tumour cell PD-L1 expression ≥ 1%	In CheckMate-274, 53.4% and 31.4% of patients in nivolumab and placebo arms, respectively, were still disease free at the end of the trial period (median follow-up, 25.5 months and 22.4 months, respectively).	Gompertz distribution Presented in Figure 32	Extrapolation of DFS data is discussed in Section 8.3.1.5
Adverse reactions (measured as occurrence): diarrhoea, fatigue, pruritus, urinary tract infection, nausea, rash, constipation	CheckMate-274	Presented in Table 33	Details are presented in Section 8.4
Adverse reactions (measured in costs): diarrhoea, fatigue, pruritus, urinary tract infection, nausea, rash, constipation	Sundhedsdatastyrelsen DRG 2022[65]	Presented in Table 45	Details are presented in Section 8.6.4
Adverse reactions (measured as utility loss): diarrhoea, fatigue, pruritus, urinary tract infection, nausea, rash, constipation	Literature sources: systematic literature review ▪ Nafees et al. (2008)[66] ▪ Gaither et al. (2020)[67]	Presented in Table 38	Details are presented in Section 8.5.4
Health-state utility: DF	CheckMate-274 collected patient-reported HSUVs using the EQ-5D-3L and mapped to EQ-5D-5L	Presented in Table 36	Details are presented in Section 8.5.2
Health-state utility: RD	CheckMate-274 collected patient-reported HSUVs using the EQ-5D-3L and mapped to EQ-5D-5L	Presented in Table 36	Details are presented in Section 8.5.2
Transition probability: from DF to RD	CheckMate-274	Cause-specific hazard and cumulative incidence Presented in Table 15 and Table 16	Details are presented in Section 8.1.8.2
Transition probability: from DF to Death	CheckMate-274	Cause-specific hazard and cumulative incidence	Details are presented in Section 8.1.8.2 and in Table 15 and Table 16
Estimation of cost and outcomes for RD	Literature sources: literature review of first-line mUC phase 3 clinical trials and HTAs of first-line mUC treatments	Estimated one-off cost and QALYs of disease recurrence	Details are presented in Sections 8.1.8.3, 8.5.5, and 8.6.6

DF = Disease Free; DFS = disease-free survival; DRG = diagnosis-related group; HSUV = health-state utility value; HTA = health technology assessment; mUC = metastatic urothelial carcinoma; PD-L1 = programmed death-ligand 1; QALY = quality-adjusted life-year; RD = Recurred Disease.

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

8.2.2.1 Patient population

The patient population of the economic evaluation aligns with the indication for adjuvant nivolumab as assessed in CheckMate-274.[54] The baseline characteristics of patients in CheckMate-274 are expected to reflect those of patients seen in Danish clinical practice in the subgroup of eligible patients with MIUC (see Section 5.1.4). Table 19 summarises patient baseline characteristics for the tumour cell PD-L1 expression ≥ 1% population from the trial that was used in the analysis, CheckMate-274.



8.2.2.2 Intervention

Adjuvant nivolumab was implemented in the economic model in line with the summary of product characteristics (SmPC) (see Table 8 for details) and according to the dosing and treatment lengths in the CheckMate-274 trial. As summarised in Table 20, Danish clinical practice is expected to follow the SmPC in terms of treatment length and discontinuation. In terms of posology, it is expected that the dosing, 3 mg/kg every 2 weeks, will be based on weight, although this indication is approved with a fixed-dosing scheme (as defined in Section 5.2). Therefore, scenario analyses were conducted to investigate the impact of alternative dosing assumptions.

Table 20. Nivolumab

Intervention	Clinical documentation (including source)	Used in the model (number/value including source)	Expected Danish clinical practice (including source if known)
Posology	The recommended dosage is 240 mg every 2 weeks (30-minute IV infusion) or 480 mg every 4 weeks (60-minute IV infusion) in the OPDIVO SmPC[5]	240 mg every 2 weeks (30-minute IV infusion)	Anticipated to be 3 mg/kg every 2 weeks (30-minute IV infusion) or 6 mg/kg every 4 weeks (60-minute IV infusion)
Length of treatment (time on treatment) (mean/median)	Mean doses of nivolumab treatment from CheckMate-274[54]	Mean number of nivolumab doses is modelled based on mean number of doses [redacted] received in CheckMate-274	Time on nivolumab treatment is anticipated to be similar to that observed in CheckMate-274
Criteria for discontinuation	Patients received study treatment for up to 1 year or until disease recurrence or until treatment was discontinued for other reasons (e.g., adverse events, withdrawal, death)[54]	Treatment discontinuation is modelled based on treatment duration in the trial	The SmPC states treatment should continue for up to 1 year or until recurrence or unacceptable toxicity, which is in line with the trial and model, and we anticipate will be practice in Denmark
The pharmaceutical's position in Danish clinical practice	CheckMate-274 included patients aged ≥ 65 years with MIUC with tumour cell PD-L1 expression ≥ 1% and who are at high risk of recurrence after undergoing radical resection	Population/positioning from the trial	The SmPC population is in line with the trial population, and we anticipate this will be the position in Danish practice

IV = intravenous; MIUC = muscle-invasive urothelial carcinoma; PD-L1 = programmed death-ligand 1; SmPC = summary of product characteristics.

8.2.2.3 Comparators

The comparator for standard of care in Denmark is close monitoring, which is represented by the placebo arm in CheckMate-274. In the economic model, this is defined as observation.

8.2.2.4 Relative efficacy outcomes

Table 21 presents efficacy outcomes from the CheckMate-274 clinical trial that are used in the model. The efficacy of nivolumab in the economic model is informed by DFS from CheckMate-274 and is believed to be well aligned with the clinical practice in Denmark.

Table 21. Summary of value

Clinical efficacy outcome	Clinical documentation	Used in the model (value)
Primary endpoint in the study: DFS	DFS is the primary endpoint in CheckMate-274[68]	Section 8.3.1 presents extrapolation of DFS data

DFS = disease-free survival.

8.3 Extrapolation of relative efficacy

8.3.1 Survival analysis

The primary treatment effect data for the economic model, the DFS data, are from the 1 February 2020 DBL (amended May 2021) of CheckMate-274. The minimum follow-up for all patients with tumour cell PD-L1 expression ≥ 1% from this database relock was 11.4 months; median follow-up was 25.5 months and 22.4 months for nivolumab and placebo, respectively. This follow-up period is shorter than the required length of the economic analysis (base case, 20 years), and 53.4% and 31.4% of patients in the nivolumab and placebo arms, respectively, were still disease free at the end of the trial period. Therefore, parametric survival curves were fitted to CheckMate-274 patient-level data and used to extrapolate DFS beyond the trial follow-up period.

In addition to extrapolation of DFS used in the base-case economic model, survival analyses were also conducted for LR survival based on the CheckMate-274 data. However, because this was only used for scenario analyses in the 4-health-state model, these analyses are presented in Appendix J.

The process of fitting parametric survival curves to patient-level data was based on methods guidance from the DMC[69] and Decision Support Unit (DSU) at the National Institute for Health and Care Excellence (NICE).[70,71] All survival analyses were conducted using the FlexSurv package in R and modelled using the FlexSurvReg function. Seven parametric models were considered for the extrapolation of the tumour cell PD-L1 expression ≥ 1% population patient-level data (exponential, Weibull, Gompertz, log-normal, log-logistic, gamma, and generalised gamma) as well as spline models with up to 2 knots (proportional odds spline model, proportional hazards spline model, and normal spline model). In short, the approach used to identify the most appropriate methods for extrapolations was as follows:

- We assessed the proportional effects assumption to determine whether the treatment arms should be modelled based on dependent or independent models.
  - Assessment of the proportional effects assumption was supported by:
    - Visual assessment of log-cumulative hazards, log-cumulative odds, and standardised normal curve plots
    - Testing the significance of the Grambsch and Therneau correlation test between Schoenfeld residuals and log of time
    - Clinical plausibility of proportional treatment effect with time

- The final choice of parametric survival distributions used for the base-case model was based on:
  - The visual fit and statistical fit (assessed via the lowest Akaike information criterion [AIC] and Bayesian information criterion [BIC] statistic) to the Kaplan-Meier data from CheckMate-274
    - Based on the Burnham and Anderson rule of thumb,[72] it was considered that a difference in AIC of less than 4 with respect to the lowest AIC was appropriate, from 4 through 10 was neutral, and more than 10 was inappropriate in line with previous arguments in an HTA of cancer treatments NICE.[73]
    - Based on the Raftery rule of thumb,[74] it was considered that a difference in BIC of more than 10 with respect to the BIC for distribution with the lowest BIC was inappropriate.
  - Comparison of the hazards of the extrapolation models against the observed hazards to further guide curve selection, ensure clinical plausibility, and ensure alignment with the background mortality assumption (i.e., to assess how well the hazard of the parametric survival models aligns with the observed data crossing/approaching background mortality hazards)
  - Clinical plausibility of survival extrapolations from CheckMate-274 compared with external data
  - If adequate fit and plausible extrapolations can be achieved with standard statistical distributions, these would be preferred over spline-based models to decrease complexity

Section 8.3.1.1 presents the summary methods and rational for the selection of base-case distributions used for DFS extrapolations. However, further analyses were conducted for completeness and are documented in full in Appendix I.

8.3.1.1 Survival analysis of DFS for the tumour cell PD-L1 expression ≥ 1% population

Figure 18 shows the Kaplan-Meier DFS curves for nivolumab and placebo. The initial drop in both arms in the early part of the data may be explained by the trial protocol because the first tumour assessment occurred at 3 months; thus, cumulative recurrence in that first 3 months from high-risk or non-responding patients would be captured at this first assessment. The drop is more pronounced in the placebo arm, implying that nivolumab may prevent early recurrence in a proportion of patients who may otherwise have experienced tumour growth or death from disease. The flattening of the curves indicates a lower risk of recurrence or death the longer a patient remains in the DF state, with almost complete stability of survival from 2 years.

8.3.1.2 External data for validation of extrapolations

As outlined in the DMC[69] and DSU[70,71] guidelines, it is important to consider fit of the extrapolated curves to the observed data within the trial to select the preferred distributions for extrapolation. However, equally important—if not more important, clinical plausibility of long-term extrapolation is highlighted in the guidelines because the extrapolated section of the survival curve is where trial data are lacking. Thus, to inform selection of distributions used for the economic model, external data that could be used to validate long-term DFS were sought.

The largest and most relevant external dataset for DFS was identified as the EORTC 30994 study presented by Sternberg et al. (2015). This study was an intergroup, open-label, randomised, phase 3 trial, that recruited patients with MIUC from hospitals across Europe and Canada. Patients entering the trial had histologically proven urothelial carcinoma of the bladder, pT3 pT4 disease, or node-positive (pN1-3) M0 disease after radical cystectomy and bilateral lymphadenectomy, with no evidence of any residual disease. Patients were randomly assigned (1:1) to either immediate adjuvant chemotherapy (cisplatin-based chemotherapy) or to deferred chemotherapy at relapse. The median DFS follow-up was 7 years, but some patients were followed for more than 10 years. Thereby, this dataset offers a valuable source of longer follow-up to assess the long-term risk of progression for patients who may be eligible to receive adjuvant treatment and to assess survival for patients in the placebo arm of CheckMate-274. Although the long-term data from EORTC 30994 can provide understanding of the underlying long-term risk of recurrence in patients with urothelial carcinoma and thus potentially inform anticipated hazard patterns over time, these data can only be regarded as relevant to validate long-term survival for the placebo arm because EORTC 30994 did not capture data on the improved efficacy of nivolumab. Therefore, Table 22 compares patient characteristics between the placebo arm of CheckMate-274 and the deferred chemotherapy arm of EORTC 30994.

Table 22. Comparison of patient characteristics between CheckMate-274 and EORTC 30994

CheckMate-274: ITT population, placebo arm (n = 356)		CheckMate-274, tumour cell PD-L1 expression ≥ 1% population, placebo arm (n = 142)		EORTC 30994 (2015), deferred chemotherapy (n = 143)	
Age (years)	**n (%)**	**Age (years)**	**n (%)**	**Age (years)**	**n (%)**
< 65	136 (38.2)	< 65	61 (43)	≤ 60	70 (49)
≥ 65	220 (61.8)	≥ 65	81 (57)	> 60	73 (51)
Median (IQR)	67	Mean (IQR)	65.9	Median (IQR)	61
Sex	**n (%)**	**Sex**	**n (%)**	**Sex**	**n (%)**
Female	81 (22.8)	Female	30 (21.1)	Female	27 (19)
Time from cystectomy	**n (%)**	**Time from initial diagnosis**	**n (%)**	**Time from cystectomy**	**n (%)**
≤ 30 days	3 (0.8)	< 1 year	129 (90.8)	≤ 30 days	15 (10)
31-60 days	70 (19.7)	≥ 1 year	13 (9.2)	31-60 days	47 (33)
61-90 days	177 (49.7)			61-90 days	81 (57)
91-120 days	95 (26.7)				
> 120 days	11 (3.1)				
pT category	**n (%)**	**pT category**	**n (%)**	**pT category**	**n (%)**
< pT2		< pT2	5 (3.5)	pT1	4 (3)
pT2	21 (5.9)	pT2	26 (18.3)	pT2	27 (19)
pT3	65 (18.3)	pT3	83 (58.5)	pT3	87 (61)
pT4a	204 (57.3)	pT4a	27 (19.0)	pT4a	24 (17)
pT4b	62 (17.4)	pT4b		pT4b	1 (< 1)
pN category	**n (%)**	**pN category**	**n (%)**	**pN category**	**n (%)**
N0 < 10 nodes removed	99 (27.8)	N0 < 10 nodes removed	38 (26.8)	N0	44 (31)
N0 ≥ 10 nodes removed	88 (24.7)	N0 ≥ 10 nodes removed	38 (26.8)	N1	55 (38)
N1	72 (20.2)	N1	33 (23.2)	N2	44 (31)
N2	76 (21.3)	N2	26 (18.3)	N3	0 (0)
N3	20 (5.6)	N3	7 (4.9)		

EORTC = European Organisation for Research and Treatment of Cancer; IQR = interquartile range; ITT = intention to treat; PD-L1 = programmed death-ligand 1.

Figure 19 presents digitised Kaplan-Meier data from EORTC 30994 together with the ITT and tumour cell PD-L1 expression ≥ 1% Kaplan-Meier data for the CheckMate-274 trial. As can be seen, the within-trial DFS data for placebo from CheckMate-274 is well aligned with the DFS data from EORTC 30994. One potential limitation with the data from EORTC 30994 for validation of extrapolations from CheckMate-274 could be that the label population from CheckMate-274 is restricted to tumour cell PD-L1 expression ≥ 1%. However, as can be seen from Figure 19, survival for the placebo arm of CheckMate-274 is similar between the ITT and the tumour cell PD-L1 expression ≥ 1% populations. Given this high degree of alignment between both data sources for the within-trial time period of CheckMate-274, it is also reasonable to assume that the EORTC 30994 data can serve as a valuable source for validating the long-term survival of the placebo arm of CheckMate-274.

In addition to providing valuable external data for validation of absolute long-term survival for the placebo arm of CheckMate-274, the EORTC 30994 data also provide valuable evidence of long-term DFS for this population, which can inform the CEM further. Clinical input was received in preparation of the model. Clinical experts stated that patients who have not had recurrent disease by 3 to 5 years are considered at very low risk of recurrence and therefore are no longer followed up by oncologists. By comparing the smoothed hazard from EORTC 30994[42] with the risk of death in a sex- and age-adjusted general population (Figure 20), it is clear that the risk of a DFS event approaches that of the general population mortality over time. Thus, the EORTC 30994 data are well aligned with the clinical input that risk of a DFS event will diminish over time compared with the general population. In CheckMate-274, a similar pattern for the smoothed hazard in relation to the general population mortality is also seen (Figure 21).

Two important inputs for the modelling and extrapolation of DFS over time can be informed by this evidence of DFS hazards converging with the general population mortality:

- The economic model should include a function that accounts for the general population in modelling DFS to avoid extrapolations to results in lower hazards than those of the general population mortality
- With decreasing risk of DFS events over time so that the DFS hazard cross general population mortality, it is clinically plausible that the treatment effect would decrease with time and that the hazards in the long-term would be similar in both arms.

Based on these findings, the model was set up to include a function to account for the general population mortality. This function was programmed so that if the extrapolated hazard for DFS became lower than the general population mortality, general population mortality would be used. Further, it was concluded that the hazard for the selected extrapolations should cross general population mortality within no more than 10 years and that the proportional hazards assumption would lack clinical validity.

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8.3.1.3 Assessment of the proportional hazards assumption

Visual inspection of the log-log–cumulative hazards and Schoenfeld residual plots was undertaken to assess proportionality of treatment effects over time. As shown in Figure 22, the log-log–cumulative hazard plots were not fully parallel over time. The visual inspection of the Schoenfeld residual plot (Figure 23) provided some evidence of proportionality presenting a downwards trend. However, the Grambsch and Therneau correlation test between Schoenfeld residuals and the log of time did not reject the proportional hazards assumption ($P = 0.25$). Thus, based on visual inspection of the figures, non-proportionality seems to be the most plausible assumption, although proportionality cannot be rejected based on the Grambsch and Therneau correlation test.

As presented previously, external clinical evidence of long-term survival in this patient population shows that risk of a DFS event compared with the general population diminishes with time. As such, intrinsically, there also will be a diminishing mortality risk for nivolumab to mitigate with time resulting in decreased treatment effect anticipated long-term. Based on the visual inspection and the external clinical evidence, non-proportionality was considered the most plausible assumption. Therefore, individual survival models were fitted to each arm of the study for the base-case analyses. For completeness, dependent models assuming proportional hazards were also fitted so that the assumption of proportional treatment effect could be assessed in scenario analyses (see Appendix I).

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8.3.1.4 Standard parametric models

Adequate extrapolations could be achieved with standard distributions (as presented below). Thus, the spline-based model has only been presented in Appendix I and made available in the model for scenario analyses.

Nivolumab

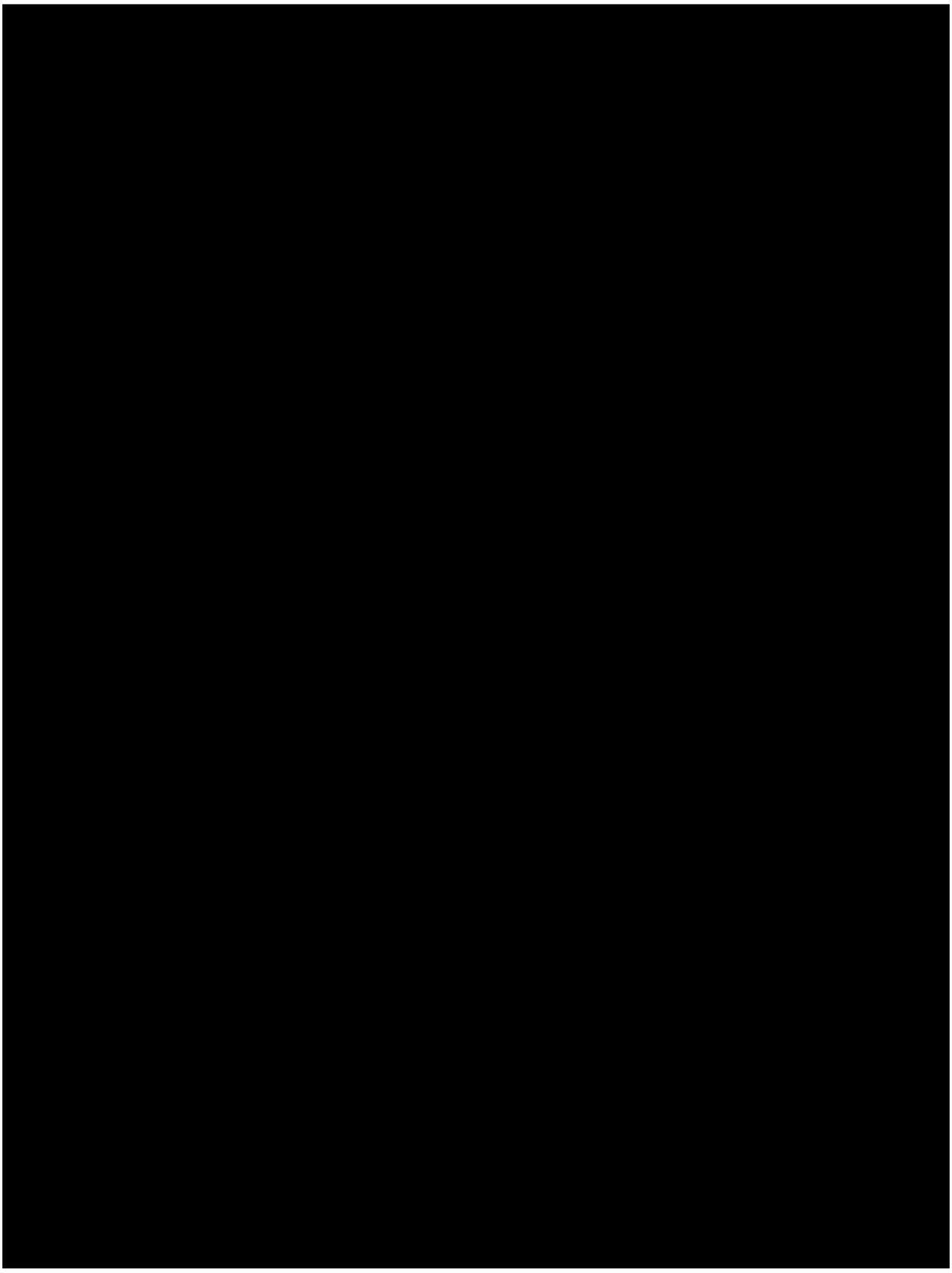
Table 23 presents goodness-of-fit statistics for the dependent standard parametric curves for nivolumab based on CheckMate-274 data. The generalised gamma distribution had the best statistical fit, and only Gompertz and log-normal distributions had AIC and BIC values with a deviance 10 (acceptable deviation; see Section 8.3.1) from best-fitting distribution.

Table 23. Akaike information criterion and Bayesian information criterion values for standard parametric models for nivolumab

Independent distributions	AIC	Rank	BIC	Rank
Generalised gamma	520.82	1	529.65	1
Gompertz	526.92	2	532.8	2
Log-normal	529.9	3	535.78	3
Log-logistic	535.47	4	541.35	4
Weibull	540.6	5	546.48	5
Gamma	542.8	6	548.68	6
Exponential	548.41	7	551.36	7

AIC = Akaike information criterion; BIC = Bayesian information criterion.

Figure 24 and Figure 25 present the independent parametric models using standard distributions. All standard parametric distributions, except for Gompertz and generalised gamma, overestimate DFS in the early periods, and all distributions except for Gompertz underestimate DFS during the latter part of the trial. This aligns with the statistical fit and shows that distributions with poor statistical fit also have a poor visual fit to the CheckMate-274 data.



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The hazards of the independent parametric extrapolation models were compared against the observed smoothed hazards; these are shown in Figure 26 to further guide curve selection. The hazard plots show how DFS risk develops over time and can often be easier to investigate with regards to clinical validity of extrapolations compared with the predicted absolute survival. As shown in Section 8.3.1.2, based on the long-term external data, it is anticipated that the risk of a DFS event will diminish with time and eventually cross that of the general population mortality. Therefore, investigating the hazard over time can reveal distributions that would result in decreasing hazards and cross general population mortality at a reasonable timepoint. Figure 26 and Figure 27 show that the Gompertz distribution is the only curve that fits the observed hazards from CheckMate-274 well; all other curves overestimate the nivolumab hazards after 20 months and onwards, which will lead to significantly underestimating long-term DFS. Generalised gamma, which had good statistical and visual fit to the overall data, overpredicts the hazard towards the later part of the data.

When investigating the hazard functions over a longer period (Figure 27), it is clear that only Gompertz and generalised gamma distributions have a hazard function that would result in crossing of general population mortality aligned within a reasonable time horizon based on evidence from the EORTC 30994 data presented in Figure 20. This again shows that the curves with poor statistical fit do not fit to or represent the observed trial data well and are not well aligned with the long-term external evidence.

Placebo

Table 24 presents goodness-of-fit statistics for the parametric curves for the placebo arm based on CheckMate-274 data. The distributions that fitted well to the nivolumab arm also have the best statistical fit to the data for the placebo arm, although the Gompertz distribution has a higher deviation than 11 in AIC and 8 in BIC from generalised gamma for the placebo arm. All other distributions have even larger deviations and therefore would not be considered acceptable regarding statistical fit.

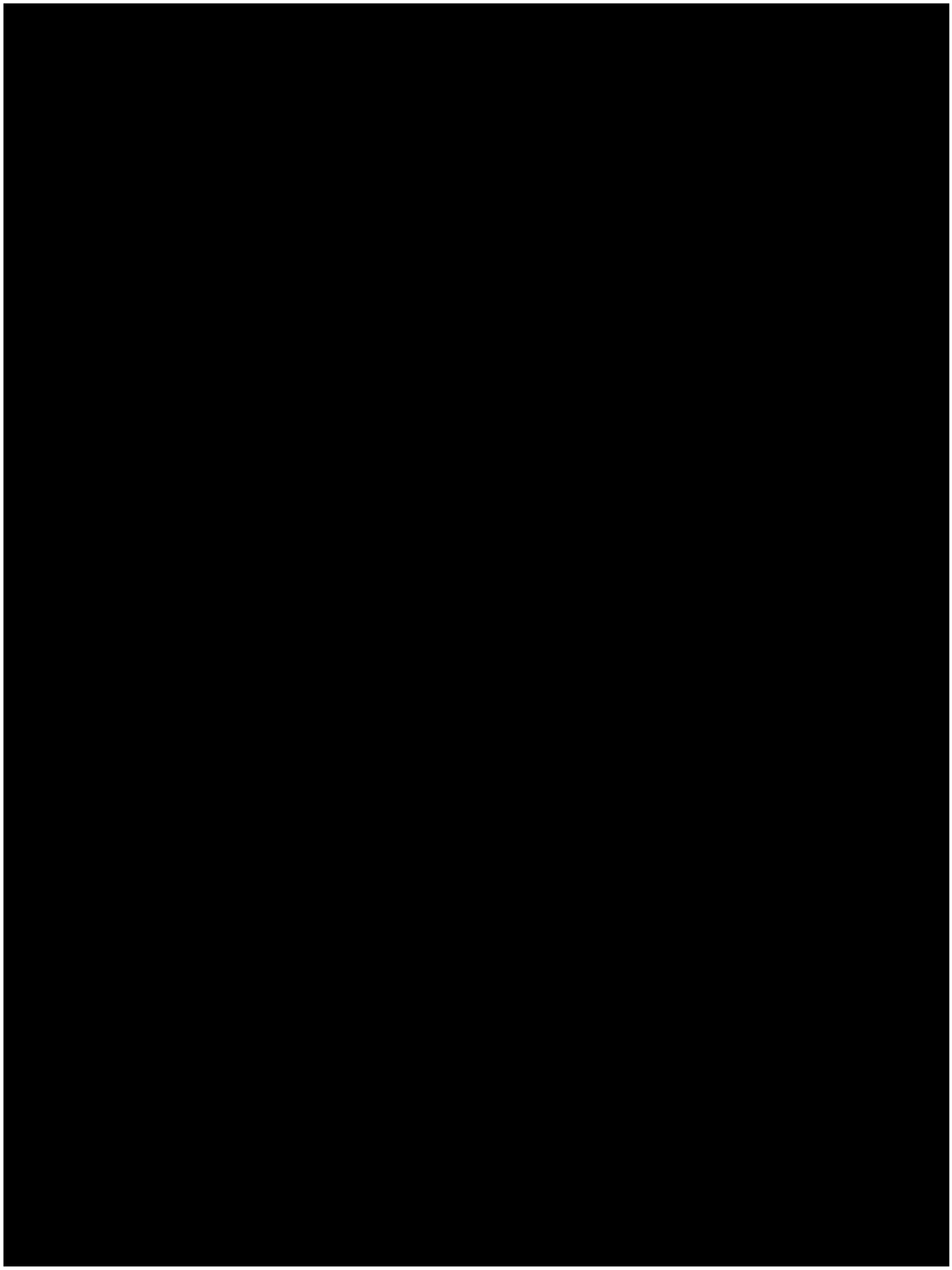
Table 24. Akaike information criterion and Bayesian information criterion values for standard parametric models: placebo

Independent distributions	AIC	Rank	BIC	Rank
Generalised gamma	654.15	1	663.02	1
Gompertz	665.46	2	671.36	2
Log-normal	669.66	3	675.57	3
Log-logistic	675.74	4	681.65	4
Weibull	691.32	5	697.22	5
Gamma	697.54	6	703.45	6
Exponential	710.62	7	713.57	7

AIC = Akaike information criterion; BIC = Bayesian information criterion.

Figure 28 and Figure 29 present the independent parametric models using standard distribution parametric fitting and extrapolations. For placebo, all standard parametric distributions, except for Gompertz and generalised gamma, overestimate DFS in the early periods, and all distributions except for Gompertz

underestimate DFS during the latter part of the trial. As shown, the distributions with the poorest statistical fit also provide the poorest visual fit to the data.



All standard distribution parametric fittings, except for Gompertz, do not fit the data well, with most of the distributions overestimating DFS in the first 20 months and then underestimating DFS for the remainder of the trial period compared with the CheckMate-274 Kaplan-Meier data (see Figure 29). The Gompertz distribution fits the trial Kaplan-Meier data reasonably well but may overestimate long-term survival as shown by the long tail in Figure 29. However, when accounting and adjusting for general population mortality (as detailed in Section 8.3.1.5) in the long-term, the long-term predictions of the Gompertz distribution become well aligned with the long-term external evidence from EORTC 30994 data.

Figure 30 and Figure 31 present the predicted hazards of distributions fitted to the placebo arm together with the smoothed hazards of the CheckMate-274 data and general population mortality. Similarly to the fitting of the nivolumab arm, the distributions with the poorest statistical fit also provide a poor fit to the smoothed hazards and poor alignment with the external evidence from EORTC 30994 in relation to crossing of general population mortality.

8.3.1.5 Selection of base-case distributions for extrapolation of DFS

As presented in Section 8.3.1.4, the only distributions that provided reasonable statistical fit to the data were Gompertz and generalised gamma for both nivolumab and placebo. Based on statistical fit only (AIC and BIC criteria), the generalised gamma distribution appears to be the best-fitting distribution for both arms. However, from visual inspection of the fitted curves to both the Kaplan-Meier data and the smoothed hazards from CheckMate-274, the Gompertz distribution provides a much better fit, particularly to the later part of the trial data with reasonable (the second best) statistical fit. However, as noted in Section 8.3.1.2, because of the declining DFS hazard with time observed in the external data reaching the general population mortality, the model has been set up to ensure that DFS hazard never can go below that of the general population mortality, which will affect the long-term extrapolation in the model.

As outlined in Section 8.3.1.1, at least equally important to the fit of the distributions within the trial period is the clinical validity of the long-term extrapolations. Therefore, Figure 32 presents both the Gompertz and generalised gamma distributions for placebo with adjustment for general population mortality compared with the long-term follow-up data from EORTC 30994 presented by Sternberg et al. (2015)[42]. As shown in Figure 32, the Gompertz distribution results in a long-term survival that is well aligned with the external long-term data. Therefore, the Gompertz distribution was considered the most clinically plausible model and thus was selected for the base-case analysis.

[redacted]

8.4 Survival from recurred disease health state

As described in Section 8.1, alternative approaches were explored for modelling of subsequent therapy in the 3-health-state model and postrecurrence survival (PRS) in the 4-health-state model was to use literature sources from the first-line mUC setting. However, based on limitations with this approach literature and assumption-based cost and outcomes were used in the base case. However, for completeness, the data for alternative modelling of subsequent therapy have been retained within the model and are described in this section. The sources used to inform first-line mUC setting were selected based on a systematic literature review of first-line mUC phase 3 clinical trials (see Section 8.1), considering study period, sample size, maturity of OS data, and relevance for the decision problem. Further, for the modelling of chemotherapy treatments, the data presented in this section were used within the base-case analysis.

8.4.1 Literature search for first-line mUC trials

Patient-level health-utility data were obtained directly from CheckMate-274. In addition a systematic literature search was conducted and is described below. It identified 2 studies relevant for health economic modelling; Bellmunt et al. (2012)[76], De Santis et al. (2012)[77]. Another 2 studies were identified outside of the systematic literature review; Powles et al. (2021)[78] was identified after the systematic literature review was completed, and Nafees et al. (2008)[66] was selected because it has been used in more than 30 different economic evaluations by organisations including NICE and the Scottish Medicines Consortium (SMC).

8.4.1.1 Literature search and strategy

A literature search was conducted on 4 February,2019, 13 February 2021 (update 1) and 27 September 2021 (update 2). Table 25 summarises the information sources that were searched. Search terms for UC and relevant interventions consisted of words searched in title/abstract and as indexed terms (i.e. Emtree and MeSH). In addition, the reference lists of the National Comprehensive Cancer Network (NCCN) [79] and the EAU treatment guidelines for MIBC [80] were screened for clinical studies (RCTs and non-randomized studies). Search terms for clinical studies were based on the filters provided by the Scottish Intercollegiate Guidelines Network (SIGN).

Table 25. Information sources searched

Source	Platform
Bibliographic databases	
Embase	ProQuest engine
Medline	ProQuest engine
Cochrane Central Register of Controlled Trials (CENTRAL)	Advanced search function on the Cochrane Library homepage
Cochrane Database of Systematic Reviews (CDSR)	Advanced search function on the Cochrane Library homepage
Conference proceedings	
American Association for Cancer Research (AACR)	Search of conference proceedings from 2016 up to September 2021 for the association
American Society of Clinical Oncology (ASCO)	
American Urology Association (AUA)	
European Association of Urology (EAU)	
European Multidisciplinary Congress on Urological Cancers (EMUC)	
European Society for Medical Oncology (ESMO)	

8.4.1.2 Selection criteria

Study selection was conducted by two independent reviewers. A full list of the selection criteria in Table 26.

Table 26. Inclusion and exclusion criteria

Topic	Inclusion criteria	Exclusion criteria
Population (P)	▪ Invasive urothelial carcinoma (according to WHO 2016 criteria) of bladder, renal pelvis and ureter (upper urinary tract) ▪ Treated with radical resection (e.g. radical cystectomy, nephrectomy) ▪ Subjects aged ≥ 18 years	▪ Non-invasive urothelial cancer ▪ Metastatic cancer ▪ Bladder preservation sparing procedure ▪ Healthy subjects ▪ Children (<18 years of age)
Interventions (I)*	▪ Adjuvant (post-surgery) treatment ▪ Platinum-based: ▪ Cisplatin combination therapy ▪ Carboplatin combination therapy ▪ Monoclonal antibodies: ▪ Nivolumab ▪ Pembrolizumab ▪ Durvalumab ▪ Atezolizumab ▪ Avelumab	Non-adjuvant interventions and interventions not included in the inclusion criteria
Comparators (C)	▪ Any of the listed interventions ▪ Placebo / SoC / Investigator's choice, this can incuded but is not limited to: ▪ Neoadjuvant chemotherapy (containing cisplatin or carboplatin)** ▪ Radiotherapy ▪ Chemotherapy ▪ Chemoradiation ▪ Watchful waiting ▪ No comparator arm	Interventions not included in the inclusion criteria
Outcomes (O)	▪ OS ▪ PFS ▪ DFS ▪ NUTRFS ▪ ORR (according to RECIST criteria)*** ▪ CR ▪ PR ▪ Duration of response ▪ Time to treatment discontinuation ▪ Time to symptom deterioration ▪ Time to progression (according to RECIST criteria)*** ▪ AE	Outcomes not included in the inclusion criteria

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Topic	Inclusion criteria	Exclusion criteria
Study design (S)	▪ Interventional trial ▪ RCTs phase II and III ▪ Non-randomized trials ▪ Non-interventional studies**** ▪ Cohort studies ▪ Single-arm studies/ uncontrolled studies ▪ Case-control studies ▪ Cross sectional studies ▪ Hospital records and database studies	▪ Systematic reviews and meta-analyses***** ▪ Other type of studies not included in the inclusion criteria (e.g. phase I RCTs, case studies, non-human studies, biomarker investigation, genome research) ▪ Studies which don't have as objective to investigate treatment efficacy/safety
Language	All languages	NA

*Interventions are based on the sources listed in Appendix 5.

**As a protocol amendment for the screening stage, neo-adjuvant chemotherapy was added to the inclusion criteria.

***RECIST: Response Evaluation Criteria In Solid Tumors (either investigator or IRC assessed)

**** Non-interventional studies are eligible for inclusion only if they report at least one efficacy outcome for one of the listed interventions

***** Data from systematic reviews and meta-analyses were not extracted into the data-extraction form. References from the four most recent (publication date) / relevant (topic and journal impact factor) publications were checked to ensure no important article is missed by the search strategy

WHO: World Health Organization, SoC: Standard of Care, OS: Overall Survival, PFS: Progression-free Survival, DFS: Disease-free Survival, NUTRFS: Non-Urothelial Track Recurrence Free Survival, ORR: Objective Overall Response Rate, PR: Partial Response, RECIST: Response Evaluation Criteria in Solid Tumors, AE: Adverse Event, RCT: Randomized Controlled Trial, NA: Not Applicable.

8.4.1.3 Study selection

In each of these steps, study inclusion and exclusion were based on the pre-defined inclusion and exclusion criteria (Table 26). During both title/abstract and full-text screening phase, excluded articles were documented with reasons for their exclusion according to the pre-defined criteria. All identified articles were screened independently by two reviewers, who consolidated their decisions and resolved any discrepancies between the two independent sets. A third reviewer was consulted if the two reviewers did not reach agreement on individual studies and a decision made. This process was used for both the screening and selection phase.

The result of the selection phase is a final list of articles included for data-extraction and reporting. A four-phase flow diagram from Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) was completed after the screening and selection step to provide an overview of the review process. The flow diagram reports the number of studies initially retrieved, the number of studies excluded at each selection step and the number of studies eventually included in the systematic review.

8.4.1.4 Data extraction

After all relevant publications were identified and received, the relevant data were extracted from the articles. Each identified study was given a unique identifier number. The extraction sheet consisted of the following main sheets:

- Trial characteristics
- Treatment regimen
- Patient characteristics
- Efficacy outcomes
- Safety outcomes
- Specific AE data HAS
- Critical appraisal RCT/Non-randomized studies following the CRD 2009 checklist
- Critical appraisal RCT/Non-randomized studies following HAS/ANAES guidelines
- Graph and tables.

8.4.1.5 Quality assessment

According to the National Institute for Health and Care Excellence (NICE) requirements, RCTs, non-randomized studies and cost-effectiveness analysis need to go through Quality Assessment (QA) using a recommended checklist. The quality assessment checklist for RCTs and non-randomized studies from [81] was applied for QA.

In addition to the QA according to the CRD 2009 checklist, a QA was conducted by assessing the level of evidence and classifying the studies into their corresponding scientific evidence grade according to the guidelines "Choices in methods for economic evaluation" developed by Haute Autorite de Sante (HAS) (2020)[82], and the checklist for clinical trials provided by ANAES (2000)[83].

QA was performed for all publications except for conference proceedings, as there would be insufficient methodological data to assess the study quality.

8.4.1.6 Definitions and notes to the reader

Unique study identifier

Each study was given an individual study identification code, which was used throughout the data extraction file and report. In the original search and the first update, these codes consisted of a combination of three letters and a four-digit number. Studies identified with ProQuest received the three-letter code PQC plus a four-digit number (e.g. PQC0001), studies identified in the Cochrane library received the code COC plus a four-digit number (e.g. COC0001). The studies identified in conference proceedings received the letter codes (e.g. ASC, AUA, EAU) plus a four-number digit. In the second update, refIDs (e.g. r1) generated by Distiller were used to identify studies throughout the data extraction file and report.

Overlapping publications

A number of publications were identified by this SLR that reported on the same study/ same set of patients. Table 27 summarises the publications identified as reporting on the same study.

Table 27. Publications reporting on the same study

Clinical trial number (trial acronym)	Publications (unique study identifier)
NCT02450331 (IMvigor010)	▪ Hussain 2020 [84] (PQC1124): Abstract with limited information ▪ IMvigor010 study: Study data via clinicaltrials.gov[85] ▪ Bellmunt 2021 [86] (r5): Full publication
N.R.	▪ Zhegalik 2020 [87] (PCQ1124): Full publication with long-term follow-up results ▪ Zhegalik 2014[88] (Coch0207): Abstract with limited information, short-term follow-up
ChiCT1900027	▪ Luo 2020 [89] (PQC1439):Full publication in English [International journal] ▪ Luo 2019[90] (PQC1403): Full publication in English [Chinese journal]
NCT0173498	▪ Zaghloul 2019[91] (PQC1178): Full publication, reporting data for PORT+AC vs. PORT ▪ Zaghloul 2019[92] (PQC1191): Full publication, reporting data for AC vs. PORT
NCT00028756	▪ Sternberg 2015[42] (PQC0048): Full publication ▪ Sternberg 2014[93] (Coch0177): Abstract with limited information
N.R.	▪ Cognetti 2012[94] (PQC0119): Full publication ▪ Cognetti 2008 [95] (Coch022): Abstract with limited information
N.R.	▪ Lehmann 2006[96] (PQC0568): Long-term OS, Only reporting on RCT patients. ▪ Stöckle 1996 [97] (PQC0324): Reports only on combination of RCT and non-RCT patients from Stockle 1995 ▪ Stockle 1995[98] (PQC0555): Combination of patients from RCT reported in Stockle 1992 with patients treated at institution but were not part of RCT. Reports on both sets of patients ▪ Stockle 1992 [99] (PQC0677): First data cut and analysis
NCT02632409 (CheckMate 274)	▪ Bajorin 2021 [50] (ASC5): Abstract with limited information ▪ Bajorin 2021 [1] (r35): Full publication

AC = adjuvant chemotherapy; N.R. = not reported; PORT = post-operative radiotherapy; RCT = randomized controlled trial.

Endpoint definitions

Discrepancies often exist between how studies define particular endpoints. For the purposes of extraction and reporting, all data were extracted under the term in which they were labelled in the study. Reported definitions were also extracted for each of the outcomes and are presented in the tables.

Changes to the PICOS in the February 2021 update search

In the updated search conducted in February 2021, the selection criteria were revised to excluding studies which meet all PICOS criteria as presented in Table 16 but presented efficacy and/or safety data for treatment arms/cohorts which included patients treated with cisplatin-based AC or carboplatin-based AC, and did not report this data separately for cisplatin-based AC patients or for carboplatin-based AC patients. Furthermore, studies which did not further specify the AC regimen other than 'AC' were also excluded. Studies which reported efficacy and/or safety data for treatment arms/cohorts which included patients treated with various cisplatin-based regimens were included; and likewise, studies reporting efficacy and/or safety data for treatment arms/cohorts which included patients treated with various carboplatin-based regimens were also included. The rationale for these additional excluding criteria is that recent studies and analyses have shown that cisplatin-based regimens perform significantly different than carboplatin-based regimens. Studies

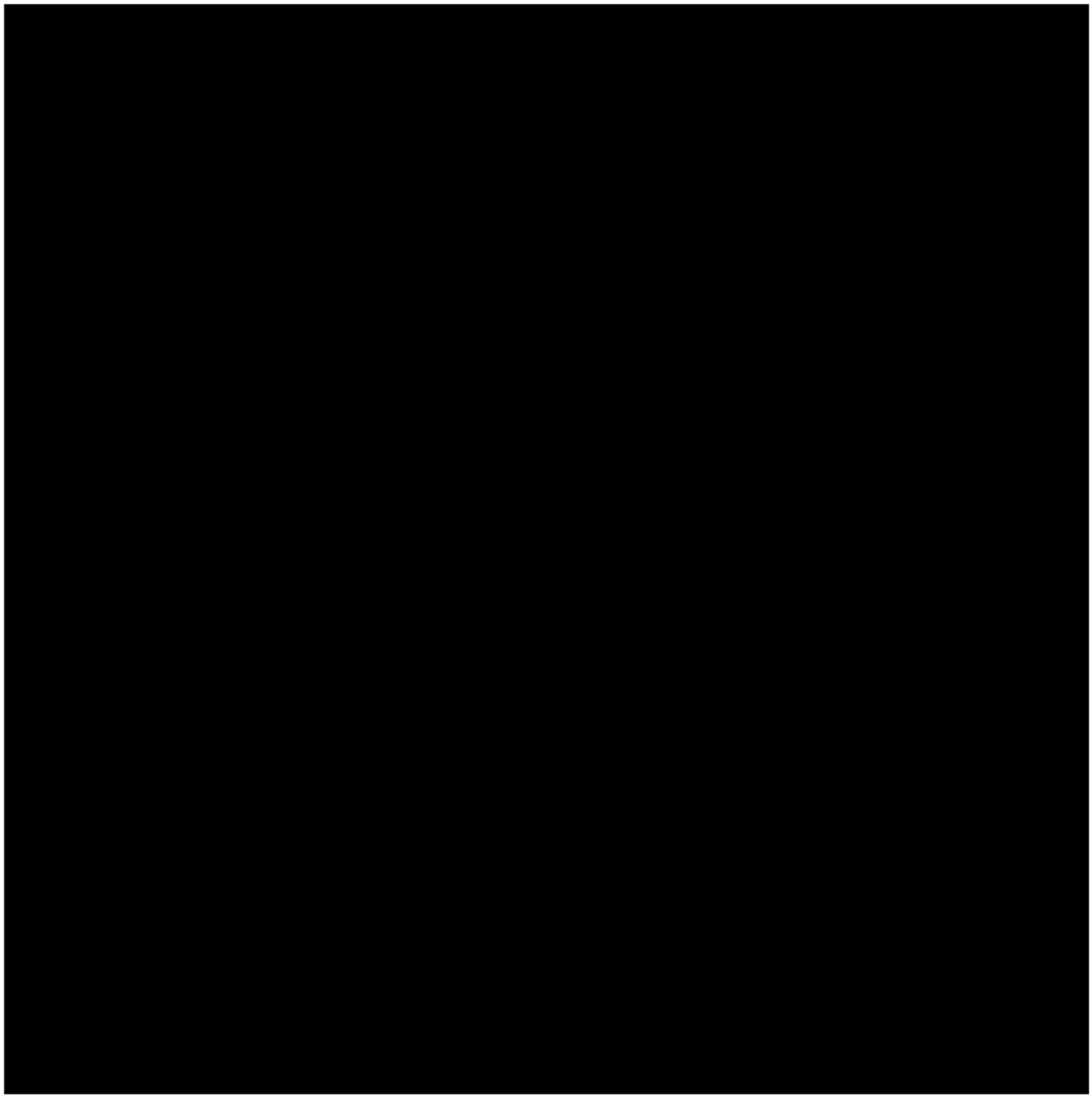
included in the original review which did not meet the modified PICOS were not excluded during the review update process. In the September 2021 update, no alterations in the search criteria were made.

8.4.1.7 Selection process

During the original and update SLR, a combined total of 2,346 publications were identified from the databases. After deduplication, the title and abstracts of 1,796 publications were screened for eligibility. After excluding 1,640 publications based on title and abstract screening, 156 full-text publications were assessed for full-text eligibility based on the pre-specified criteria (Table 25). Of these, 61 were deemed relevant for inclusion. Screening of references from identified literature reviews and the NCCN and EAU treatment guidelines yielded an additional nine eligible publications for inclusion and relevant abstracts identified from conference proceedings added a further seven records for inclusion.

In total, 77 publications were included in the SLR reporting on 66 unique studies (Figure 33).

While reviewing the SLR results, the question arose whether all studies comparing systemic adjuvant therapy with neoadjuvant treatment (including platinum-based regimens) were identified. It was expected that all studies investigating the efficacy/safety of adjuvant treatments were included, regardless of comparator. Since single-arm trials could be included as study design, the comparator arm criteria were not strictly applied as a single intervention arm of a comparative trial could also be relevant for further analysis. Therefore, the inclusion/exclusion criteria for the screening stage were amended to specify NAC was a comparator of interest. To confirm this expectation was correct, rescreening was performed by a single reviewer. All studies that were originally excluded as duplicate, or by population, outcomes or study design were assumed to be ineligible, the same criteria applied regardless of comparator arm. Studies excluded based on intervention or comparator at either title/abstract or full-text screening stage were rescreened. No relevant studies investigating adjuvant treatment were seen within these references. Therefore, it was concluded that all studies comparing adjuvant vs. neoadjuvant therapy were indeed included in the SLR results.



The 77 included publications reported on 66 unique studies. Of these, 2 studies were considered relevant for health economic modelling: Bellmunt et al. (2012)[76], De Santis et al. (2012)[77].

The current standard of care in Denmark for first-line mUC patients are gemcitabine plus cisplatin chemotherapy. Patients for whom gemcitabine plus cisplatin chemotherapy is not suitable can be offered PD-1/PD-L1 targeted immunotherapy if they express the biomarker PD-L1 at the required level or chemotherapy with carboplatin plus gemcitabine or gemcitabine alone. For chemotherapy in Denmark for first-line mUC patients, the studies selected to inform PRS in the model represented cisplatin in combination with gemcitabine from Bellmunt et al. (2012)[76] for patients that can tolerate cisplatin-based therapy in first-line mUC, and De Santis et al. (2012)[77] for cisplatin-ineligible patients that instead receive carboplatin in combination with gemcitabine. For patients who receive immunotherapies (atezolizumab or pembrolizumab) in first-line mUC, the survival for these patients is generated by applying an HR to the study by De Santis et al. (2012)[77], with patients eligible for first-line mUC immunotherapies treatment being cisplatin ineligible and PD-L1 positive. The HR was derived through an ITC using data from the pembrolizumab trial KEYNOTE-361 study,[78] and details are presented in Section 8.4.6.

8.4.2 Bellmunt et al. (2012)[76]

Bellmunt et al. (2012)[76] details the finding of the phase 3 randomised clinical trial EORTC 30987 investigating paclitaxel in combination with cisplatin and gemcitabine (PCG) compared with gemcitabine plus cisplatin (GC) for the treatment of patients with locally advanced or metastatic urothelial cancer without prior systemic therapy.[76] 626 patients across 137 institutions with a mean age of 61 years were randomly assigned to either the PCG (n = 312) or GC (314) treatment arms. 80.5% of patients (n = 504) have died after a median follow-up of 4.6 years. The median OS was 15.8 months (95% CI, 13.6-17.5) for the PCG arm, and 12.7 months (95% CI, 11.0-14.4) in the GC arm. This difference was not found to be statistically significant with a HR of 0.85 (95% CI, 0.72-1.02; *P* = 0.075). The median PFS was 8.3 months in the PCG arm compared with 7.6 months in the PCG arm with a HR of 0.87 (95% CI, 0.74-1.03; *P* = 0.113).

Analysis by WHO performance status (1v0) in the ITT population regardless of treatment arm, showed a statistically significant difference with a HR of 1.5 (95% CI, 1.26-1.79; *P* < 0.001).

Bellmunt et al. (2012)[76] is recognised as quality study for cisplatin-eligible patients in first-line mUC given its high sample size and long follow-up period, with almost complete maturity in the OS data.

8.4.3 De Santis et al. (2012)[77]

De Santis et al. (2012)[77] reports the findings of the phase 2/3 randomised multicentred clinical trial EORTC study 30986, for the treatment of patients with advanced urothelial cancer, whom were cisplatin ineligible as assessed by a WHO performance score of 2 or more (n = 42, 17.6%), or impaired renal function assessed by 30 < GFR < 60 mL/min (n = 131, 55.0%) or both (n = 65, 27.3%). 238 patients across 29 institutions over 7 years with a mean age of 71 years were randomised across 2 carboplatin-based chemotherapy regimens, GC (n = 119) and methotrexate plus carboplatin plus vinblastine (M-CAVI) (n = 119). Overall survival was the primary endpoint, PFS and response rates were also assessed as secondary endpoints.[77]

No statistically significant difference was found between the 2 treatment arms for both OS and PFS in the ITT population. A median OS of 9.3 months was observed in the GC arm and 8.1 months in the M-CAVI arm with a HR of 0.94 (95% CI, 0.72-1.22). This difference became significant when only the confirmed responses were included (*P* = 0.01). The median PFS was 5.8 months in the GC arm and 4.2 months in the M-CAVI arm with a HR of 1.04 (95% CI, 0.80-1.35). The number of criteria patients met for being cisplatin ineligible was found to be indicative of survival, a higher OS was found in patients who only met one criterion.[77]

De Santis et al. (2012)[77] was the highest quality study identified from the systematic literature review for the cisplatin-ineligible patient group in first-line mUC. The data are almost fully mature, and the study has been used in previous NICE technology appraisals (TA522) for similar purpose to inform carboplatin in combination with gemcitabine as a comparator.

8.4.4 Use of first-line mUC to inform PRS

After recurrence, the probability of death in the model is applied as a static probability across both treatment arms, with an assumption that patients receive either cisplatin with gemcitabine or carboplatin in combination with gemcitabine. Key baseline patient characteristics across CheckMate-274 and the studies informing postrecurrence are in keeping, with median ages over 60 years old, and site of primary tumour being mostly in the bladder (Table 28).

Table 28. Comparison of baseline characteristics in studies informing postrecurrence survival

	CheckMate-274	Bellmunt et al.	De Santis et al.	Powles et al.
Median age	67	61	70	69
% Male	76.2%	81.0%	75.6%	74%
Site of primary tumour: bladder	79.0%	82.5%	75.6%	77%

Survival related to the RD health state is based on survival analysis conducted to extrapolate the Bellmunt et al. (2012)[76] and De Santis et al. (2012)[77] OS data to fulfil the lifetime horizon of the CEM.

The methodology from Guyot et al. (2012)[100] was used to have patient-level data from the reported KM curves. The main intuition of the methodology is as follows. The KM estimate of the survival function at event time t_m is:

$$S^{KM}(t_m) = \prod_{j=1}^{m} \frac{n_j - d_j}{n_j},$$

where $m = 1,2,..,r$ denotes the time interval. The number of events that occur at the start of the interval is d_m and the number of patients still at risk just before the start of the interval n_m. If there is no censoring, the KM curve and total number of patients identify both n_m and d_m for all time intervals using the relationship:

$$S^{KM}(t_m) = S^{KM}(t_{m-1}) \frac{n_m - d_m}{n_m}.$$

However, in practice there is usually censoring, so that $n_{m+1} = n_m - d_m - c_m$ with c_m being the number of individuals censored on the interval. To identify n_m and d_m, an assumption is made that censoring occurs at a constant rate within each of the time intervals. This assumption is reasonable if the censoring pattern is non-informative. A numerical algorithm is available to estimate $\hat{d}_m$, $\hat{n}_m$and the number of censored observations at each timepoint, from which individual patient data (IPD) can be simulated. If the number of patients at risk are reported, either once or at several timepoints, the algorithm uses this information. The algorithm uses the x-axis and y-axis coordinates of KM curve as input data. Once pseudo-IPD are generated, parametric survival curves can be fitted.

8.4.5 Survival extrapolation

Survival extrapolation was performed based on the same principles as for the analyses performed for the CheckMate-274 data, fitting both standard parametric and spline models.

8.4.5.1 Cisplatin-eligible patients: Bellmunt et al. (2012)[76]

The OS curve of the Gem-Cis arm in Bellmunt et al. (2012)[76] was used to inform the DRS for the cisplatin-ineligible PD-L1+ subgroup.

Seven standard parametric models and 6 cubic spline models were fitted. The base case model was selected based on AIC, BIC, and visual inspection. Only independent models were fitted, as only the Gem-Cis arm of the trial was evaluated.

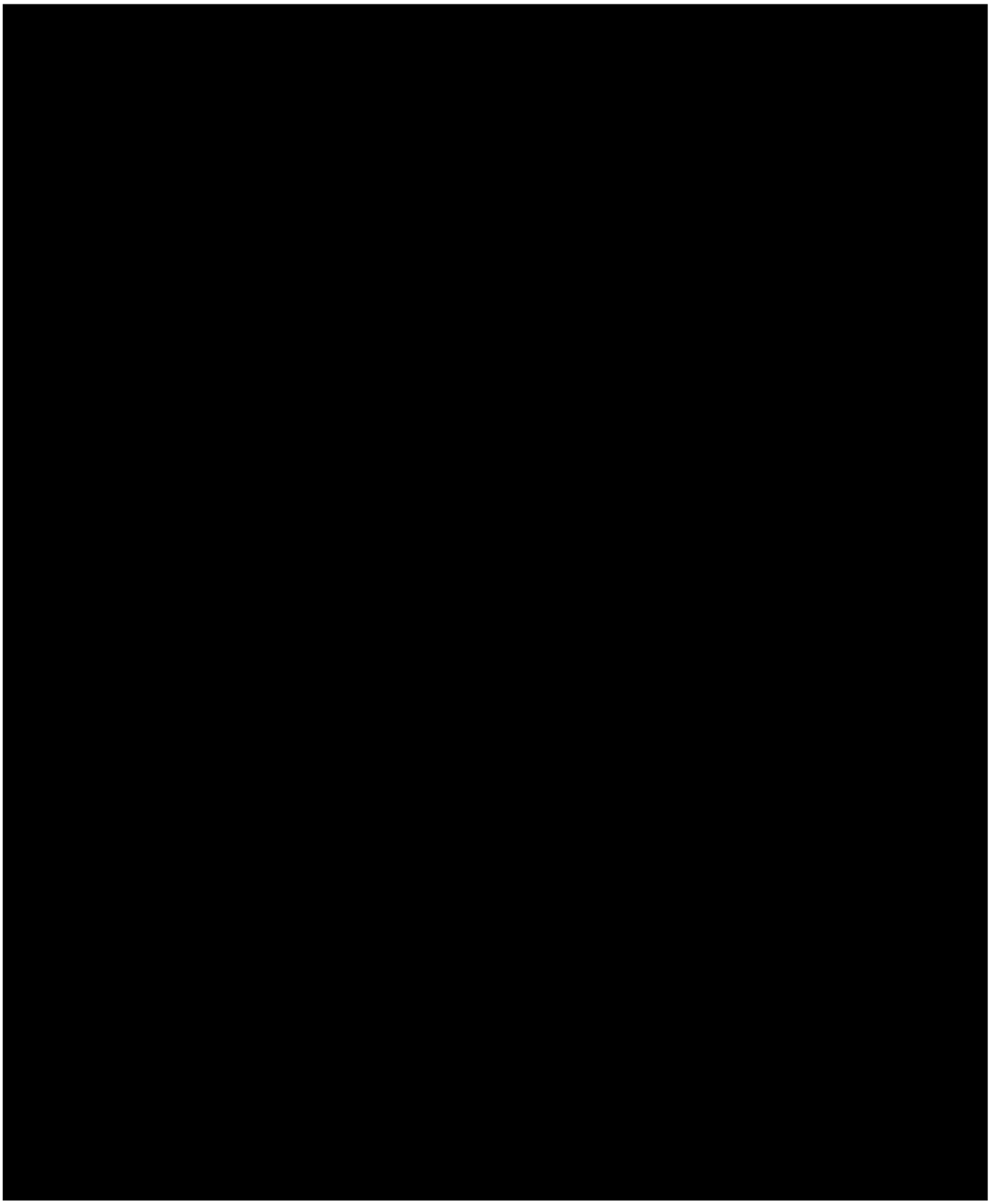
Table 29 presents the AIC and BIC values of the fitted models. Considering both AIC and BIC values, the best performing model is the log-logistic for the standard parametric model and the 2-knot hazard for the spline models. Overall, the majority of the spline models had a better fit than the standard parametric models. The second best– and third best–fitting curves in standard parametric model were the log-normal and the generalised gamma models, while for the spline models these were the 2-knot normal and 2-knot odds models, respectively.

Table 29. AIC and BIC values of independent models

Bellmunt et al. (2012)[76]	AIC	BIC
Standard parametric models		
Exponential	1,963	1,966
Gamma	1,962	1,970
Generalised gamma	1,929	1,940
Gompertz	1,952	1,959
Log-logistic	**1,919**	**1,926**
Log-normal	1,927	1,935
Weibull	1,965	1,972
Spline models		
1-knot hazard	1,921	1,932
2-knot hazard	**1,906**	**1,921**
1 knot normal	1,929	1,940
2-knot normal	1,908	1,923
1-knot odds	1,919	1,930
2-knot odds	1,908	1,923

AIC = Akaike's information criterion BIC = Bayesian information criterion.

Among the standard parametric models, the survival extrapolation is best captured by the log-logistic and log-normal distributions until 40 months, but after that timepoint, the Gompertz model present shows a better fit. The 2-knot hazard model is the best fitting among the spline models, followed by the 2-knot odds model. The standard parametric models and the majority of the spline models are unable to capture the plateau seen at the end of the trial. The spline models perform better than standard parametric models when it comes to fitting the shape of the KM curve (Figure 34and Figure 35).



Hazard plots of the survival extrapolations are presented in Figure 36 and Figure 37. The observed smoothed hazard pattern for the Gem-Cis arm in Bellmunt et al. (2012)[76] is non-monotonic, which explains why the exponential (constant hazards), Weibull, Gompertz, and gamma curves (monotonic increasing or decreasing hazards) are less suited. When considering the hazards for the first 30 months, the spline models seem to provide a better fit, compared with the standard parametric model models, although the hazards are

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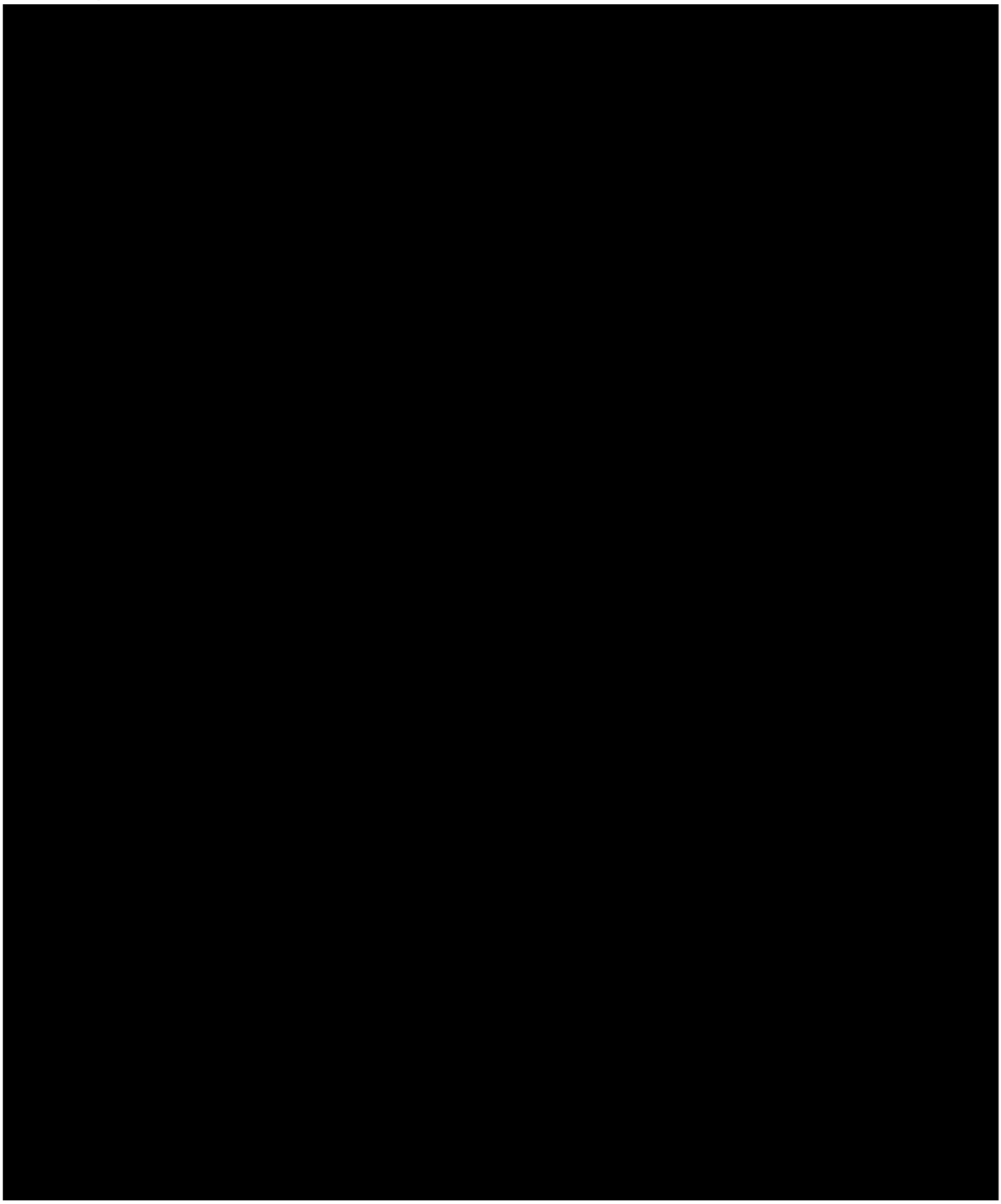
overestimated. The best curve based on AIC and BIC, the log-logistic curve, provides a good visual fit, although after 30 months it overestimates the hazard of the original curve. Overall, the hazards of the spline models fit better to the observed curve than the standard parametric models. The best-fitting models are the 2-knot hazard, 2-knot normal and 2-knot odds models.



A summary of the 2-, 5-, and 40-years landmark survivals from the different models with the restricted mean survival time (RMST) and median survival for the OS curve are presented in Table 30. This table shows that the log-logistic (the best-fitting curve on AIC and BIC among the standard parametric models) overestimated the

landmark survival at 2-years, as well as the median survival, while the 5 years survival and the RMST were underestimated compared with the observed data.

The 2-knot hazard model, which is the best fitting among the spline models according to AIC and BIC, provide a similar landmark survival for with 2 and 5 years as the observed data, but the median survival time was overestimated. Both the log-logistic the 2-knot hazard models underestimated the RMST compared with the observed data.

The second and third best–fitting curves based on AIC and BIC were the 2-knot normal and 2-knot odds respectively. Both models slightly overpredicted the 2 years survival compared with the observed data, while for 5 years they showed a similar survival as the observed KM curve. The RMSTs are overestimated, while the median survivals are underestimated in both models, compared with the original curve.

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Table 30. Median landmark survival and restricted mean survival time

	Survival median (months)	LCI	UCI	2-year survival (%)	Comparison with observed data[a]	5-year survival (%)	Comparison with observed data[a]	RMST last observation (months)	RMST 40 years (months)	Diff. median survival (months)	Diff. RMST last observation (months)
Exponential	15.16	13.46	17.17	0.33	+	0.06	-	21.21	21.87	−2.66	0.49
Gamma	15.64	13.86	17.83	0.33	+	0.05	-	21.07	21.52	−3.14	0.63
Generalised gamma	13.35	11.55	15.24	0.30	+	0.09	-	21.43	25.37	−0.85	0.27
Gompertz	13.12	10.99	15.46	0.31	+	0.11	-	21.75	35.92	−0.62	−0.05
Log-logistic	13.24	11.77	14.95	0.28	+	0.08	-	20.49	25.35	−0.74	1.21
Log-normal	13.47	11.77	15.42	0.30	+	0.09	-	21.33	24.75	−0.97	0.37
Weibull	15.27	13.2	17.54	0.33	+	0.06	-	21.19	21.8	−2.77	0.51
1-knot hazard	12.38	10.85	14.33	0.28	+	0.11	-	21.69	27.08	0.12	0.01
2-knot hazard	12.56	11.31	13.81	0.25	=	0.12	=	21.64	36.03	−0.06	0.06
1-knot normal	13.42	11.54	15.5	0.30	+	0.09	-	21.36	24.9	−0.92	0.34
2-knot normal	12.34	11.18	13.77	0.26	+	0.12	=	21.75	35.22	0.16	−0.05
1-knot odds	12.93	11.36	14.8	0.28	+	0.10	-	21.19	28.43	−0.43	0.51
2-knot odds	12.45	11.1	13.83	0.26	+	0.12	=	21.78	37.64	0.05	−0.08
Calculation based on observed data	12.5	11.6	14.4	0.25		0.12		21.7	N/A		

LCI = lower confidence interval; RMST = restricted mean survival time; UCI = upper confidence interval.

[a] Compared with the 2&5 survival of the observed data, + indicates estimate is higher than observed data, - indicates estimate is lower than observed data, = indicates no difference. The difference between the RMST at last observation and at 40 years is due to long-term survival in 10 to 15% of patients, based on expert opinion. These patients experience a survival trend similar to the general population. The calculation based on observed data is not possible as those data have not yet fully matured.

Source: Bellmunt et al. (2012)[76]

Based on the statistical fit criteria and visual inspection of the survival extrapolations and smoothed hazard curves, **the 2-knot hazard** distribution was chosen for the base case. This choice was validated by the experts during the VAB 2021, in which they confirmed that the selected curve seems to fit the data very well; and the survival extrapolation of the 2-knot hazard models looks reasonable.[101]

8.4.5.2 Cisplatin-ineligible patients (all-comers and PD-L1+): De Santis et al. (2012)[77]

The OS curve of the Gem-Car arm in De Santis et al. (2012)[77] was used to inform the baseline survival for the cisplatin-ineligible PD-L1+ subgroup.

Seven standard parametric models and 6 cubic spline models were fitted to the OS curve. A base-case model was selected based on AIC, BIC and visual inspection. Only independent models were fitted, as only the Gem-Car arm of the trial was evaluated.

Table 31 presents the AIC and BIC values of the fitted models. Considering both AIC and BIC values, the best performing model is the log-logistic for the standard parametric model and the 1-knot normal for the spline models. Overall, the majority of the spline models performed better than standard parametric models. The second best– and third best–fitting curves in standard parametric model are the log-normal and the generalised gamma models, while for the spline models these are the 1-knot odds and 1-knot hazard models, respectively. Since the difference between the AIC and BIC values of the log-logistic, log-normal, 1-knot normal, 1-knot hazard and 1-knot odds models are below 2 points, we do not consider that there will be a substantial difference between these model fits. As such, all these models can be considered for model selection.

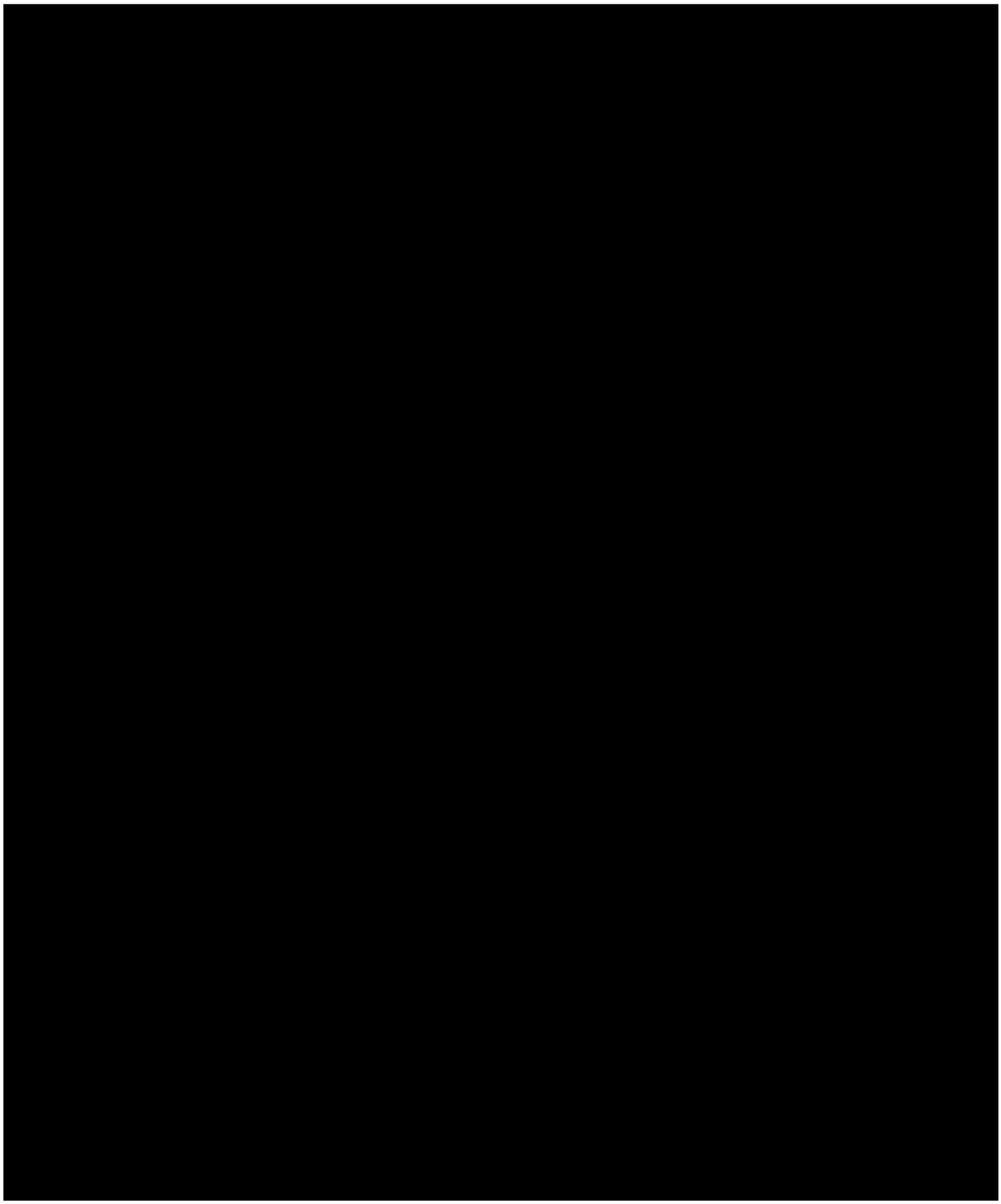
Table 31. AIC and BIC values of independent models

	AIC	BIC
Standard parametric modes		
Exponential	788	791
Gamma	781	786
Generalised gamma	777	785
Gompertz	790	796
Log-logistic	**775**	**781**
Log-normal	776	781
Weibull	784	790
Spline models		
1-knot hazard	777	786
2-knot hazard	779	790
1-knot normal	**776**	**785**
2-knot normal	778	789
1-knot odds	777	785
2-knot odds	779	790

AIC = Akaike's information criterion BIC = Bayesian information criterion.
Source: De Santis et al. (2012)[77]

The spline models performed better than standard parametric models when it came to fitting the shape of the KM curve (Figure 38 and Figure 39). Among the standard parametric models, the survival extrapolation seems

best captured by the log-logistic and the log-normal distributions. All curves fitted within the 95% CI except for the beginning before 6 months, where the exponential and the gamma distributions underestimated the survival. For the spline models, differences were negligible. All models fell within the 95% CI of the observed KM curve.



Hazard plots of the survival extrapolations are presented in Figure 40 and Figure 41. The observed smoothed hazard pattern for the Gem-Car arm in De Santis et al. (2012)[77] is non-monotonic, which explains why the exponential (constant hazards), Weibull, Gompertz, and gamma curves (monotonic increasing or decreasing

hazards) are less suited. When considering the hazards for the first 30 months, the spline models are providing a better fit, than the standard parametric models, although the hazards are slightly overestimated. The best curve based on AIC and BIC, the log-logistic curve, provides a good visual fit until 30 months. However, as the increase after 30 months of the original curve is due to the low number of patients at risk, this increase should not be considered valid, and should be neglected when comparing the survival models with the observed curve after approximately 40 months. The hazards of the spline models all fit the observed curve well. The best-fitting models based on AIC and BIC are the 1-knot normal, 1-knot odds, and 1-knot hazard models, for which the latter provided the best fit based on visual inspection.

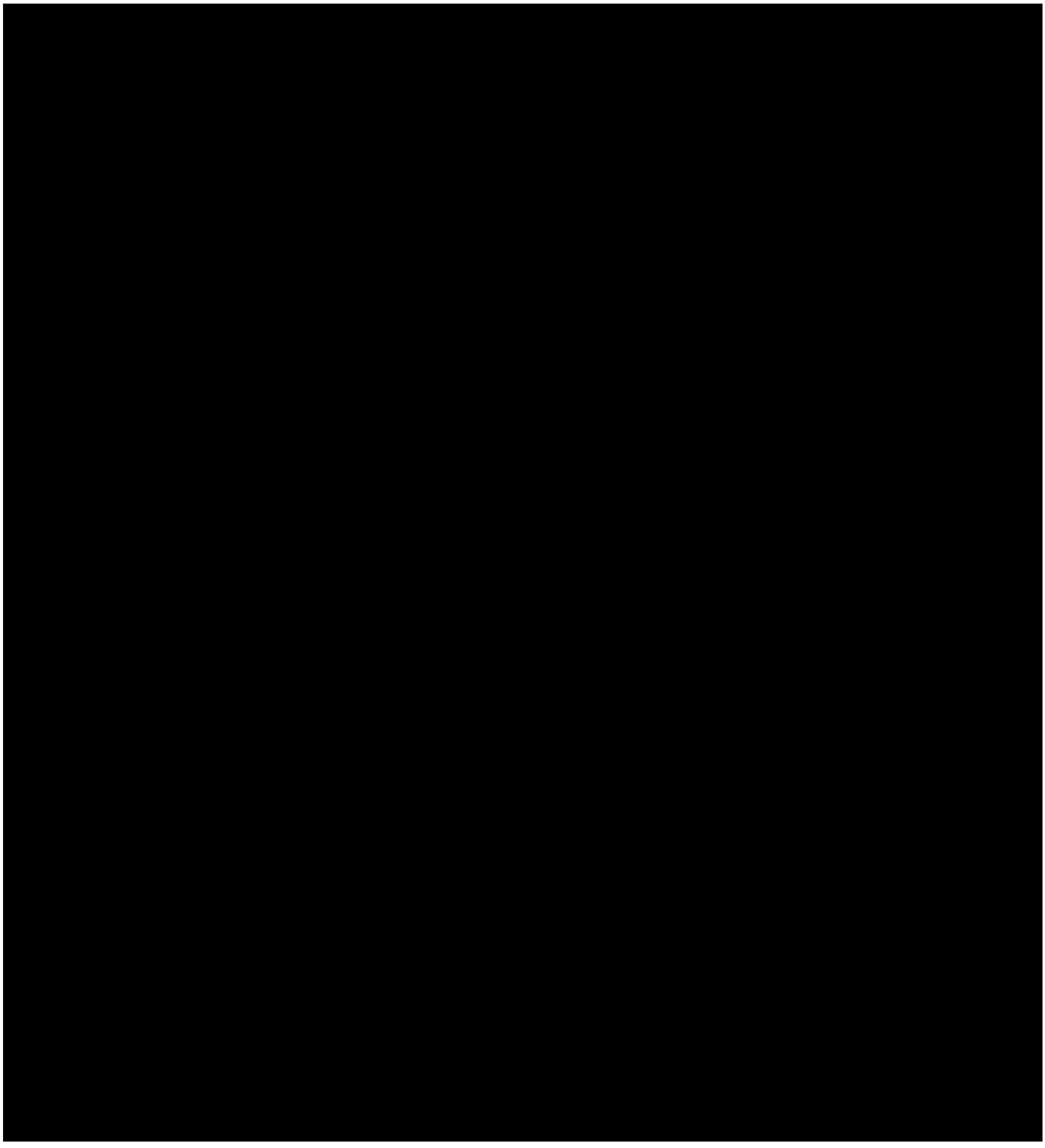


Table 32 shows that, for the observed De Santis et al. (2012)[77] curve, the log-logistic model (the best-fitting curve on AIC and BIC among the standard parametric models) overestimates the 5 years absolute survival as well as the median survival compared with the observed data, while the 2-years survival remained the same as in the observed data. The RMST was overestimated compared with the observed value.

The 1-knot normal model, which is the best fitting among the spline models according to AIC and BIC, estimated a similar landmark survival at 2 and 5 years compared with the observed data, but the RMST and median survival time are slightly overestimated compared with the observed value.

The second and third-best overall fitting curves (besides the best standard parametric model and spline model) based on AIC and BIC, are the log-normal and generalised gamma, respectively. Both models overpredict the 2 years survival compared with the observed data. The 5 years survival of the log-normal model is slightly overestimated compared with the observed data, while it no difference is observed for the generalised gamma model. The RMSTs are overestimated in in both models compared with the original value. The median survival time is overestimated in the generalised gamma model, while it is underestimated in the log-normal model, compared with the original value.

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Table 32. Median landmark survivals and restricted mean survival time

	Survival median (months)	LCI	UCI	2-year survival (%)	Comparison with observed data[a]	5-year survival (%)	Comparison with observed data[a]	RMST last observation (months)	RMST 40 years (months)	Diff. median survival (months)	Diff. RMST last observation (months)
Exponential	9.4	7.76	11.26	0.17	+	0.01	=	12.53	12.6	−0.01	−0.14
Gamma	10.48	8.86	12.19	0.14	=	0.00	-	12.31	12.32	−1.09	0.08
Generalised gamma	9.54	7.99	11.52	0.15	+	0.01	=	12.47	12.65	−0.16	−0.08
Gompertz	9.6	7.84	11.78	0.17	+	0.01	=	12.47	12.51	−0.22	−0.08
Log-logistic	9.45	8.12	11.13	0.14	=	0.03	+	12.92	14.26	−0.06	−0.53
Log-normal	9.25	7.78	11.03	0.15	+	0.02	+	12.72	13.16	0.13	−0.33
Weibull	10.5	8.81	12.47	0.15	+	0.00	-	12.4	12.4	−1.12	−0.01
1-knot hazard	9.44	7.9	11.24	0.15	+	0.01	=	12.48	12.62	−0.06	−0.09
2-knot hazard	9.53	7.98	11.21	0.14	=	0.02	+	12.51	12.71	−0.14	−0.12
1-knot normal	9.66	8.18	11.67	0.14	=	0.01	=	12.41	12.61	−0.28	−0.02
2-knot normal	9.53	8.08	11.41	0.14	=	0.02	+	12.49	12.81	−0.15	−0.1
1-knot odds	9.59	8.08	11.35	0.14	=	0.02	+	12.59	13.51	−0.2	−0.2
2-knot odds	9.61	8.17	11.49	0.14	=	0.02	+	12.53	13.32	−0.23	−0.14
Calculation based on observed data	9.39	8.25	11.48	0.14		0.01		12.39	N/A		-

LCI = lower confidence interval; RMST = restricted mean survival time; UCI = upper confidence interval.

[a] Compared with the 2&5 survival of the observed data, + indicates estimate is higher than observed data, - indicates estimate is lower than observed data, = indicates no difference. Last observation was observed at 5.95 years. The RMST at last observation is very similar to the RMST at 40 years for all extrapolation models fitted which highlights the almost full maturity in the observed data.

Source: De Santis et al. (2012)[77]

Based on the statistical fit criteria and visual inspection of the survival and smoothed hazard curves, the 1-knot hazard distribution is chosen for the base case (Figure 42).

8.4.6 Pembrolizumab in first-line mUC

To model the efficacy of pembrolizumab in first-line mUC (assumed to also represent atezolizumab), data from the KEYNOTE-361 phase 3 trial were used. KEYNOTE-052 also represents the first-line mUC setting but is a single-arm study, making its comparative efficacy versus first-line mUC chemotherapy challenging to analyse. KEYNOTE-361 compared the efficacy and safety of pembrolizumab monotherapy to platinum-chemotherapy for first-line treatment of mUC. In particular, data for PD-L1 positive cisplatin-ineligible patients were of interest, using OS data from KEYNOTE-361 for patients with PD-L1 combined positive score of at least 10 who were chosen to receive carboplatin (cisplatin ineligible).

Figure 43 shows the blue OS curve of pembrolizumab compared with the red OS curve of carboplatin-based chemotherapy. The 2 curves overlap and cross multiple times during the study follow-up, indicating similar efficacy. However, there is a slight separation in the 2 from about 2 years, but this is not well established in the data with less than 30 patients still at risk in each arm from this point. Despite these characteristics in the data, the within-study HR of 0.82 was estimated. This was further estimated in an ITC including the De Santis study, which resulted in a HR for pembrolizumab versus carboplatin-based first-line mUC chemotherapy of 0.83, with 95% CI of 0.57, 1.18). This HR was applied to the De Santis reference curve, to derive a PRS curve for pembrolizumab.

[redacted]

8.4.7 Adverse reaction outcomes

The CEM included all-causality, grade 3-4 AEs with an incidence of at least 15% (measured for any grade) in any treatment arm for the ITT population (see Table E-2). No AEs were assumed for the placebo (observation) arm in the analysis as a conservative assumption. Table 33 summarises the AEs included in the model and the percentage of patients experiencing each AE in each model arm.

Table 33. All-causality, grade 3-4 adverse events with an incidence of at least 15% (any grade) for all treated patients

Adverse reaction outcome	Nivolumab	Placebo (observation)
Diarrhoea	[redacted]	[redacted]
Fatigue	[redacted]	[redacted]
Pruritus	[redacted]	[redacted]
Urinary tract infection	[redacted]	[redacted]
Nausea	[redacted]	[redacted]
Rash	[redacted]	[redacted]
Constipation	[redacted]	[redacted]

CSR = clinical study report

Note: 15% incidence in the ITT population. See full table in Appendix E, table E-1

Source: Clinical study report (CSR) (data on file)[54]

8.5 Documentation of health-related quality of life

8.5.1 Overview of health-state utility values

The CheckMate-274 trial collected patient-reported health-state utility values (HSUVs) using the EQ-5D-3L questionnaire. Analyses were conducted based on the prespecified patient-reported outcome statistical analysis plan. The primary purpose of the analysis was to identify mean EQ-5D values for the economic model in terms of utility values assigned to the DF and RD health states. The patient-reported outcomes within CheckMate-274 were collated using the EQ-5D-3L, which consists of 5 dimensions (Mobility, Self-care, Usual Activities, Pain/Discomfort, and Anxiety), with each dimension having 3 levels (no problems, some problems,

extreme problems). The EQ-5D-3L is a descriptive system used to compute a utility index with scores ranging from −0.594 (worst imaginable health state) to 1 (best imaginable health state). Appendix I presents full analysis results, but the key results used in the model are presented in this section.

8.5.2 Health-state utility values used in the health economic model

As stated above, patient-level utility data from CheckMate-274 were used to analyse the DF and RD HSUVs. Overall utility values were used in the base-case analysis. In alignment with the DMC guidelines, all utility values were mapped from the EQ-5D-3L to the EQ-5D-5L using a parametric mapping algorithm developed by van Hout and Shaw (2021)[102] based on an ordinal logistic regression accounting for unobserved heterogeneity using a latent factor and without age and gender as covariates. The R programme developed by the authors was adapted in this study by applying the Danish EQ-5D-5L value set based on the heteroscedastic censored hybrid model.[77]

Health-utility inputs were estimated based on the following analysis populations:

- ITT population (n = 709 patients; nivolumab arm = 353, placebo arm = 356)
- ITT population with tumour cell PD-L1 expression ≥ 1% (n = 282; nivolumab arm = 140, placebo arm = 142)

Descriptive statistics (n, mean, standard deviation [SD], median, first quartile, third quartile, minimum, maximum, and 95% CI) of changes in health-utility values from baseline were estimated and summarised for the following health states for each of the analysis populations listed above:

- Overall (pooled from both treatment arms)
  - Disease free
  - Recurrence state (Note: Recurrence health state was further split into local only and distant, including both distant and local recurrence.)
  - On treatment
  - Off treatment
  - Nivolumab
  - Placebo
  - Disease free while on treatment
  - Disease free while off treatment
  - Recurrence while off treatment
- By treatment arm
  - Disease free on nivolumab
  - Disease free on placebo
  - Recurrence on nivolumab
  - Recurrence on placebo
  - On treatment (nivolumab)
  - Off treatment (nivolumab)
  - Disease free while on treatment (nivolumab)

- Disease free while off treatment (nivolumab)
- Disease free off treatment (placebo)
- Recurrence while off treatment (nivolumab)
- Recurrence off treatment (placebo)

8.5.2.1 Assessment of changes in health utilities by health state using MMRM analysis

Linear mixed-effects models with random intercepts were used to estimate the impact of recurrence and treatment status on changes in EQ-5D-5L health-utility scores from baseline. The mixed-effects models used the restricted maximum likelihood estimation method and included intercept as random effects to account for the differences in intercept between patients. An unstructured covariance matrix was applied to obtain the random effects variance components. The dependent variable for the mixed model repeated measure (MMRM) model was change in EQ-5D-5L health-utility values from baseline across all assessment visits (including on-treatment visits, follow-up visits 1 and 2, and survival follow-up visits). The covariates in the MMRM models included:

- Baseline utility score
- Treatment arm (nivolumab vs. placebo)
- On/off treatment
- Recurrence (recurrence vs. disease free; and local only recurrence, distant recurrence vs. disease free)

The MMRM models shown in Table 34 were constructed for each analysis population.

Table 34. Linear mixed-effects regression models

Parameters	Level	Model 1	Model 2	Model 3	Model 4
Intercept		X	X	X	X
Baseline utility value		X	X	X	X
Recurrence (1)[a]	Yes vs. no (disease free)	X	X	X	X
Recurrence (2)[a]	Local only, distant (distant only or both distant and local) vs. no	X	X	X	X
On/off treatment	On vs. off	X	X	X	X
Treatment arm	Nivolumab vs. placebo	X	X	X	X
Two-way interaction of recurrence and treatment arm			X		
Two-way interaction of recurrence and on/off treatment			X		
Two-way interaction of on/off treatment and treatment arm				X	
Three-way interaction of recurrence, on/off treatment, and treatment arm					X

[a] Recurrence (1) yes vs. no and recurrence (2) local, distant vs. no were modelled separately.

The least squares mean change scores (95% Cis and *P* values) were estimated for each health state listed in Section 8.5.2 based on each of the MMRM models. Regression coefficients for covariates included in each of the MMRM models and differences in least squares mean changes (95% Cis and *P* values) between health states (defined by a given covariate) were also estimated and summarised.

The MMRM analyses were conducted for each of the populations (i.e., ITT population; ITT population with tumour cell PD-L1 expression ≥ 1%; and subgroups A, B, and C). All analyses were performed using SAS version 9.4. No imputation of missing data was performed for the planned analyses. Full results for the analysis

are presented in Appendix I, with the key results and estimations used for the economic model presented below.

Table 35 presents the baseline utility values for the overall population by each treatment arm, as well as for the ITT and tumour cell PD-L1 expression ≥ 1% populations. As can be seen from the results, the utility values are relatively consistent across all subgroups, with only minor differences in baseline utility.

Table 35. Baseline health utilities by analysis population

Population	Statistic	Nivolumab	Placebo	Overall
ITT	No. of patients	[redacted]	[redacted]	[redacted]
	Mean (SD)	[redacted]	[redacted]	[redacted]
	95% CI	[redacted]	[redacted]	[redacted]
ITT with tumour cell PD-L1 expression ≥ 1%	No. of patients	[redacted]	[redacted]	[redacted]
	Mean (SD)	[redacted]	[redacted]	[redacted]
	95% CI	[redacted]	[redacted]	[redacted]

SD = standard deviation.

For the economic model, utility values based on the overall population were deemed the most appropriate to use because there was no statistical difference in QOL in DFS between the arms. The overall utilities with HSUVs based on recurrence pooled across both treatment arms are presented in Table 36 per DF and RD health state. The model is set up to use either health-state utilities specific to the ITT all-comers population of CheckMate-274 or specific to the tumour cell PD-L1 expression ≥ 1% population. The latter was used in the base-case analysis so that data are aligned with the label population. However, the data for the ITT population could be assumed to be more robust given the larger sample size, and it is unlikely that PD-L1 status will influence the patients' perceived QOL. Therefore, the use of the ITT utility values were tested in a scenario.

Table 36. Overall utilities by health state

Population and health state	Overall utilities (SE)
ITT	
DF	[redacted]
RD	[redacted]
Tumour cell PD-L1 expression ≥ 1%	
DF	[redacted]
RD	[redacted]

DF = Disease Free; ITT = intention to treat; PD-L1 = programmed death-ligand 1; RD = Recurred Disease; SE = standard error.

8.5.3 Age adjustment of utility values

In alignment with the DMC guidelines, the HSUVs in the model were adjusted for age to account for the increasing comorbidity and declining QOL with increasing age.[104] Table 37 presents the index used to adjust the utility values per age category.

Table 37. Age-related utility deterioration

Age bracket (years)	General population utility	Estimated adjustment index from baseline	Data source for general population utility values
50-69	0.818	1.000	[104]
70-79	0.813	0.994	
80+	0.721	0.881	

8.5.4 Utility decrements for adverse events

Utility decrements were included in the model to capture the impact of treatment-emergent AEs on HRQOL. Table 38 shows utility decrements derived from relevant publications because no MIUC-specific data were identified in the literature. If no disutility value was available from the HTA submissions or other published literature, the disutility was assumed to be 0. The utility values reported by Nafees et al. (2008)[66] have been used in more than 30 different economic evaluations by organisations including NICE and the Scottish Medicines Consortium (SMC); therefore, they were chosen for the analysis. However, there is a more recent study from Nafees et al. (2017)[105]. Of note, the 2008 study used the standard gamble (SG) valuation method, whereas the 2017 study used time–trade-off (TTO). Evidence suggests that TTO and SG methods do not produce the same estimates, and differences between them may be greater in more severe states, whereas the TTO method tends to produce lower utilities. Thus, given the assumption of no side effects from the placebo arm in the model, use of higher disutilities from the Nafees et al. (2008)[66] publication should be seen as a conservative assumption.

Table 38. Disutility by adverse event (grade 3 and 4 adverse events with an incidence rate of at least 2% for all treatments included in the analysis)

Adverse event	Reported utility decrement	Standard error	Default disutility decrement used in model	Data source for utility decrement
Diarrhoea	–0.047	–0.016	–0.047	Nafees et al. (2008)[66]
Fatigue	–0.073	–0.018	–0.073	Nafees et al. (2008)[66]
Pruritus	–0.032	–0.012	–0.032	Assume same as rash
Urinary tract infection	–0.020	–0.002	–0.020	Gaither et al. (2020)[67]
Nausea	–0.048	–0.005	–0.048	Nafees et al. (2008)[66]
Rash	–0.032	–0.012	–0.032	Nafees et al. (2008)[66]
Constipation	0.000	0.000	0.000	Assumption

8.5.5 One-off quality-adjusted life-years associated with the RD health state (subsequent therapy)

As presented in Section 8.1.8.3, there is uncertainty surrounding the costs and outcomes associated with each subsequent therapy option. Therefore, in the model, costs, LYs, and QALYs associated with each treatment option in the first-line mUC setting are programmed such that they can be easily modified by the user. As presented in Section 5.2.1, the current standard of care in Denmark is chemotherapy treatment (gemcitabine plus cisplatin) followed by avelumab maintenance therapy. In addition, cisplatin-ineligible and PD-L1–positive patients could be candidates for immuno-oncology treatments such as pembrolizumab or atezolizumab. Regarding QALYs and LYs, Table 39 presents base-case estimates for these therapies. Some information is available from clinical trials and HTA submission documents, and certain treatment outcomes can be modelled discretely in an accurate manner within the model. However, reliable information on costs and outcomes is

not readily available regarding the immunotherapy options. Therefore, some assumptions have been made out of necessity, and the model is built to be flexible such that it is simple to alter the LYs and QALYs assigned to each subsequent therapy.

Table 39 summarises the LYs and QALYs used in the base case for the economic model. For chemotherapy, LYs and QALYs were estimated within the economic model using the survival extrapolations conducted on external data as described in Section 8.4 and the utility values for RD from CheckMate-274. Specifically, this was modelled as a submodel within the CEM estimating the proportion of patients in the RD health state and Death over a lifetime horizon. The estimated LYs and QALYs from this approach were then applied for all patients who transitioned to RD and who received chemotherapy.

As described earlier, estimating LYs and QALYs for other treatments was more challenging because of data availability and information about assumptions pertaining to, for example, the modelling approach used in assessments of these treatments. Thus, the estimation of QALYs gained for immuno-oncology treatments (avelumab, pembrolizumab, atezolizumab) was based on the incremental gain of treatment with avelumab reported in the assessment conducted by the Statens legemiddelverk (2021)[60] in Norway. The incremental QALYs gained for avelumab in that assessment were then added to gemcitabine plus cisplatin and gemcitabine plus carboplatin estimated within the current model. Further, as there is no reliable estimation of QALYs gained for atezolizumab and pembrolizumab, the same incremental gain over chemotherapy that was used for avelumab was assumed for these treatments. However, given that atezolizumab and pembrolizumab would only be indicated for cisplatin-ineligible patients, the increment was only added to estimated QALYs for gemcitabine plus carboplatin.

A similar approach was taken for LYs (although not used directly in the analysis) except that LYs for atezolizumab and pembrolizumab were based on an assumption.

Table 39. Base-case estimates for life-years and quality-adjusted life-years

Subsequent treatment option	LYs	QALYs	Source/assumption
Gemcitabine + cisplatin	2.26	1.68	Estimated within the cost-effectiveness model.
Gemcitabine + carboplatin	1.12	0.84	Estimated within the cost-effectiveness model.
Pembrolizumab	1.89	1.43	Assumed to have same LYs and QALYs gained as avelumab, which is added to the LYs and QALYs associated with gemcitabine + carboplatin because of restriction of immunotherapies to cisplatin-ineligible patients.
Atezolizumab	1.89	1.43	
Maintenance after chemotherapy			
Avelumab	0.77 (incremental gain in addition to LYs from first-line chemotherapy treatment)	0.59 (incremental gain in addition to QALYs from first-line chemotherapy treatment)	Based on reported incremental QALY gain of 0.59 for avelumab. This is then added on top of QALY for gemcitabine + cisplatin and gemcitabine + carboplatin for the proportion of patients receiving avelumab maintenance treatment. LYs based on NoMA's assessment.

LY = life-year; NoMA = Norwegian Medicines Agency; QALY = quality-adjusted life-year.

8.6 Resource use and costs

Danish-specific estimates of costs were used in the model. Unit costs were obtained from Danish public sources and the published literature. If resource utilisation data were not available from the literature, resource utilisation data were based on clinical input. Costs were included in the model in 2022 Danish krone; when costs were only available from previous years, they were inflated to the current price year.

To account for the patient's travel cost for each hospital visit, the travel cost is added to each visit that occurred in resource use costs for DF and RD health states, administration, monitoring, AEs, and subsequent treatment in the model. The value of travel costs is estimated based on the state tax-free driving allowance (travel allowance) of DKK 3.51 per kilometre (2022). According to the DMC guidelines, the distance to a hospital was 20 km in driving distance in 2016, which corresponds to the travel cost to and from hospital of

approximately DKK 140 per visit. In addition, we included patient time assumed to be equivalent to DKK 181 per hour as presented in the DMC guidelines.[106] Table 40 presents travel costs for the Danish patients.

Table 40. Patients' travel costs by unit

Resource	Unit cost (DKK)
Travel cost per visit	140.00
Patient cost per visit (to and from hospital)	181.00

Source: Medicinrådet (2022)[106]

It was assumed that patients had all blood samples taken at the same checkup or outpatient visit; therefore, the patient transport costs were not included for resource use associated with each individual blood test in the model.

The following types of costs were included in the model:

- Drug acquisition costs (Section 8.6.1)
- Treatment administration costs (Section 8.6.2)
- Monitoring costs (Section 8.6.3)
- AE costs (Section 8.6.4)
- Disease management costs (Section 8.6.5)
- Subsequent therapy costs (Section 8.6.6)
- End-of-life costs (Section 8.6.7)

8.6.1 Drug acquisition costs

In this section, costs are reported for nivolumab as the only intervention in the decision. However, Appendix K presents drug acquisition costs for subsequent therapies. In the base-case analysis, a flat dosage of nivolumab 240 mg every 2 weeks was assumed. The model also includes the functionality to apply either the weight-based dosage or administration every 4 weeks. No drug costs were assigned to the comparator (i.e., observation).

Table 41 summarises the drug acquisition costs per vial/pack along with the mean number of doses used in the CEM. Drug costs were obtained from Danish national sources. Only the recommended dose was used in the base-case analysis.

Table 41. Dosing details of included treatments

Drug	Tablet dose/vial concentration	Pack size/vial volume	Cost per vial/pack (DKK)	Dose	Cost per dose (DKK)	Mean number of doses
Nivolumab	10 mg/mL	24 mL	22,003.74	240 mg Q2W	22,003.74	[redacted]
		10 mL	9,168.23			
		4 mL	3,690.69			

CSR = clinical study report; Q2W = every 2 weeks.

Sources: dose: CheckMate-274 CSR[57]; cost per dose: Laegemiddelstyrelsen (2022)[107]

8.6.1.1 Time on treatment

The mean number of doses from CheckMate-274 is used in the model to inform the treatment cost calculations for treatment acquisition, administration, and monitoring costs. Because of the treatment stopping rule in the trial, all treatment-related costs are accrued within the first year of the analysis. The time-on-treatment data from CheckMate-274 are shown to be almost fully mature (Table 42), with only 1 patient in the placebo arm still on treatment and none in the nivolumab arm still being treated. Therefore, no extrapolation for this endpoint is required for use in the CEM. Thus, costing of nivolumab is based on the mean number of doses [redacted]) observed in CheckMate-274.[21]

Table 42. Time-to-discontinuation treatment status from CheckMate-274: tumour cell PD-L1 expression ≥ 1% population

Status, n (%)	Nivolumab	Placebo	Total
Ongoing treatment	0 (0.0)	1 (0.7)	1 (0.4)
Completed treatment	67 (48.2)	50 (36)	117 (42.1)
Discontinued treatment	72 (51.8)	88 (63.3)	160 (57.6)

8.6.2 Treatment administration costs

The administration costs associated with all treatments were anticipated to be captured by diagnosis-related group (DRG) tariffs (11MA98), which reflect the diagnosis code (DC679M) associated with bladder cancer with metastases and the procedure code (BWAA6) for intravenous medication in the Danish setting. Table 43 presents the cost per administration used in the model. No administration costs were applied for observation.

Table 43. Administration costs per included treatment

Treatment	No. of administrations required	Type of administration	Cost per administration (DKK)	Source
Nivolumab	1.00	Complex parenteral chemotherapy delivery Outpatient setting	2,038.00	DRG Tariffs 2022 (DRG11MA98)[65]

DRG = diagnosis-related group.

8.6.3 Drug monitoring costs

The monitoring costs reflect treatment-specific resource use such as labs and scans, which are required to ensure patients are tolerating the treatment well. These resources are typically outlined within the product labels and require local clinical input. Therefore, these costs are both treatment specific and required in addition to the disease management costs for patients in the DF health state. Table 44 summarises the unit costs used in the cost-effectiveness analysis based on the Danish-specific costs from 2022, alternatively adjusted for 2022 inflation rate.

Table 44. Monitoring costs per included treatment

Monitoring cost for nivolumab	Frequency per 4 weeks	Source	Unit cost (DKK)	Source
Outpatient visit	0.92	Expert input BMS data on file (2021)[108]	2,910.00	DRG Tariffs 2022 (DRG07MA98)[65]
Hepatic function test	0.92		15.37	Laboratoriemedicinske vejledninger (NPU19651)[109]
Renal function	0.92		15.37	Laboratoriemedicinske vejledninger (NPU18669)[109]
Thyroid test	0.92		21.51	Laboratoriemedicinske vejledninger (NPU03577)[109]
Total cost per 4 weeks			**2,725.02**	

8.6.4 Adverse event costs

Costs related to the occurrence of an AE were applied to the proportion of patients estimated to experience the AE. Costs were included for all-causality, grade 3-4 AEs with an incidence of at least 15% (measured for any grade) in any treatment arm for the ITT population. To determine the costs of AEs, the proportion of patients estimated to be treated in each setting was multiplied by the costs of each AE. Adverse event costs were sourced from Danish national sources and are shown in Table 45.

Table 45. Cost of All-causality, grade 3-4 adverse events with an incidence of at least 15% (any grade) for all treated patients

Adverse event	DRG code	Cost per event (DKK)	Notes
Diarrhoea	DRG04MA98	2,180.00	
Fatigue	DRG23MA03	4,460.00	
Pruritus	DRG09MA98	2,041.00	The same unit cost as rash is assumed.
Urinary tract infection	DRG11MA98	2,038.00	
Nausea		0	Assumed to be handled during monitoring visits.
Rash	DRG09MA98	2,041.00	
Constipation	DRG06MA11	2,180.00	The same unit cost as diarrhoea is assumed.

DRG = diagnosis-related group.
Source: Sundhedsdatastyrelsen (2022)[65]

The proportion of patients experiencing each event was multiplied by the average cost per event and then summed to derive a total AE cost per comparator, which was applied in the first model cycle (Table 46).

Table 46. Total adverse event costs

Treatment	Average total adverse event cost per patient (DKK)
Nivolumab	222.76
Observation	0.00

8.6.5 Disease management costs

8.6.5.1 Resource use costs

Table 47 and Table 48 present the disease management costs for patients in the DF and RD health states. These are presented as resources required every 4 weeks to provide care to patients after radical resection to remove MIUC, regardless of treatment. Disease management costs apply to patients in DF and RD whereby disease management resource use is differentiated by health state, as validated by clinical experts from the virtual advisory board (VAB).[108] In the model, it is assumed that patients only incur disease management costs until year 5, after which they are considered to be at low risk of recurrence and no further follow-up is required.

Disease management costs for DF are differentiated by years 1 and 2 and year 3 to 5 in the cost-effectiveness analysis as presented in Table 47. According to National clinical treatment guidelines for bladder tumours in Denmark, urology consultant resource use, urethroscopy, and both CT scan and blood tests (kidney + prostate-specific antigen) are required at 4 and 12 months during the first and second year of disease management.[110] From year 3 onwards, urology consultant, urethroscopy, and CT scan and blood tests (kidney + prostate-specific antigen) are required once per year.[110] Similarly disease management costs for RD are differentiated by year 1 and 2 and year 3 to 6 in the analysis as presented in Table 48. In line with National clinical treatment guidelines for bladder tumours in Denmark, urology consultant resource use, urethroscopy, and both CT scan and blood tests (kidney + prostate-specific antigen) are required at every fourth month during the first and second year of disease management.[110] From year 3 onwards, urology consultant, urethroscopy, and CT scan and blood tests (kidney + prostate-specific antigen) are required every sixth month for up to 3 years.[110] In the CEM, the resource use costs are based on the Danish-specific costs from 2022, alternatively adjusted for 2022 inflation rate.

Table 47. Disease management costs (disease-free health state)

Resource	No. required per 4 weeks	Source (resource use)	Unit cost (DKK)	Source (unit cost)
Year 1 to Year 2				
Urology consultant	0.15	Nationale kliniske retningslinier for behandling af blæretumorer i Danmark[110]	2,038.00	DRG Tariffs 2022 (DRG11MA98)[65]
Urethroscopy	0.15		4,068.00	DRG Tariffs 2022 (DRG11PR02)[65]
CT scan	0.15		2,411.00	DRG Tariffs 2022 (DRG30PR06)[65]
Blood tests (kidney + prostate-specific antigen)	0.15		15.37	Laboratoriemedicinske vejledninger (NPU02593)[109]
Total cost per 4 weeks:			**1,308.18**	
Year 3 to Year 5				
Urology consultant	0.08	Nationale kliniske retningslinier for behandling af blæretumorer i Danmark[110]	2,038.00	DRG Tariffs 2022 (DRG11MA98)[65]
Urethroscopy	0.08		4,068.00	DRG Tariffs 2022 (DRG11PR02)[65]
CT scan	0.08		2,411.00	DRG Tariffs 2022 (DRG30PR06)[65]
Blood tests (kidney + prostate-specific antigen)	0.08		15.37	Laboratoriemedicinske vejledninger (NPU18669)[109]
Total cost per 4 weeks:			**654.09**	

CT = computed tomography; DRG = diagnosis-related group; NICE = National Institute for Health and Care Excellence.

Table 48. Disease management costs (recurred disease health state)

Resource	No. required per 4 weeks	Source (resource use)	Unit cost (DKK)	Source (unit cost)
Year 1 to year 2				
GP consultation	0.23	Nationale kliniske retningslinier for behandling af blæretumorer i Danmark[110]	148.35	Lægeforeningen 2022 (consultation - 0101)[111]
Community nurse visit	0.23		441.00	Medicinrådet, Sygeplejersker (nurse) 2022[112]
Health home	0.23		839.37	Medicinrådet, Opsøgende hjemmebesøg (skrøbelige ældre) (outreach home visits) 2022[112]
Dietician	0.23		323.00	Medicinrådet, Ernæringsassistenter (nutritionists) 2022[112]
Oncology	0.23		2,038.00	DRG Tariffs 2022 (DRG11MA98)[65]
Total cost per 4 weeks:			**871.56**	
Year 3 to year 6				
GP consultation	0.15	Nationale kliniske retningslinier for behandling af blæretumorer i Danmark[110]	148.35	Lægeforeningen 2022 (consultation - 0101)[111]
Community nurse visit	0.15		441.00	Medicinrådet, Sygeplejersker (nurse) 2022[112]
Health home	0.15		839.37	Medicinrådet, Opsøgende hjemmebesøg (skrøbelige ældre) (outreach home visits) 2022[112]
Dietician	0.15		323.00	Medicinrådet, Ernæringsassistenter (nutritionists) 2022[112]
Oncology	0.15		2,038.00	DRG Tariffs 2022 (DRG11MA98)[65]
Total cost per 4 weeks:			**581.04**	

DRG = diagnosis-related group; GP = general practitioner; NICE = National Institute for Health and Care Excellence.

8.6.6 One-off subsequent therapy costs

In alignment with QALYs for the subsequent treatments and as presented in Section 8.1.8.3, there are uncertainty surrounding the costs and outcomes associated with each subsequent therapy option. With regards to costs, Table 49 presents base-case estimates. For all treatments except avelumab, the cost of subsequent therapy has been based on published data reporting on duration of therapy used to estimate treatment-related costs, including drug, administration, and monitoring costs (see Appendix K for detailed costs and resources for each treatment).

For avelumab, the cost has been calculated based on the reported total cost of avelumab maintenance treatment estimated in the Norwegian Medicines Agency (NoMA) assessment of avelumab. However, to be able to adjust the cost from the NoMA assessment as much as possible to the Danish setting and allow for scenario analyses regarding avelumab unit costs, the following calculations where performed. Based on the published total cost for NoMA's preferred scenario in the avelumab assessment, the proportion of the cost pertaining to drug acquisition costs (avelumab cost) and other costs were estimated. This was done by identifying the cost of avelumab by re-creating the treatment duration for NoMA's preferred assumption of modelling treatment duration (generalised gamma distribution and an assumption of 5% of patients continuing treatment beyond 24 months) through digitisation of curves presented in the assessment report. Based on the

estimated mean duration of therapy (area under the curve) and the presented Norwegian cost of avelumab per dose, the proportion of total cost stemming from drug acquisition costs could be identified. This then allowed the "other costs" part (administration, monitoring, health state, and subsequent treatment) to be identified. In the economic model, these other costs were included based on purchasing power parity adjustment from Norwegian to Danish costs, whereas the avelumab acquisition cost was estimated based on the mean duration of therapy and the Danish unit cost of avelumab.

In addition to the treatments listed in Table 49, the model includes additional options of subsequent therapies that are not standard of care in Denmark but that could be included in scenario analyses should DMC consider them relevant for decision-making.

Table 49. One-off subsequent therapy costs

Subsequent treatment option	One-off estimated cost (DKK)	Assumptions
Gemcitabine + cisplatin	140,633	Based on published mean duration of therapy drug, administration, and monitoring costs
Gemcitabine + carboplatin	124,892	
Pembrolizumab	1,226,103	
Atezolizumab	754,951	
Avelumab maintenance after chemotherapy	964,567	Costs other than avelumab drug acquisition cost based on other costs estimated from the NoMA assessment adjusted with 2021 purchasing power parity of 0.578.

NoMA = Norwegian Medicines Agency.

In addition to the uncertainties around the outcome for the subsequent therapies, there are uncertainties around the distributions of the subsequent therapies given in first-line mUC in Denmark (Table 50). Therefore, advice was sought as part of the request for assessment. The feedback received from the DMC supported BMS's proposed distribution of therapy, which thus has been used in the base-case analysis. However, as for the one-off costs and QALYs, these proportions are readily adjustable in the model should DMC wish to explore alternative assumptions.

Table 50. Distribution of subsequent treatments applied in the base-case model

Subsequent treatment option	Proportion receiving treatment[a]
Gemcitabine + cisplatin	62.9%
Gemcitabine + carboplatin	25.7%
Pembrolizumab	0.0%[b]
Atezolizumab	11.4%[b]
Avelumab maintenance after chemotherapy	63.8%

[a] Total percentage exceeds 100% because avelumab is given as maintenance therapy after gemcitabine + cisplatin and gemcitabine + carboplatin.

[b] For the distribution of immunotherapies, it has been assumed that all patients will be treated with atezolizumab in the base case.

8.6.7 End-of-life (terminal care) costs

The model considered the cost of terminal care to account for the increased cost of care during the final months of life for patients with cancer. The cost was applied as a one-time cost of DKK 71,612.00 in the cycle when death occurred. The cost is estimated based on the DRG tariffs (DRG26MP48), corresponding to specialised palliative care for a patient expected to stay in hospital for longer than 12 days.

8.7 Results

8.7.1 Base-case overview

Table 51 provides an overview of the key base-case model settings.

Table 51. Base-case overview

Model parameters	Base-case deterministic value	Sources/notes
Perspective	Limited societal perspective	Includes patient travel and patient cost per visit, which is based on Danish guidelines
Time horizon	Lifetime (20 years)	Based on Danish guidelines
Model framework	3-health-state Markov	
Cycle length	1 week	To reflect treatment cycles based on SmPC
Weight	73.90 kg	CheckMate-274 CSR[57]
Body surface area	1.89 m^2	Based on RADS, Baggrundsnotat for medicinsk behandling af ikke-småcellet lungecancer (NSCLC) i stadium IV
Utilities	Overall utility values	
Age-adjusted utility values	Yes	Based on Danish guidelines
Adverse event inclusion by severity grade	Grade 3-4 (Based on ITT population)	
Method of calculating DFS	Independent Gompertz	CheckMate-274 CSR, February 2021 data cut
Approach for application of costs and outcomes in DR health state	One-off first-line mUC outcomes applied to the DR health state	
Treatment-related costs	Mean number of doses	CheckMate-274 CSR[57]
Nivolumab dose	Flat dose	Aligned with CheckMate-274 CSR[57]
Nivolumab frequency	Q2W	CheckMate-274 CSR[57]
Vial sharing	No	No impact given flat dose

CSR = clinical study report; DFS = disease-free survival; DR = Distant Recurrence; mUC = metastatic urothelial carcinoma; NSCLC = non–small cell lung cancer; Q2W = every 2 weeks; SmPC = summary of product characteristics.

8.7.2 Base-case results

Table 52 presents the base-case results. Table 53 and Table 54 present the breakdown of the cost an QALYs per treatment. The patient costs were estimated by taking the difference in aggregated costs when societal perspective is selected from when payer perspective is chosen in the model (see Table 53). The aggregated costs constituted disease management, administration, monitoring, adverse events and subsequent treatment which included patient costs in their estimation.

Table 52. Base-case deterministic cost-effectiveness results

Technologies	Total costs (DKK)	Total LYs	Total QALYs	Inc.[a] costs (DKK)	Inc.[a] LYGs	Inc.[a] QALYs	Inc.[a] cost per LYG	Inc.[a] cost per QALYs
Nivolumab	960,174	7.99	6.60	327,805	2.08	1.78	157,446	184,626
Observation	632,370	5.91	4.82					

LYG = life-year gained; QALY = quality-adjusted life-year.

[a] Incremental cost refers to estimated values for nivolumab minus that of the observation.

Table 53. Base-case cost breakdown

Technologies	Disease management (DKK)	Acquisition (DKK)	Administration /monitoring (DKK)	Subsequent treatment (DKK)	End of life (DKK)	Total Patient costs (DKK)
Nivolumab	124,209	378,464	66,550	362,900	27,590	29,086
Observation	79,071	–	–	521,483	31,391	16,832

Table 54. Base-case utility breakdown

Technologies	DF health state	RD health state
Nivolumab	5.81	0.79
Observation	3.69	1.14

DF = Disease Free; RD = Recurred Disease.

8.8 Sensitivity analyses

To fully explore uncertainty, deterministic sensitivity analysis (DSA) and probabilistic sensitivity analysis (PSA), and scenario analyses were conducted to assess the impact of uncertainty in model inputs and impact of the chosen assumptions on the cost-effectiveness results.

Sources of uncertainty in the model include parameter uncertainty and structural and methodological uncertainty:

- A one-way DSA was undertaken by varying each parameter by its standard error, 95% CI, or ± 20% of the expected value (base case) based on data availability.
- PSA was used to assess the variation in the model results from the uncertainty around each parameter in the model. Model parameters were sampled from parametric distributions to generate estimates of the costs and effects in each treatment arm.
- The model offers various user selection menus and dropdowns to different non-numerical options of model structure/ structural assumptions such as different utility value sets. The impact of those alternative options is addressed through scenario analysis.

8.8.1 Deterministic sensitivity analysis

One-way sensitivity analysis was undertaken by varying key parameters by their standard error, 95% CI, or ± 20% of the expected values (base case) based on data availability. The following parameters were included as part of the one-way sensitivity analysis:

- Discount rate varied from 0% to 6%
- Body weight and body weight varied by ± 20%
- Costs included disease management, , administration, and monitoring and varied by ± 20%
- Utilities: DF health state (overall and treatment specific) varied by 95% CI

Table 55. Parameters included in the deterministic sensitivity analysis and respective lower and upper values

Parameter	Lower value	Base-case value	Upper value
Discount rate costs	0.00%	3.50%	6.00%
Discount rate QALY	0.00%	3.50%	6.00%
Mean body surface area, m^2	1.51	1.89	2.27
Disease management costs: DF	DKK 1,204.03	DKK 1,505.04	DKK 1,806.05
Administration cost: nivolumab	DKK 1,887.20	DKK 2,359.00	DKK 2,830.80
Monitoring costs: nivolumab	DKK 2,416.25	DKK 3,020.31	DKK 3,624.38
Utility DF: nivolumab	0.83	0.85	0.87
Utility DF: observation	0.83	0.85	0.87

DF = Disease Free; HR = hazard ratio; QALY = quality-adjusted life-year;.

8.8.2 Deterministic sensitivity analysis results

Table 56 summarises the DSAs for nivolumab versus observation. All parameters in the one-way sensitivity analysis were varied by 20%. Figure 44 indicates that, across most parameters tested, the ICURs for nivolumab versus observation do not change by any significant magnitude. The ICURs from the sensitivity analyses were compared with the base-case ICUR to determine the absolute and proportional change. The ICUR was found to be most sensitive to changes in the following 2 parameters: the discount rate for outcomes and DF utility. Varying all other parameters, one at a time, had less than 5.5% impact on the ICUR.

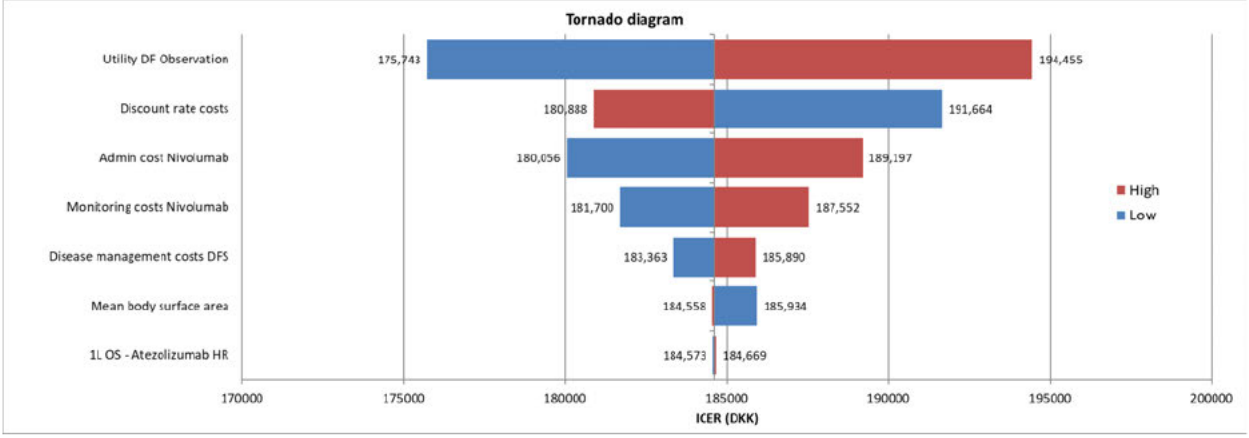
Table 56. One-way sensitivity analyses results

Parameter	Base-case value	Analysis	Values for DSA	Incremental cost per QALY (DKK)	ICUR: absolute change (DKK)	ICUR: proportional change
Base case				184,626		
Discount rate costs	3.50%	Lower	0.00%	191,664	7,037.49	3.81%
	3.50%	Higher	6.00%	180,888	−3,737.74	−2.02%
Discount rate QALY	3.50%	Lower	0.00%	136,446	−48,180.28	−26.10%
	3.50%	Higher	6.00%	223,967	39,341.12	21.31%
Mean body surface area	1.89	Lower	1.51	185,934	1,308.17	0.71%
		Higher	2.27	184,558	−68.68	−0.04%
Disease management costs: DF	1,505.04	Lower	1,204.03	183,363	−1,263.71	−0.68%
		Higher	1,806.05	185,890	1,263.71	0.68%

Parameter	Base-case value	Analysis	Values for DSA	Incremental cost per QALY (DKK)	ICUR: absolute change (DKK)	ICUR: proportional change
Administration cost: nivolumab	2,359.00	Lower	1,887.20	180,056	−4,570.51	−2.48%
		Higher	2,830.80	189,197	4,570.51	2.48%
Monitoring costs: nivolumab	3,020.31	Lower	2,416.25	181,700	−2,925.90	−1.58%
		Higher	3,624.38	187,552	2,925.90	1.58%
Utility DF: nivolumab	0.85	Lower	0.83	200,611	15,985.12	8.66%
		Higher	0.87	171,001	−13,625.67	−7.38%
Utility DF: observation	0.85	Lower	0.83	175,743	−8,883.21	−4.81%
		Higher	0.87	194,455	9,829.05	5.32%

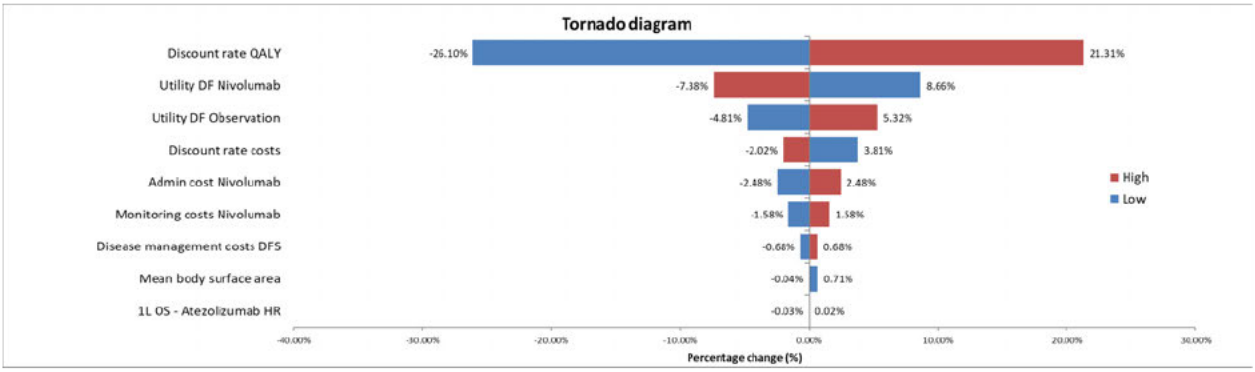
DF = Disease Free; DSA = deterministic sensitivity analysis; ICUR = incremental cost-utility ratio; QALY = quality-adjusted life-year.

Figure 44. Tornado diagram for DSA of nivolumab versus observation showing impact on the ICUR



DSA = deterministic sensitivity analysis; ICER = incremental cost-effectiveness ratio; ICUR = incremental cost-utility ratio; OS = overall survival; DFS = disease-free survival; RD = recurred disease; LR = local recurrence; HR = hazard ratio; QALY = quality-adjusted life-year

Figure 45. Tornado diagram for DSA of nivolumab versus observation showing the percentage change from baseline ICUR



DSA = deterministic sensitivity analysis; ICER = incremental cost-effectiveness ratio; ICUR = incremental cost-utility ratio; OS = overall survival; DFS = disease-free survival; RD = recurred disease; LR = local recurrence; HR = hazard ratio; QALY = quality-adjusted life-year.

8.8.3 Scenario analyses

In addition to addressing parameter uncertainty, a number of scenario analyses were undertaken to address uncertainty around model assumptions made. Table 57 outlines the scenario analyses conducted and results of the scenario analyses described above are presented in Table 58.

Table 57. Model scenarios

Model input	Base case	Scenarios	Justification
Scenario 1: Shorter time horizon	20 years	15 years	Alternative time horizons
Scenario 2: Longer time horizon	20 years	25 years	
Scenario 3: Method of calculating DFS	Independent Gompertz	Independent generalised gamma	To fully explore different approaches to extrapolating DFS by using the distribution with best within-trial fit but less clinically plausible long -term survival
Scenario 4: Method of calculating DFS	Independent Gompertz	Dependent Gompertz	To explore the impact of assuming proportional effect
Scenario 5: Modelling subsequent immunotherapy	Atezolizumab	Pembrolizumab	Testing the assumption that all patients receiving immunotherapy as first-line mUC would get pembrolizumab instead of atezolizumab
Scenario 6: 20% increase in subsequent treatment costs		20% higher cost of all subsequent treatments	Assessing the sensitivity of the results due to increase in cost of subsequent treatments
Scenario 7: 20% decrease in subsequent treatment costs		20% lower cost of all subsequent treatments	Assessing the sensitivity of the results due to decrease in cost of subsequent treatments
Scenario 8: Model subsequent treatments based on discreet outcomes	One-off costs and outcomes	Model cost and outcomes based on fully discreet modelling of cost and outcomes	Exploring the impact of modelling subsequent treatment based on approach 2a or 2b
Scenario 9: 4-health-state Markov model	3-health state	4-health state	Investigating the impact of modelling with differentiation between local and distant recurrence
Scenario 10: Weight-based dosing with vial sharing	Flat dose Q2W	Weight-based dosing Q2W	Assessing impact of weight-based dosing allowing for vial sharing to investigate impact of optimal drug usage on an individual level
Scenario 11: Flat dose Q4W	Flat dose Q2W	Flat dose Q4W	Investigate impact of flat dose Q4W

DFS = disease-free survival; mUC = metastatic urothelial carcinoma; Q2W = every 2 weeks; Q4W = every 4 weeks.

Table 58. Scenario analyses results

Scenarios	Incremental costs (DKK)	Incremental LYs	Incremental QALYs	Incremental cost per LY (DKK)	Incremental cost per QALY (DKK)	Difference from base case (DKK)
Base case	327,805	2.08	1.78	157,446	184,626	–
Scenario 1: Shorter time horizon	318,838	1.75	1.52	182,482	209,437	13%
Scenario 2: Longer time horizon	333,269	2.26	1.91	147,535	174,563	–5%
Scenario 3: Method of calculating DFS	340,567	1.94	1.66	175,307	205,486	11%
Scenario 4: Method of calculating DFS	311,937	2.25	1.92	138,536	162,455	–12%
Scenario 5: Modelling subsequent immunotherapy	317,689	2.08	1.78	152,587	178,929	–3%
Scenario 6: 20% increase in subsequent treatment costs	296,088	2.08	1.78	142,212	166,763	–10%
Scenario 7: 20% decrease in subsequent treatment costs	359,521	2.08	1.78	172,679	202,490	10%
Scenario 8: Model subsequent treatments based on discreet outcomes	351,910	2.30	1.94	152,707	181,637	–2%
Scenario 9: 4-health-state Markov model	359,598	2.08	1.78	172,750	202,108	9%
Scenario 10: Weight-based dosing with vial sharing	301,377	2.08	1.78	144,752	169,741	–8%
Scenario 11: Flat dose Q4W	294,530	2.08	1.78	141,464	165,885	–10%

DFS = disease-free survival; LY = life-year; Q4W = every 4 weeks; QALY = quality-adjusted life-year.

8.8.4 Probabilistic sensitivity analyses

A PSA was performed with 1,000 simulations. The objective of the PSA is to assess the uncertainty associated with key parameters used in the model. The probabilistic mean results are presented as the base-case cost-effectiveness results. In addition, the over probabilistic analysis is also presented to show the variation across iterations to fully characterise uncertainty.

To conduct PSA, probabilistic distributions based on means and standard errors (or counts of events when appropriate for distributions) were assigned to each input in the model and used to randomly generate new plausible values. In instances where measure of uncertainty could not identified a standard error of 10% was assumed for the parameter. Each new sampled value was applied in the model, with the results of the model under each new value being recorded. This process was then repeated for a large number of iterations. The series of results recorded in the PSA was used to quantify the overall variation in results.

Table 59 summarises the key parameters and distributions applied in the PSA. The distributions selected follow the recommendations outlined in the handbooks in health economic evaluation.

Table 59. Summary of probabilistic distributions applied in the PSA

Parameter cluster	Parameters	Distribution
Clinical data	Proportions of first events that were a LR, DR or Death	Dirichlet distribution for proportions of first events
	Survival distribution parameters for DFS	Multivariate normal distribution, with correlation between shape, and scale parameter for DFS analysis parameters
	HRs for subsequent treatment DFS	Log-normal distribution for HRs
Cost data	Disease management costs – DF, RD	Gamma distribution
	Acquisition cost	
	Administration cost	
	Monitoring cost	
	AE cost	
	Other costs	
Utility data	Utility weights assigned to DF and RD states	Beta distribution
	Disutility of AEs	Gamma distribution

AE = adverse event; DF = Disease Free; DFS = disease-free survival; DR = Distant Recurrence; HR = hazard ratio; LR = Local Recurrence; PSA = probabilistic sensitivity analysis; RD = Recurred Disease.

8.8.5 Probabilistic sensitivity analyses results

The cost-effectiveness acceptability curve against observation is shown in Figure 46. Nivolumab reaches 95% probability of cost-effectiveness at a willingness-to-pay (WTP) threshold of DKK 500,000 and above.

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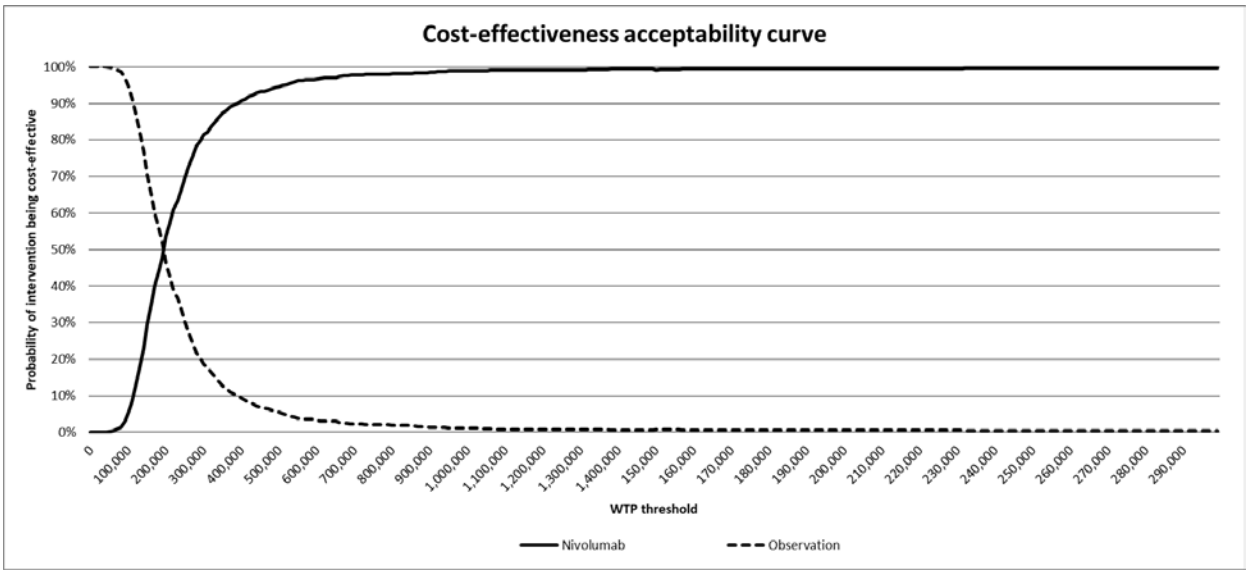
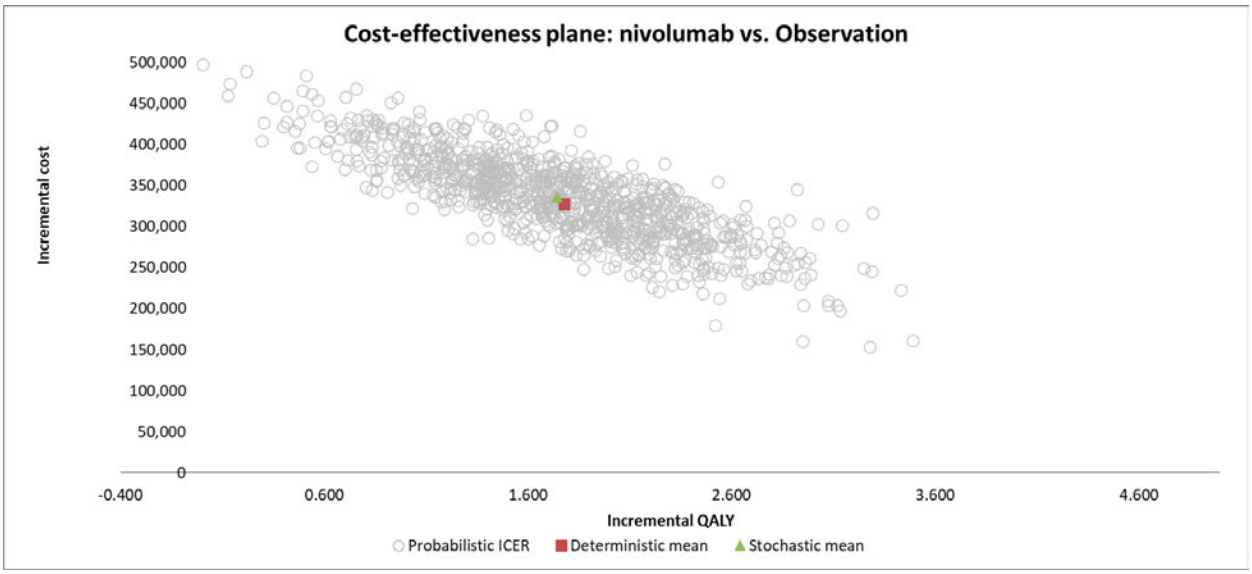
Figure 46. Cost-effectiveness acceptability curve



WTP = willingness to pay.

Figure 47 presents the cost-effectiveness planes for nivolumab versus observation. The figure shows that all of the 1,000 iterations finish in the northeast quadrant meaning that nivolumab resulted in more QALYs and higher costs compared with observation for all iterations run.

Figure 47. Cost-effectiveness plane: nivolumab versus observation



ICER = incremental cost-effectiveness ratio; QALY = quality-adjusted life-year.

9 Budget-impact analysis

The impact of introducing nivolumab in the treatment landscape of MIUC was estimated using a 5-year budget-impact model. According to the DMC's methodological guidance, the budget-impact results reflect the healthcare payer perspective; therefore, results do not include the patient and transport costs, and the discount rate for costs is to set to zero in the analysis.

9.1 Market share

This section provides an overview of nivolumab uptake. Table 60 shows uptake figures used in the budget-impact analysis.

Table 60. Market shares

	Year 1	Year 2	Year 3	Year 4	Year 5
Situation without nivolumab					
Nivolumab	0%	0%	0%	0%	0%
Observation	100%	100%	100%	100%	100%
Situation with nivolumab					
Nivolumab	50.00%	70.00%	70.00%	70.00%	70.00%
Observation	50.00%	30.00%	30.00%	30.00%	30.00%

Table 61 shows the resulting number of patients based on the uptake shown above.

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Table 61. Number of patients based on market share

	Year 1	Year 2	Year 3	Year 4	Year 5
Situation without nivolumab					
Nivolumab	0	0	0	0	0
Observation	52	52	52	52	52
Situation with nivolumab					
Nivolumab	26	36	36	36	36
Observation	26	16	16	16	16

9.2 Budget impact

9.2.1 Base-case analysis

The introduction of nivolumab leads to an increase in budgets over all 5 years compared with a situation without nivolumab (Table 62). The budget-impact costs are estimated based on the base-case parameters outlined in Table 51, with the exception of healthcare perspective and discount rates for costs, which were set to the payer's perspective and zero, respectively.

As can be seen from the results, there are considerable treatment costs even in the situation without nivolumab in which patients are not receiving active adjuvant treatment. The cost in the situation without nivolumab is primarily owing to the cost of first-line treatment for patients with recurrent disease. Thus, the budget-impact analysis shows the importance from a budgetary perspective of reducing recurrence of disease.

Table 62. Base-case results: budget impact

Budget years	Year 1 (DKK)	Year 2 (DKK)	Year 3 (DKK)	Year 4 (DKK)	Year 5 (DKK)
Situation without nivolumab	22,459,050	27,796,173	29,791,859	30,596,481	31,018,538
Situation with nivolumab	29,449,934	37,322,570	39,441,398	40,449,548	41,024,473
Budget impact	**6,990,884**	**9,526,397**	**9,649,539**	**9,853,067**	**10,005,935**

10 Discussion on the submitted documentation

10.1 Clinical evidence

The efficacy and safety of nivolumab have been demonstrated in CheckMate-274. This trial shows that, for patients with MIUC with tumour cell PD-L1 expression ≥ 1% who are at high risk of recurrence, nivolumab extends DFS, improves other clinical outcomes, and is associated with no deterioration in HRQOL, compared with placebo.

10.2 Strengths and limitations of the clinical evidence

CheckMate-274 is a large, multinational (including 3 sites in Denmark) randomised controlled trial. It is the only phase 3 randomised controlled trial evaluating nivolumab in the adjuvant setting for patients with MIUC at high risk of recurrence. This was to be expected because, at the time CheckMate-274 was conducted, nivolumab was a new treatment and unapproved for this patient population. A quality assessment based on guidance provided by CRD (2009)[113] assessed the likelihood of selection, performance, attrition, and detection bias and determined that CheckMate-274 has a low risk of bias (see Appendix A.2). However, the assessment noted that it was unclear if treatment allocation was adequately concealed. This could be a potential limitation of the study.

Nivolumab is positioned as an adjuvant treatment option after radical resection (cystectomy or nephroureterectomy) for patients who are not eligible for or who have refused adjuvant chemotherapy. For these patients, the standard of care in Denmark is no active treatment/no adjuvant therapy. CheckMate-274 compares nivolumab with placebo: this is appropriate when the standard of care is no active treatment/no adjuvant therapy. Thus, CheckMate-274 provides appropriate evidence for the efficacy of nivolumab in this patient population in Denmark.

Analysis of the tumour cell PD-L1 expression ≥ 1% population—that is, the label population—was a prespecified primary endpoint in the CheckMate-274 trial. This means that the trial was adequately powered, and the results are valid for decision-making.

Although CheckMate-274 was appropriately powered to detect treatment differences in both the all-randomised and tumour cell PD-L1 expression ≥ 1% patient subgroups, the benefits of nivolumab were found to be different for additional subgroups. The effect size for DFS was greater for patients with MIUC in the bladder than for patients with MIUC in the upper urinary tract and for patients who had received neoadjuvant chemotherapy than for those who had not received it. Because the trial was not designed to assess efficacy in these subgroups, there is uncertainty in these results. Additional translational analyses have been planned to explore this further. The results of CheckMate-274 are based on interim analyses, and no results are available yet about the efficacy of nivolumab on the secondary outcome of OS. However, further data over a longer follow-up period are forthcoming.

10.3 Strengths and limitations of the economic evidence

The current analysis of adjuvant nivolumab in MIUC compared with the current standard of care (i.e., observation) is expected to result in 1.78 additional QALYs at an additional cost of DKK 327,805. Thus, the resulting ICER for introducing adjuvant nivolumab in MIUC in Denmark is DKK 184,626.

All analyses presented for the base case and scenarios are based on list prices for the acquisition costs of nivolumab and other therapies included within the analysis.

Modelling of early lines of therapy, such as adjuvant therapy, has some inherent challenges because of the long-term survival (e.g., in relation to later lines of metastatic treatment) and impact of subsequent therapies on survival. This is the case even in the current analysis in which data on OS are lacking. However, as presented in results, the absolute majority of the QALYs gained is accrued in the DF health state and not in the RD health state. Thus, this shows that key benefits of nivolumab are composed of where trial data are available and not where assumptions have been needed regarding modelling of subsequent treatment.

The base-case analysis is based on a 3-health-state Markov model because this was determined to be the most suitable approach accounting for data availability and disease. However, alternative options of model structure and data were investigated through the model development process and are presented as part of the submission for transparency and to minimise decision uncertainty. Similarly, alternative methods for modelling subsequent treatments were explored but were found to have limited impact on the results. This extensive work on exploring alternative structural options for the model shows that the results are robust to alternative methods.

For the data used in the model, resource use data were based on Danish clinical guidelines as well as Danish unit costs. Utility data used in the model were calculated based on Danish guidelines using conversion to EQ-5D-5L with the Danish tariff.

The choice of method for survival extrapolation can often have a significant impact on the results. Thus, great care was taken to ensure that the most clinically plausible distributions were selected. In addition to statistical and visual fit to both survival data and hazard over time, the extrapolated curves were validated against external data as well as clinical plausibility in relation to general population mortality. The selected distribution for the base case had very good alignment with the external data compared with other distributions, and alternative distributions tested in scenarios did not have a large impact on the results.

11 List of experts

An advisory board was held on 25 June 2021 that involved clinical and health economic key opinion leaders from England, Canada, and the United States.[82]

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

The indication for nivolumab included in this submission received EC approval on 1 April 2022 based on the pivotal trial CheckMate-274. Therefore, at the time of submission, CheckMate-274 is the only study relevant to this indication. CheckMate-274 has been reported in 4 publications: Bajorin et al. (2021)[50], Bajorin et al. (2021)[1], Galsky et al. (2021)[20], and Galsky et al. (2021)[51].

Appendix A.1 Summary of included studies

Table A-1 presents an overview of the study design of CheckMate-274.

Table A-1. Overview of study design for studies included in the technology assessment/analysis

Study/ID	Aim	Study design	Patient population	Intervention and comparator (sample size (n))	Primary outcome and follow-up period	Secondary outcome and follow-up period
CheckMate-274 (CA209274)	To evaluate the efficacy and safety of adjuvant nivolumab, as compared with placebo, in patients with muscle-invasive urothelial carcinoma after radical surgery (with or without previous neoadjuvant cisplatin-based combination chemotherapy)	Double-blind, multicentre, randomised phase 3 trial	Adults with high-risk muscle-invasive urothelial carcinoma at radical resection: Those who received neoadjuvant cisplatin: ypT2-pT4a or ypN+ Those who have not received neoadjuvant cisplatin: pT3-pT4a or pN+ and were not eligible for or refused adjuvant cisplatin chemotherapy. Analysis was undertaken for all randomised patients and for patients with tumour cell PD-L1 expression ≥ 1%.	**Intervention (n = 356):** Nivolumab (240 mg IV) over 30 minutes every 2 weeks for up to 1 year or until disease recurrence or discontinuation from the trial **Comparator (n = 353):** Placebo administered IV over 30 minutes every 2 weeks for up to 1 year or until disease recurrence or discontinuation from the trial	Disease-free survival (time from randomisation until death from any cause or first recurrence whichever occurred first), for all randomised patient and for patients with tumour cell PD-L1 expression ≥ 1%.	Overall survival (time from randomisation until death of any cause) Non–urothelial-tract recurrence-free survival (the time from randomisation until the first local non–urothelial tract or distant recurrence or death of any cause), whichever occurred first) Disease-specific survival (the time from randomisation until death due to urothelial carcinoma) Incidence rates of adverse events, serious adverse events, deaths, and laboratory abnormalities Distant metastasis-free survival (time from randomisation until first distant recurrence (non-local) or date of death (of any cause), whichever occurred first) General health status using the EQ-5D-3L Cancer-specific health-related quality of life using EORTC QLQ-C30

IV = intravenous; EORTC QLQ-C30 = European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire–Core Module.
Source: Bajorin et al. (2021)[1]

Appendix A.2 Quality assessment

The quality assessment of CheckMate-274 was conducted based on guidance provided by the Centre for Reviews and Disseminations for assessing the quality of studies included in systematic reviews and assesses the likelihood of selection, performance, attrition, and detection bias (Table A-2).[87]

Table A-2. CheckMate-274: quality assessment

Study questions	CheckMate-274
Was randomisation carried out appropriately?	Yes
Was the concealment of treatment allocation adequate?	Unclear
Were the groups similar at the outset of the study in terms of prognostic factors?	Yes
Were the care providers, participants, and outcome assessors blind to treatment allocation?	Yes
Were there any unexpected imbalances in drop-outs between groups?	No
Is there any evidence to suggest that the authors measured more outcomes than they reported?	No
Did the analysis include an intention-to-treat analysis? If so, was this appropriate and were appropriate methods used to account for missing data?	Yes

Note: Responses will be yes/no/unclear, which should accompany a justification for the selected response.
Sources: Bajorin et al. (2021)[1]; CRD (2009)[87]

Appendix A.3 Unpublished data

No unpublished data relating to the efficacy and safety results for nivolumab are included in this submission.

Appendix B. Main characteristics of included studies

Table B-1 and Figure B-1 summarise the methodology and other key aspects of the CheckMate-274 trial.

Table B-1. CheckMate-274 (CA209274): summary of trial methodology

Trial name: CheckMate-274	NCT number: 02632409
Objective	To compare the DFS for nivolumab vs. placebo in patients with tumour cell PD-L1 expression ≥ 1% and in all randomised patients
Publications – title, author, journal, year	Bajorin DF, Witjes JA, Gschwend J, Schenker M, Valderrama BP, Tomita Y, et al. First results from the phase 3 CheckMate 274 trial of adjuvant nivolumab vs placebo in patients who underwent radical surgery for high-risk muscle-invasive urothelial carcinoma (MIUC). J Clin Oncol. 2021;39(6 Suppl):391. doi:http://dx.doi.org/10.1200/JCO.2021.39.6_suppl.391 Bajorin DF, Witjes JA, Gschwend JE, Schenker M, Valderrama BP, Tomita Y, et al. Adjuvant nivolumab versus placebo in muscle-invasive urothelial carcinoma. N Engl J Med. 2021 Jun 3;384(22):2102-14. doi:http://dx.doi.org/10.1056/NEJMoa2034442. Galsky MD, Witjes JA, Gschwend J, Braverman J, Broughton E, Nasroulah F, et al. Impact of recurrence on health-related quality of life in patients at high risk of recurrence after radical surgery for muscle-invasive urothelial carcinoma (MIUC): results from the phase 3 CheckMate 274 trial. Presented at the American Society of Clinical Oncology Annual Meeting; 4-8 June 2021. Virtual. Galsky MD, Witjes JA, Gschwend JE, Schenker M, Valderrama BP, Tomita Y, et al. Disease free survival with longer follow-up from the phase 3 CheckMate 274 trial of adjuvant nivolumab in patients who underwent surgery for high-risk muscle-invasive urothelial carcinoma. Presented at the SUO 22nd Annual Meeting; 1-3 December 2021.
Study type and design	Double-blind, multicentre, randomised placebo-controlled phase 3 trial. 709 patients were randomised in a 1:1 ratio to the nivolumab or placebo treatment arm and stratified by pathologic nodal status (N+ vs. N0/x with < 10 nodes removed vs. N0 with ≥ 10 nodes removed), tumour cell PD-L1 expression (≥ 1%, < 1%/indeterminate), and use of cisplatin-based neoadjuvant chemotherapy (yes vs. no). The company, patients, investigators, and site staff were blinded during treatment. The company remain blinded to some data (overall survival, and disease-specific survival)
Sample size (n)	709
Main inclusion and exclusion criteria	Inclusion criteria: ▪ Must have had invasive urothelial cancer at high risk of recurrence originating in the bladder, ureter, or renal pelvis ▪ Must have had radical surgical resection (e.g., radical cystectomy), performed within the last 120 days ▪ Must have disease-free status as determined by imaging within 4 weeks of dosing ▪ Tumour tissue must be provided for biomarker analysis ▪ Patients who have not received prior neoadjuvant cisplatin chemotherapy must be ineligible for or refuse cisplatin-based adjuvant chemotherapy Exclusion criteria: ▪ Partial bladder or partial kidney removal (e.g., partial cystectomy or partial nephrectomy) ▪ Secondary Treatment (e.g., adjuvant systemic chemotherapy for bladder cancer) following surgical removal of bladder cancer ▪ Patients with active, known or suspected autoimmune disease ▪ Prior malignancy active within the previous 3 years except for locally curable cancers that have been apparently cured ▪ Condition requiring systemic treatment with either corticosteroids or other immunosuppressive medications within 14 day of study drug administration ▪ Positive test for hepatitis B virus surface antigen (HBV s Ag) or hepatitis C virus ribonucleic acid (HCV antibody) indicating acute or chronic infection

Trial name: CheckMate-274	NCT number: 02632409
Intervention	Nivolumab (240 mg IV over 30 minutes) every 2 weeks for up to 1 year or until disease recurrence or discontinuation from the trial
Comparator(s)	Placebo administered IV over 30 minutes every 2 weeks for up to 1 year or until disease recurrence or discontinuation from the trial
Follow-up time	Study duration = 60 months Planned follow-up = 17 months

	All randomised population	Tumour cell PD-L1 expression ≥ 1%
27 August 2020 database lock		
Median follow-up, months	20.9 (NIVO), 19.5 (PBO)	22.11 (NIVO), 18.69 (PBO)
Minimum follow-up, months	5.9	6.3
1 February 2021 database lock		
Median follow-up, months	24.4 (NIVO), 22.5 (PBO)	25.5 (NIVO), 22.4 (PBO)
Minimum follow-up, months	11.0	11.4

Is the study used in the health economic model?	Yes
Primary, secondary and exploratory endpoints	**Endpoints included in this application:** The coprimary endpoint (analysed in patients with tumour cell PD-L1 expression ≥ 1% and all randomised patients) is disease-free survival The cosecondary endpoints (analysed in patients with tumour cell PD-L1 expression ≥ 1% and all randomised patients) are NUTRFS, distant metastasis-free survival, Cancer-specific health-related quality of life, General health status, and Safety. **Other endpoints:** The following secondary or exploratory endpoints are included in the trial but are not included in this application because the company remain blinded to the results: ▪ **Overall survival** (time from randomisation until death of any cause) ▪ **Disease-specific survival** (time from randomisation until death due to urothelial carcinoma) The following secondary or exploratory endpoints are included in the trial but are not included in this application: ▪ **Time to recurrence** (time from randomisation until the first recurrence (local urothelial tract, local non–urothelial tract or distant) or death due to disease, whichever occurs first) ▪ **Second progression-free survival** (time from randomisation to the date of investigator-defined disease progression after the subsequent next-line systemic anticancer therapy, or the start of second subsequent next-line systemic anticancer therapy, or death from any cause, whichever comes first)
Method of analysis	▪ Analyses were conducted on all randomised patients and repeated in patients with tumour cell PD-L1 expression ≥ 1% ▪ The Kaplan-Meier method was used to estimate rates of DFS, NUTRFS, and DMFS ▪ The statistical model used for calculating hazard ratio and *P* values was stratified Cox proportional hazard and stratified log-rank test.
Subgroup analyses	Randomised patients were stratified by the following: ▪ Pathologic nodal status ▪ Tumour cell PD-L1 expression ≥ 1% ▪ Use of cisplatin-based neoadjuvant chemotherapy

Trial name: CheckMate-274	NCT number: 02632409

Other relevant information

DFS = disease-free survival; DMFS = distant metastasis-free survival; HBV = hepatitis B virus; HCV = hepatitis C virus; IV = intravenous; NCT = National Clinical Trial; NIVO = nivolumab; NUTRFS = non–urothelial-tract recurrence-free survival; PBO = placebo; PD-L1 = programmed death-ligand 1.

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

Baseline demographic and disease characteristics for all randomised patients and all randomised patients with tumour cell PD-L1 expression ≥ 1% were generally well-balanced across the treatment groups and representative of the target patient population—those who have undergone radical resection of MIUC originating in the bladder or upper urinary tract and are at high risk of recurrence (Table C-1).[1] Most of all randomised patients had bladder as the tumour location and 43% of the patients had received prior cisplatin-based neoadjuvant therapy.[1]

Table C-1. Baseline characteristics of patients in studies included for the comparative analysis of efficacy and safety

	All randomised patients		All randomised patients with tumour cell PD-L1 expression ≥ 1%	
	Placebo n = 356	Nivolumab n = 353	Placebo n = 142	Nivolumab n = 140
Age, mean (range), years	65.9 (42-88)	65.3 (30-92)	65.9 (45-84)	64.4 (34-92)
Male, %	77.2	75.1	78.9	72.1
Race				
White, %	76.4	74.8	76.8	74.3
Asian, %	21.1	22.7	19.7	23.6
Black or African American	0.8	0.6	1.4	0
American Indian or Alaska Native	0	0.3	0	0.7
Other	1.4	1.7	1.4	1.4
Not reported	0.3	0	0.7	0
ECOG PS				
0, %	62.1	63.5	59.9	61.4
1, %	35.1	34.6	37.3	36.4
2, %	2.5	2.0	2.8	2.1
Tumour type				
Urinary bladder, %	78.9	79.0	82.4	80.7
Renal pelvis, %	14.6	12.5	9.9	13.6
Ureter, %	6.5	8.5	7.7	5.7
Pathologic tumour stage at resection, all randomised				
pTx, %	0	1.4	0	2.9
pT0, %	2.0	1.4	2.1	2.1
pTis, %	0.8	1.1	0	0
pT1, %	3.9	3.7	1.4	2.9
pT2, %	18.3	17.6	18.3	13.6
pT3, %	57.3	58.4	58.5	62.1
pT4a, %	17.4	16.1	19.0	16.4
Nodal status at resection				
N0 or NX with < 10 nodes removed, %	27.8	26.6	26.8	27.1

	All randomised patients		All randomised patients with tumour cell PD-L1 expression ≥ 1%	
	Placebo n = 356	Nivolumab n = 353	Placebo n = 142	Nivolumab n = 140
N0 with ≥ 10 nodes removed, %	24.7	25.8	26.8	30.0
N1, %	20.2	20.1	23.2	20.7
N2, %	21.3	23.8	18.3	20.0
N3, %	5.6	3.4	4.9	2.1
Previous neoadjuvant cisplatin therapy				
Yes, %	43.5	43.3	43.0	40.7
PD-L1 expression status				
≥ 1%, %	39.9%	39.7%		

ECOG = Eastern Cooperative Oncology Group; PS = performance status; PD-L1 = programmed death-ligand 1.
Note: Percentages may not total 100 because of rounding.
Source: Bajorin et al. (2021)[1 54]

Appendix C.1 Comparability of patients across studies

Only one study, CheckMate-274, is included in this application.

Appendix C.2 Comparability of the study populations with Danish patients eligible for treatment

CheckMate-274 compares nivolumab with placebo: this is appropriate when the standard of care is no active treatment/no adjuvant therapy. In Denmark, adjuvant treatments are not recommended for patients after radical resection.[15,16] The CheckMate-274 trial had a mean age of 65.3 (30-92) for the nivolumab group and 65.9 (42-88) for the placebo group.[1] Therefore, CheckMate-274 was considered to reflect the MIUC population in Denmark.

Appendix D. Efficacy and safety results per study

Appendix D.1 Definition, validity and clinical relevance of included outcome measures

Table D-1. Definition, validity, and clinical relevance of included outcome measures used in CheckMate-274

Outcome measure	Definition	Validity	Clinical relevance
Disease-free survival	Time from randomisation until death from any cause or first recurrence whichever occurred first	DFS (rather than OS) was selected as the primary endpoint for CheckMate-274 given the potential risk of significant confounding in OS estimates in the target population. Specifically, if a patient recurs with metastatic or unresectable disease, additional agents that are expected to improve OS may be initiated, potentially impacting the reliability of OS assessment.[114] Therefore, DFS was chosen as the primary outcome given the curative aim of radical resection, absence of measurable disease to follow postresection, and intent to ascertain whether prophylactic immunotherapy after a complete resection prevents recurrence. FDA[114] and EMA[115] guidance on clinical trial endpoints in oncology recognise DFS as an acceptable primary endpoint, particularly in adjuvant settings after definitive surgery where the treatment goal is to prolong the disease-free state. Both regulatory bodies state that DFS may be considered a relevant, direct measure of patient clinical benefit.	
Non–urothelial-tract recurrence-free survival	Time from randomisation until the first recurrence [local non–urothelial tract or distant] or death from any cause, whichever occurs first	While DFS captures any recurrences that may lead to patient burden (e.g., surgery for local recurrence or systemic therapy for distant recurrence), NUTRFS specifically captures recurrences associated with a worse prognosis, thereby providing an additional, clinically important assessment of efficacy.	
Distant metastasis-free survival	Time from randomisation until first distant recurrence (non-local) or death from any cause, whichever occurs first	Distant metastasis-free survival is considered to be predictive of OS [116 117]. Delaying metastatic disease and its associated morbidity is important for clinicians and patients.	
Cancer-specific health-related quality of life	Measured using EORTC QLQ-C30	The EORTC QLQ-C30 is the most commonly used quality-of-life instrument in bladder oncology trials, followed by EQ-5D[118]	Both measures assess broad HRQOL concepts
General health status	Measured using the EQ-5D-3L		

Outcome measure	Definition	Validity	Clinical relevance
Safety	Frequency of deaths, serious adverse events, AEs leading to discontinuation, overall AEs, select AEs, immune-mediated AEs, other events of special interest, special clinical laboratory assessments, and vital sign measurements	AEs were classified using the Medical Dictionary for Regulatory Activities (MedDRA) version 23.0, and the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE) version 4.0	Commonly used for AE reporting in oncology clinical trials

AE = adverse event; DFS = disease-free survival; HRQOL = health-related quality of life; MedDRA = Medical Dictionary for Regulatory Activities; NCI-CTCAE = Common Terminology Criteria for Adverse Events; NUTRFS = non–urothelial-tract recurrence-free survival; OS = overall survival; EORTC QLQ-C30 = European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire–Core Module.

Appendix D.2 Results per study

Table D-2. Results of CheckMate-274 (NCT02632409)

Outcome	Study arm	N	Result (CI)	Estimated absolute difference in effect			Estimated relative difference in effect			Description of methods used for estimation
				Difference	95% CI	*P* value	Difference	95% CI	*P* value	
DFS	Nivolumab	140	56 events	−21.50%	−30.55% to −10.29%		HR, 0.53	0.38-0.75	0.001	Relative differences were obtained from the study Galsky et al. (2021)[20] Absolute differences were calculated from the study reported HRs using the calculation in the Håndbog for Medicinrådets proces og metode vedr. nye lægemidler og indikationsudvidelser Version 2.6
	Placebo	142	85 events							
NUTRFS	Nivolumab	140	55 events	−20.55%	−29.21% to −9.26%		HR, 0.54	0.39-0.77		
	Placebo	142	82 events							
DMFS	Nivolumab	140	48 events	−14.87%	−23.29% to −4.09%		HR, 0.60	0.41-0.88		
	Placebo	142	64 events							
Cancer-specific health-related quality of life	Nivolumab	353	NA	NA	NA	NA	NA	NA	NA	No statistical tests were performed on change from baseline scores between treatment arms.
	Placebo	356								
General health status	Nivolumab	353		NA	NA	NA	NA	NA	NA	No statistical tests were performed on change from baseline scores between treatment arms.
	Placebo	356								

CI = confidence interval; DFS = disease-free survival; DMFS = distant metastasis-free survival; HR = hazard ratio; NA = not applicable; NUTRFS = non–urothelial-tract recurrence-free survival.

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

A summary of the safety data is provided in Section 7.1.2.5 of the dossier. Safety results from the first interim analysis (based on the August 2020 DBL) are presented in Table E-1 for the all-treated population, Table E-2 for the all treated tumour PD-L1 Expression Level ≥ 1% population and Table E-3 for treatment-related select adverse events.

Data regarding deaths from the second interim analysis (based on the February 2021 DBL) is presented in for both the all treated population and the all treated tumour PD-L1 Expression Level ≥ 1% population in Table E-4.

Table E-1. Safety Results for All Treated Patients, at the August 2020 database lock

Safety parameters	Placebo (N = 348)	Nivolumab (N = 351)
[redacted]	[redacted]	[redacted]

Safety parameters	Placebo (N = 348)		Nivolumab (N = 351)	
[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]
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[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]				
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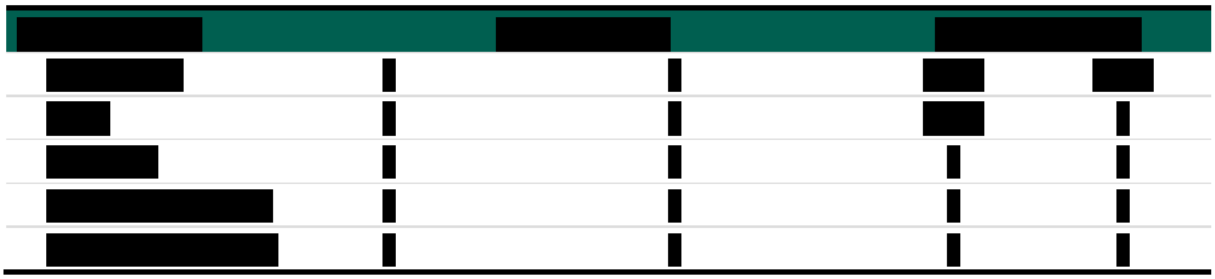


AE = adverse event; DC = discontinuation; IMAE = immune-mediated adverse event; OESI = other event of special interest; SAE = serious adverse event.

Note: All events are within 30 days of the last dose of study drug, unless otherwise indicated.

[a] After this report was generated, another death occurred due to study drug toxicity. Therefore, the total number is 3. This is reported in Section 7.1.2.5 of the dossier.

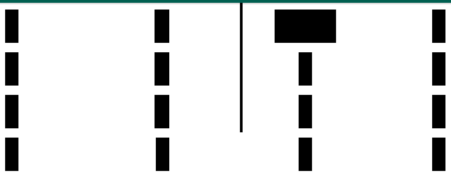
Source: BMS data on file (2020)[54]

Table E-2. Safety Results for All Treated Patients with Tumour PD-L1 Expression Level ≥ 1%, at the August 2020 database lock

Safety parameters	Placebo (N = 139)		Nivolumab (N = 139)	
	No. of patients (%)			
Deaths				
Primary reason for death				
Disease				
Study drug toxicity				
Unknown				
Other				
	AE grade			
Any Grade	**Grade 3-4**	**Any Grade**	**Grade 3-4**	
All-causality SAEs				
Drug-related SAEs				
All-causality AEs leading to DC				
Drug-Related AEs leading to DC				
All-causality AEs				
≥ 15% of Subjects in Any Treatment Arm				
Diarrhoea				
Fatigue				
Pruritus				
Urinary tract infection				
Nausea				
Rash				
Constipation				
Drug-related AEs				
≥ 10% of Subjects in Any Treatment Arm				
Pruritus				
Fatigue				
Diarrhoea				
Rash				

Safety parameters	Placebo (N = 139)	Nivolumab (N = 139)
Hypothyroidism		
Lipase increased		
All-Causality Select AEs		
Endocrine		
Gastrointestinal		
Hepatic		
Pulmonary		
Renal		
Skin		
Hypersensitivity/Infusion Reactions		
Drug-Related Select AEs		
Endocrine		
Gastrointestinal		
Hepatic		
Pulmonary		
Renal		
Skin		
Hypersensitivity/Infusion Reactions		
All-causality IMAEs within 100 days of last dose		
Treated with Immune Modulating Medication		
Rash		
Pneumonitis		
Hepatitis		
Nephritis/Renal Dysfunction		
Diarrhoea/Colitis		
Hypersensitivity		
All-causality Endocrine IMAEs within 100 days of last dose		
With or Without Immune Modulating Medication		
Hypothyroidism		
Hyperthyroidism		
Adrenal Insufficiency		
Diabetes Mellitus		
Thyroiditis		
Hypophysitis		
All-causality OESIs within 100 days of last dose		
With or Without Immune Modulating Medication		
Myositis/Rhabdomyolysis		
Demyelination Event		
Myasthenic Syndrome		
Myocarditis		
Pancreatitis		

Safety parameters	Placebo (N = 139)	Nivolumab (N = 139)
Uveitis		
Encephalitis		
Graft Versus Host Disease		
Guillain-Barre Syndrome		



AE = adverse event, DC = discontinuation, IMAE = immune-mediated adverse event, MedDRA = Medical Dictionary for Regulatory Activities, CTC = Common Terminology Criteria, OESI = other event of special interest, SAE = serious adverse event

Source: BMS data on file (2020)[54]

Table E-3. Treatment-related select adverse events, at the at the August 2020 database lock.

	Nivolumab (N=351)		Placebo (N=348)	
No. (%)	Any Grade	Grade ≥3	Any Grade	Grade ≥3
Gastrointestinal	65 (18.5)	6 (1.7)	39 (11.2)	3 (0.9)
Diarrhea	59 (16.8)	3 (0.9)	38 (10.9)	1 (0.3)
Colitis	7 (2.0)	3 (0.9)	3 (0.9)	2 (0.6)
Frequent bowel movements	1 (0.3)	0	1 (0.3)	0
Immune-mediated enterocolitis	1 (0.3)	1 (0.3)	0	0
Hepatic	29 (8.3)	6 (1.7)	17 (4.9)	1 (0.3)
ALT increased	15 (4.3)	2 (0.6)	12 (3.4)	0
AST increased	13 (3.7)	1 (0.3)	8 (2.3)	0
Blood alkaline phosphatase	8 (2.3)	1 (0.3)	2 (0.6)	0
increased				
Blood bilirubin increased	3 (0.9)	0	3 (0.9)	0
Transaminases increase	3 (0.9)	1 (0.3)	1 (0.3)	0
Drug-induced liver injury	2 (0.6)	1 (0.3)	1 (0.3)	0
GGT increased	2 (0.6)	0	2 (0.6)	1 (0.3)
Bilirubin conjugated increased	1 (0.3)	0	0	0
Hepatic failure	1 (0.3)	1 (0.3)	0	0
Liver injury	1 (0.3)	1 (0.3)	0	0
Hepatitis	0	0	1 (0.3)	1 (0.3)
Pulmonary*†	19 (5.4)	5 (1.4)	5 (1.4)	0
Pneumonitis*	16 (4.6)	3 (0.9)	5 (1.4)	0
ILD	2 (0.6)	1 (0.3)	0	0
Immune-mediated pneumonitis†	1 (0.3)	1 (0.3)	0	0
Renal	25 (7.1)	4 (1.1)	12 (3.4)	0
Blood creatinine increased	20 (5.7)	1 (0.3)	11 (3.2)	0
Acute kidney injury	3 (0.9)	2 (0.6)	1 (0.3)	0
Blood urea increased	2 (0.6)	0	1 (0.3)	0

No. (%)	Nivolumab (N=351)		Placebo (N=348)	
	Any Grade	Grade ≥3	Any Grade	Grade ≥3
Autoimmune nephritis	1 (0.3)	1 (0.3)	0	0
Immune-mediated nephritis	1 (0.3)	0	0	0
Renal failure	1 (0.3)	0	1 (0.3)	0
Skin	143 (40.7)	6 (1.7)	62 (17.8)	0
Pruritus	81 (23.1)	0	40 (11.5)	0
Rash	53 (15.1)	2 (0.6)	19 (5.5)	0
Maculo-papular rash	19 (5.4)	2 (0.6)	4 (1.1)	0
Erythema	9 (2.6)	0	2 (0.6)	0
Eczema	6 (1.7)	0	0	0
Dermatitis	5 (1.4)	0	1 (0.3)	0
Papular rash	3 (0.9)	0	2 (0.6)	0
Urticaria	3 (0.9)	0	0	0
Macular rash	2 (0.6)	1 (0.3)	1 (0.3)	0
Toxic skin eruption	2 (0.6)	0	0	0
Blister	1 (0.3)	1 (0.3)	0	0
Dermatitis acneiform	1 (0.3)	0	5 (1.4)	0
Erythema multiforme	1 (0.3)	0	0	0
Pemphigoid	1 (0.3)	1 (0.3)	0	0
Psoriasis	1 (0.3)	0	0	0
Pruritic rash	1 (0.3)	0	1 (0.3)	0

Source: Bajorin et al. (2021)[1]

Table E-4. Deaths reported at the February 2021 database lock

	Placebo	Nivolumab
Deaths		
All treated population, N (%)	[redacted]	[redacted]
All treated Patients with Tumour PD-L1 Expression Level ≥ 1%, N (%)	[redacted]	[redacted]

Source: BMS data on file (2022)[119],BMS data on file (2022)[120]

Appendix F. Comparative analysis of efficacy and safety

Head-to-head trial data are used; therefore, no comparative analysis has been undertaken.

Appendix G. Mapping of HRQOL data

EQ-5D-3L data were obtained directly from the CheckMate-274 trial and used to calculate utilities based on the Danish value set and methods for mapping to EQ-5D-5L (see Section 8.5).

Appendix H. Probabilistic sensitivity analyses

The probabilistic sensitivity analyses is presented in Section 8.8.5 together with a summary of data and distributions used. The full list of distributions, mean value and measure of uncertainty can be found in the Excel economic model on the "Model_parameters" sheet. On this sheet the data pertaining to the probabilistic sensitivity analyses can be found in column K to S. In addition it is possible to alter the data used for uncertainty (e.g., standard error for the majority of the input parameters). This can be done on the input sheets for Safety data, Costs, Subsequent therapy and Outcomes in the model.

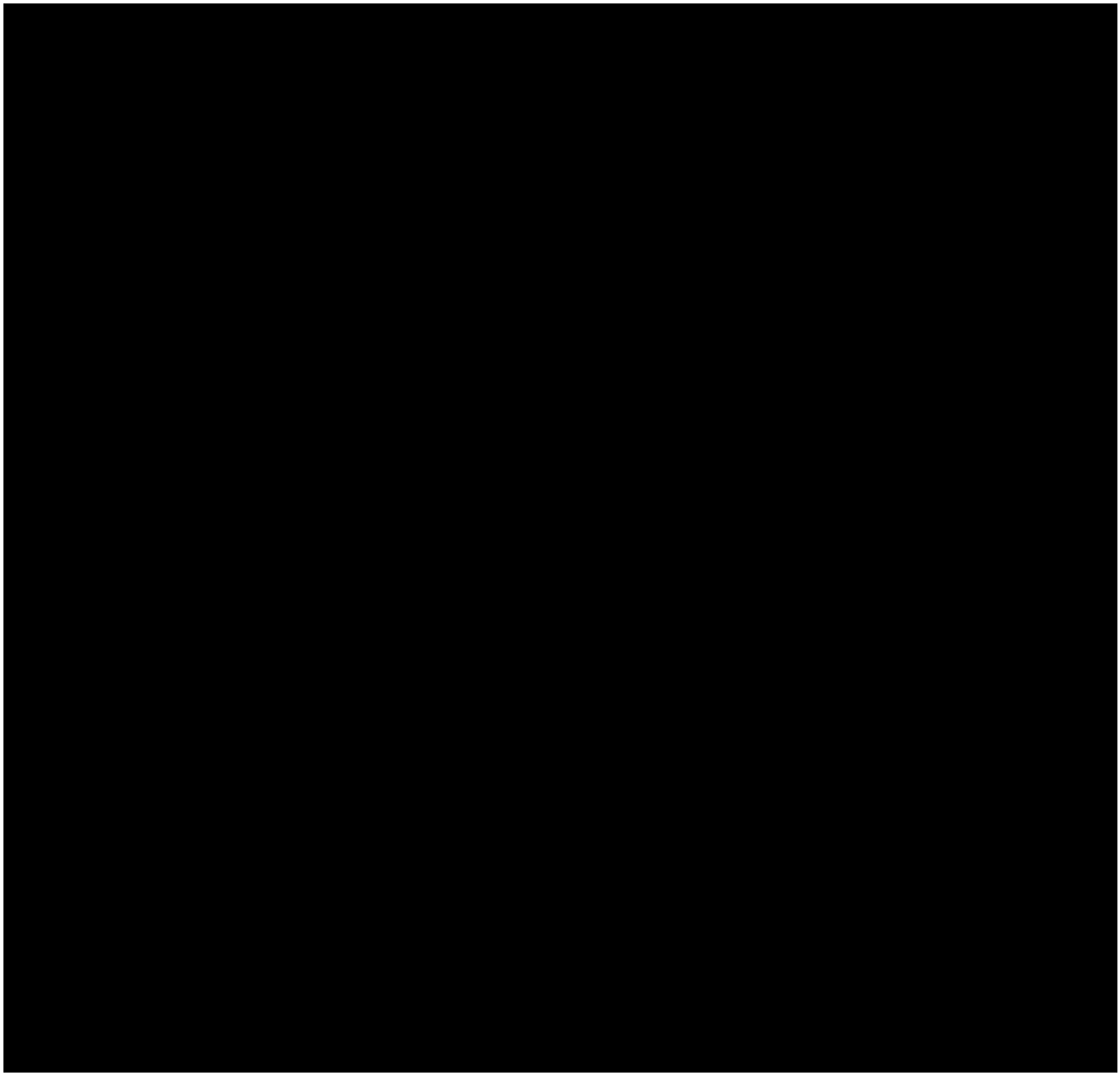
Appendix I. CheckMate-274 supplementary efficacy results

The efficacy data reported in Section 6 of this dossier relate to the results of the second interim analysis and to the tumour cell PD-L1 expression > 1% subgroup. Here, data from the first and second interim analysis for the all-randomised patient subgroup and data from the first interim analysis for the tumour cell PD-L1 expression ≥ 1% subgroup are also reported for completeness

Appendix I.1 All randomised patients: First and second interim analyses

Appendix I.1.1 Disease-free survival

At the first interim analysis, CheckMate-274 met its primary endpoint of statistically improved DFS with nivolumab compared with placebo at the prespecified interim analysis.[1] With a minimum follow-up of 5.9 months, nivolumab showed a statistically significant and clinically relevant improvement in DFS vs. placebo in the all-randomised patient population with median DFS of 20.8 months for nivolumab versus 10.8 months for placebo (HR, 0.70; 98.22% CI, 0.55-0.90; $P < 0.001$).[1] Median follow-up was 20.9 months and 19.5 months for all randomised patients in the nivolumab and placebo arms, respectively.[1] By the first surveillance assessment (at 3 months) the Kaplan-Meier curves for DFS had separated, favouring nivolumab (Figure I-1). At 6 months, DFS rates were 74.9% vs. 60.3% for nivolumab and placebo, respectively.[1]

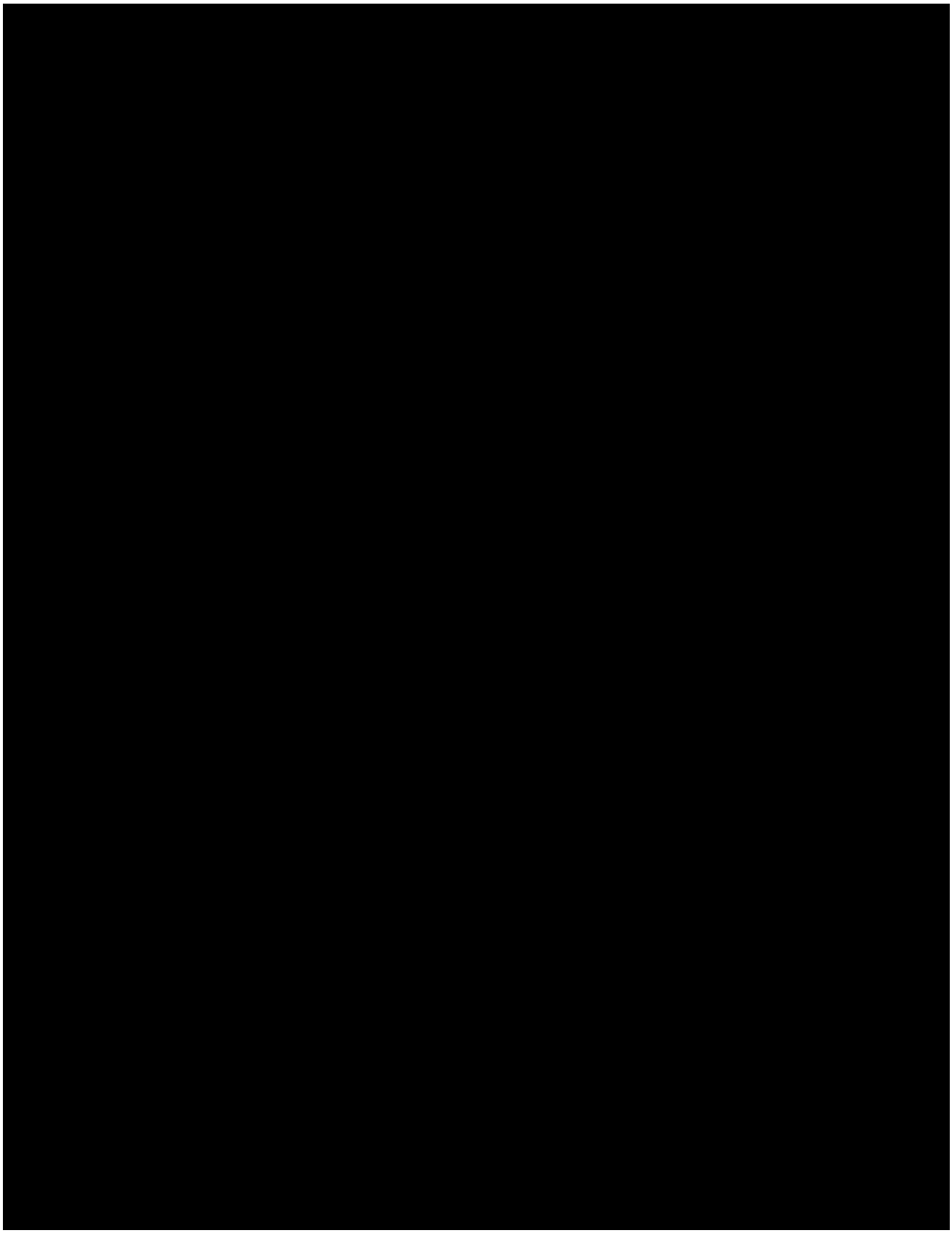


At the second interim analysis and with a minimum follow-up of 11 months, nivolumab continued to show a statistically significant and clinically relevant improvement in DFS versus placebo in the all-randomised patient population, with a median DFS of 22.0 months for nivolumab versus 10.9 months for placebo (HR, 0.70; 95% CI, 0.57-0.85; *P* < 0.001) (Figure I-2).[20] Median follow-up was 24.4 months and 22.5 months for all randomised patients in the nivolumab and placebo arms, respectively.[20] By the first disease assessment (3 months), the Kaplan-Meier curves for DFS had separated, favouring nivolumab. At 6 months, DFS rates were 75.0% versus 60.5% for nivolumab and placebo, respectively, and this separation was maintained at 12 months.[20]

Appendix I.1.2 DFS: subgroup analysis for all randomised patients

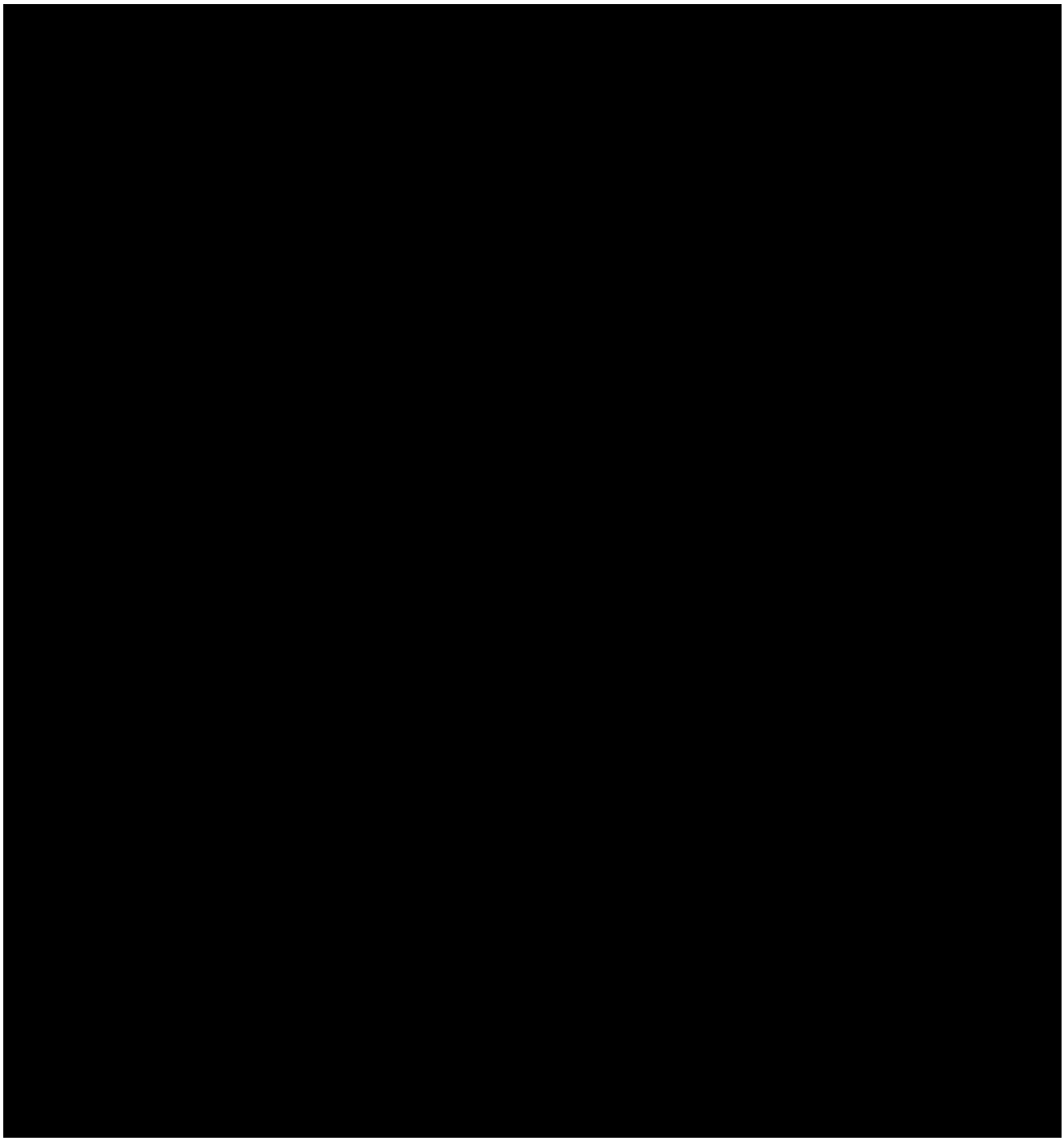
In CheckMate-274, patients were stratified according to prior neoadjuvant cisplatin-based therapy use, PD-L1 expression, and nodal status.[1] At the first interim analysis the DFS benefit of nivolumab vs. placebo was observed in each of these subgroups (HR < 1) although heterogeneity was observed in particular to prior neoadjuvant cisplatin-based therapy use and PD-L1 expression (Figure I-3).[1]

Subgroup analyses favoured nivolumab over placebo in nearly all other subgroups analysed.[1] Although 2 of the initial tumour origin subgroups (renal pelvis and ureter) demonstrated an HR > 1, these analyses were not robust because of the small sample sizes and low number of events, limiting the reliability of these particular results.[1] Overall, CheckMate-274 was not designed to detect statistically significant differences in the treatment effect in subgroups outside the tumour cell PD-L1 expression ≥ 1% subgroup; therefore, subgroup results should be interpreted with caution.[1]



At the second interim analysis the DFS benefit of nivolumab versus placebo continued in the prior neoadjuvant cisplatin-based therapy use, PD-L1 expression, and nodal status subgroups (HR < 1) (Figure I-4).[20] Even amongst the relatively lower-risk node-negative patients with 10 or more nodes removed, a treatment benefit with nivolumab was noted.[20]

The subgroup analysis also continued to favour nivolumab over placebo in nearly all other subgroups analysed (Figure I-4).[20] Two of the initial tumour origin subgroups (renal pelvis and ureter) demonstrated an HR > 1. However, these analyses were not robust because of the small sample sizes and low number of events, limiting the reliability of these particular results.[20] Overall, CheckMate-274 was not designed to detect statistically significant differences in the treatment effect in subgroups except the tumour cell PD-L1 expression ≥ 1% subgroup; therefore, subgroup results should be interpreted with caution.[20]



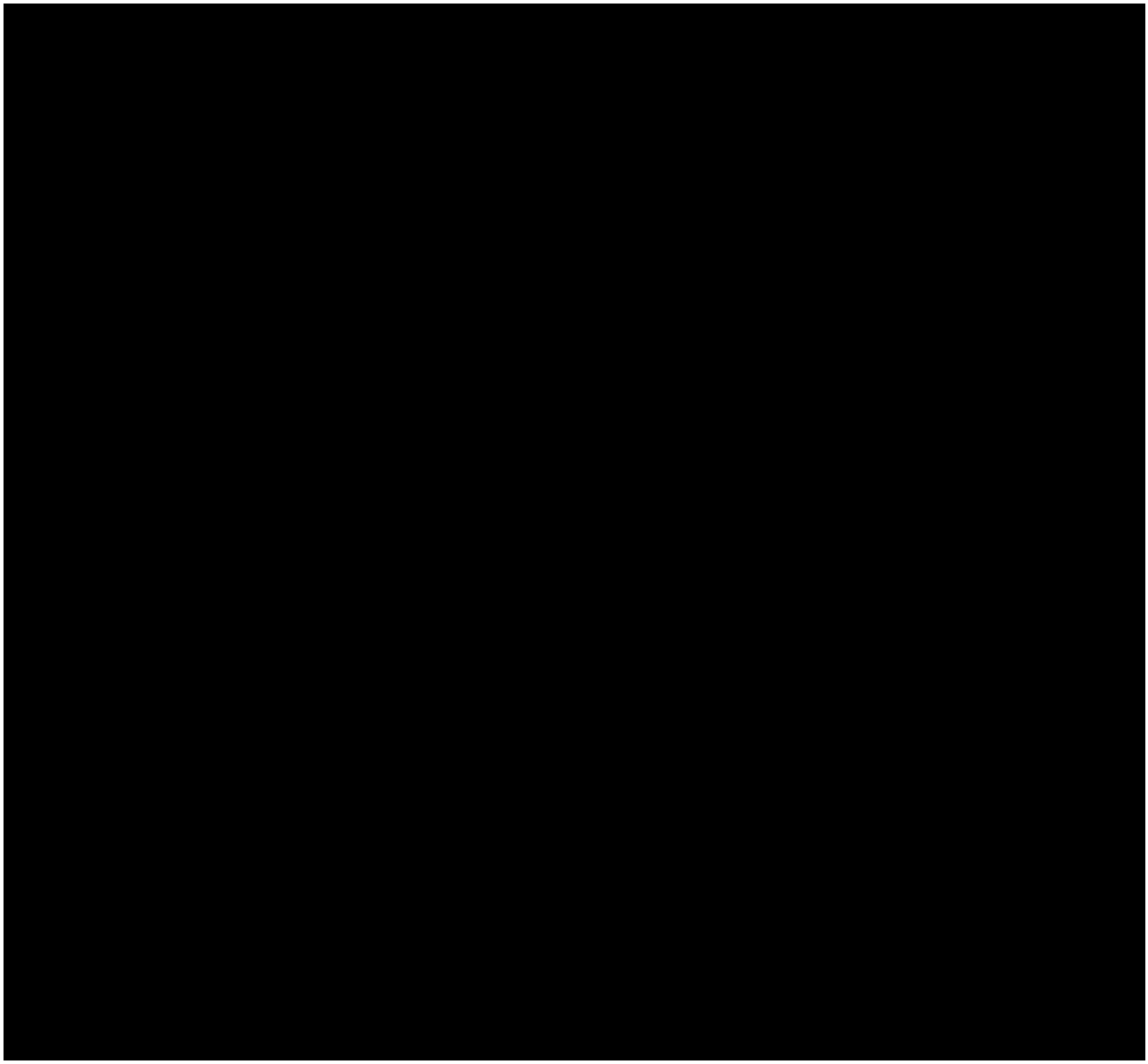
Appendix I.1.3 Non–urothelial-tract recurrence-free survival

At the first interim analysis, nivolumab treatment reduced the risk of distant metastasis or death by 25% compared with placebo in all randomised patients.[1] Median DMFS amongst patients treated with nivolumab was 40.5 months compared with 29.5 months for patients treated with placebo (HR, 0.75; 95% CI, 0.59-0.94) (Figure I-5).[1] At 6 months, DMFS rates were higher in the nivolumab arm than in the placebo arm (82.5% vs. 69.8%).[1]

At the second interim analysis, nivolumab treatment continued to result in a clinically meaningful improvement in NUTRFS in all randomised patients (26.0 vs. 13.7 months with nivolumab vs. placebo; HR, 0.71; 95 CI, 0.58-0.88).[20] By the first disease assessment (at 3 months) the Kaplan-Meier curves for NUTRFS had separated, favouring nivolumab (Figure I-6).[20] At 6 months, NUTRFS rates were 77.1% in the nivolumab arm compared with 62.9% in the placebo arm.[20]

Appendix I.1.4 Distant metastases free survival

At the first interim analysis, nivolumab treatment reduced the risk of distant metastasis or death by 25% compared with placebo in all randomised patients.[1] Median DMFS amongst patients treated with nivolumab was 40.5 months compared with 29.5 months for patients treated with placebo (HR, 0.75; 95% CI, 0.59-0.94) (Figure I-7).[1] At 6 months, DMFS rates were higher in the nivolumab arm than in the placebo arm (82.5% vs. 69.8%).[1]



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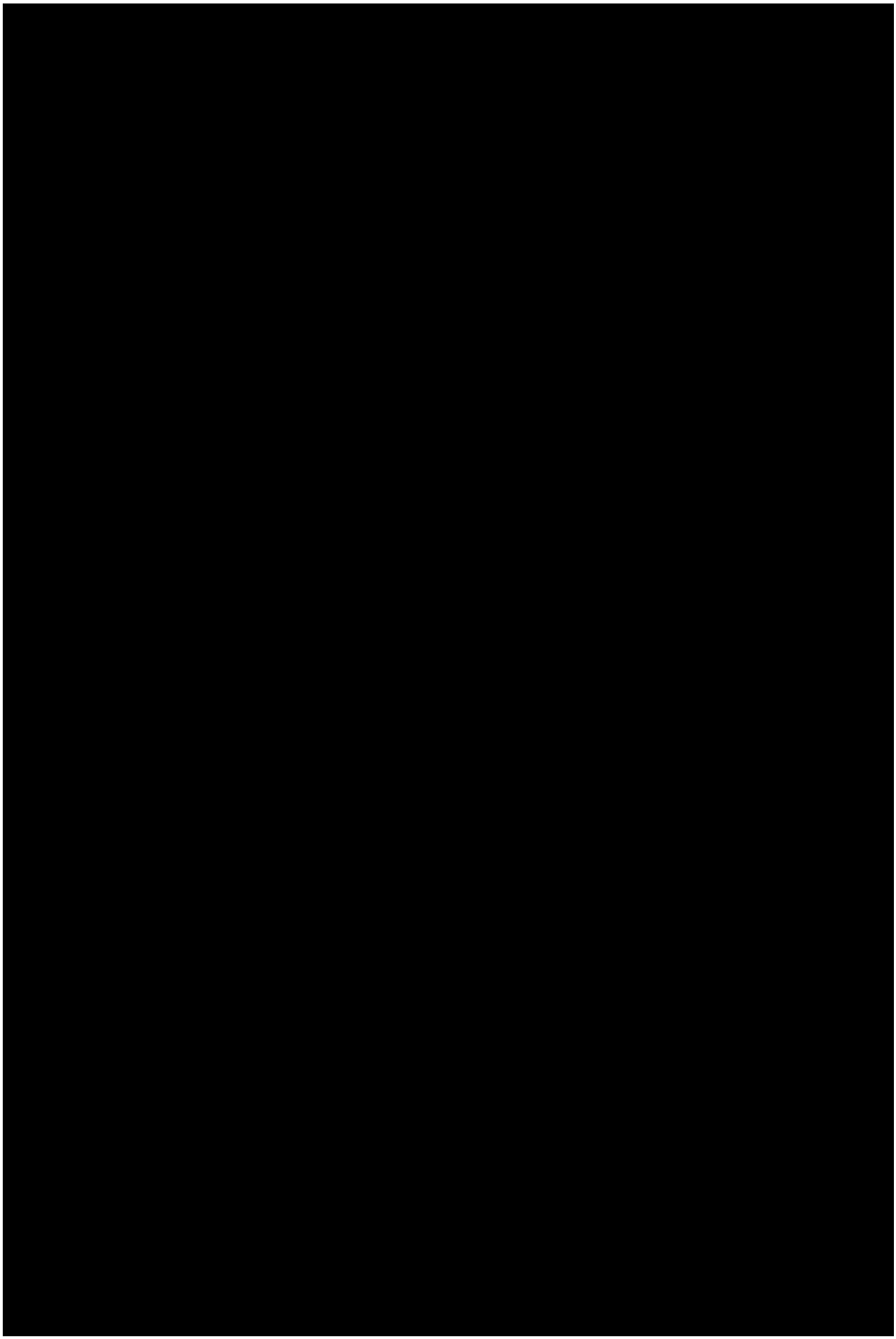
Appendix I.1.5 Patient-reported outcomes

Patients who have undergone radical surgery for MIUC often have impaired HRQOL.[52] During the CheckMate-274 study, HRQOL was assessed using the EORTC QLQ-C30 and EQ-5D-3L questionnaires. HRQOL assessments were completed on cycle 1 day 1 (baseline), then every second cycle (4 weeks) for the first 6 months of treatment and every third cycle (6 weeks) thereafter until discontinuation of study treatment.

The first interim analysis showed that HRQOL was maintained for patients in both treatment arms in all randomised patients (Figure I-9 and Figure I-10), although no statistical tests were performed on change from baseline scores between treatment arms.[1]



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A post hoc analysis of HRQOL using data from CheckMate-274 was conducted by Galsky et al. (2021)[51]. The analysis involved 645 patients with evaluable EORTC QLQ-C30 results from the CheckMate-274 trial population, of which 210 (33%) had recurrence. The results showed that patients with disease recurrence had a significantly higher risk of confirmed deterioration in all HRQOL outcomes than patients without recurrence. Therefore, recurrence has a significant negative impact on HRQOL, and treatments that delay recurrence after radical surgery for high-risk MIUC, such as nivolumab may prevent or delay HRQOL deterioration.

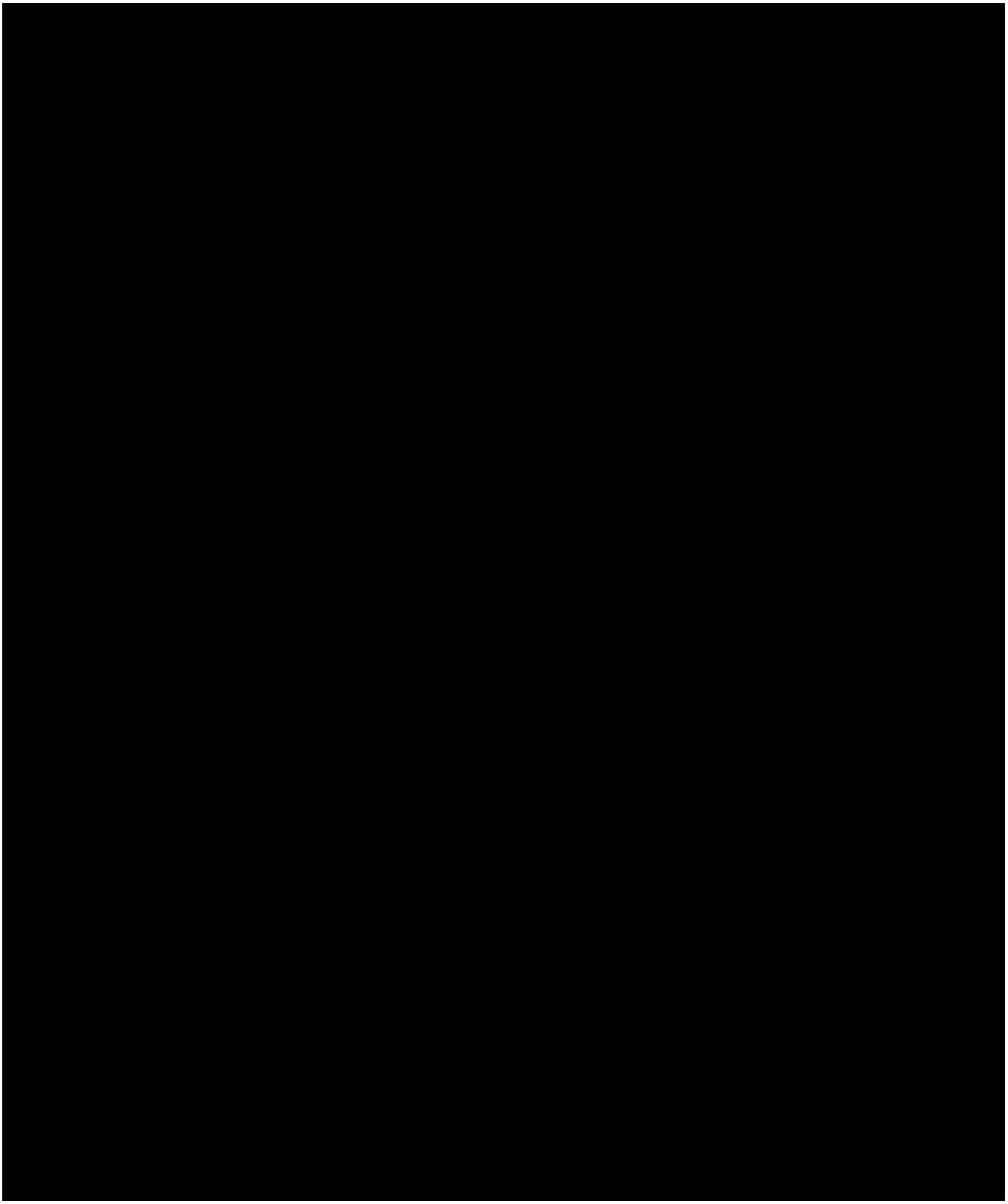
Appendix I.2 Tumour cell PD-L1 expression ≥ 1% population, first interim analysis

Appendix I.2.1 Tumour cell PD-L1 expression ≥ 1% population: DFS

At the first interim analysis, nivolumab treatment resulted in a statistically significant and clinically relevant improvement in DFS compared with placebo in patients with tumour cell PD-L1 expression ≥ 1% (HR, 0.55; 98.72% CI, 0.35-0.85; *P* < 0.001) (Figure I-11).[1] As with the all-randomised patient population, by the first surveillance assessment (at 3 months), the Kaplan-Meier curves for DFS had separated, favouring nivolumab. At 6 months DFS rates were 74.5% versus 55.7% for nivolumab and placebo, respectively.[1] These results are superseded by the second interim analysis, reported in Section 7.1.2 of the dossier.

Appendix I.2.2 Tumour cell PD-L1 expression ≥ 1%: DFS—subgroup analysis

At the first interim analysis, and for all randomised patients with tumour cell PD-L1 expression ≥ 1%, subgroup analysis for DFS showed a benefit of nivolumab versus placebo for most subgroups (HR < 1). These results are superseded by the second interim analysis, reported in Section 7.1.2 of the dossier.

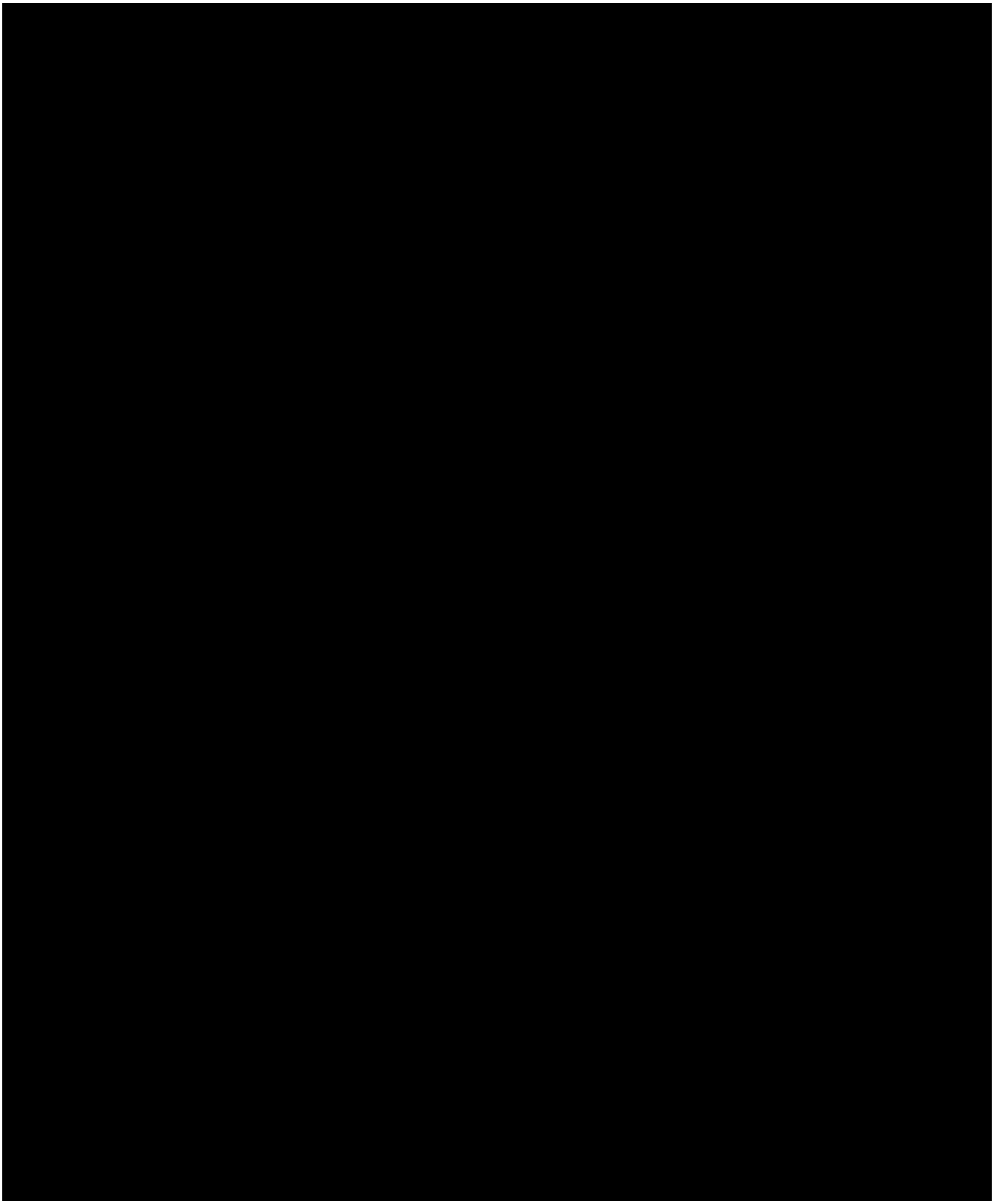


Appendix I.2.3 Tumour cell PD-L1 expression ≥ 1%: NUTRFS (superseded first interim analysis)

At the first interim analysis, nivolumab treatment also resulted in a clinically meaningful improvement in NUTRFS compared with placebo in patients with tumour cell PD-L1 expression ≥ 1% (HR, 0.55; 95% CI, 0.39-0.79) (Figure I-13).[1] By the first disease assessment (at 3 months) the Kaplan-Meier curves for NUTRFS had separated, favouring nivolumab.[1] At 6 months, NUTRFS rates were 75.3% in the nivolumab arm and 56.7% in the placebo arm.[1] These results are superseded by the second interim analysis, reported in Section 7.1.2 of the dossier.

Appendix I.2.4 DMFS (superseded first interim analysis)

At the first interim analysis, nivolumab treatment resulted in a clinically meaningful improvement in DMFS compared with placebo in patients with tumour cell PD-L1 expression ≥ 1%, (HR, 0.61; 95% CI, 0.42-0.90) (Figure I-14).[1] At 6 months, DMFS rates were higher in the nivolumab arm than in the placebo arm (78.7% vs. 65.7%).[1] These results are superseded by the second interim analysis, reported in Section 7.1.2 of the dossier.



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Appendix J. Markov 4-health state

A 4-health-state semi-Markov model can be selected to evaluate the incremental cost-effectiveness of nivolumab versus observation in patients with MIUC after radical resection. The key difference for the 4-health-state model compared with the base-case 3-health-state model is the introduction of an LR health state. However, aspects related to treatment cost and modelling of DR health state are aligned with the 3-health-state model. Thus, the focus on this section is to present the specific incorporation of the LR health state. Data pertaining to other parts of the model are not specifically commented on in this section unless affected by the change in model structure.

Appendix J.1 4-Health-state model structure

The model structure is composed of 4 key health states:

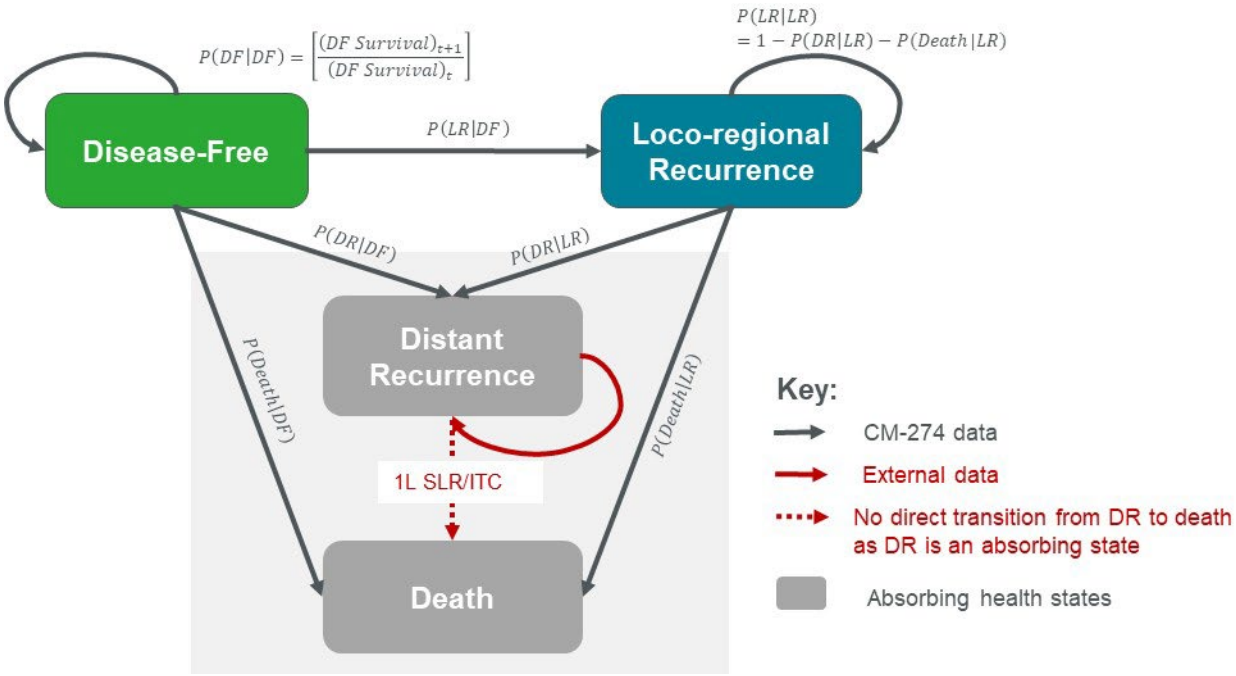
- **DF**: Disease Free
- **LR**: Local Recurrence
- **DR**: Distant Recurrence
- **Death**

Figure J-1 provides a visual depiction of the 4-health-state model structure. The 4 health states represent the primary stages of MIUC disease: DF after radical resection with the possibility to prescribe adjuvant therapy, LR represents the appearance of any new invasive urothelial carcinoma (defined as T2 or greater) in the urothelial tract or pelvic soft tissues/nodes, DR represents any non-local recurrence, and death. Health-related QOL is expected to worsen as patients progress through these health states.

Patients in the DF health state receive adjuvant treatment with nivolumab or observation and are at a risk of recurrence (local or distant) and death. Patients entering LR health state receive treatment with either surgery or radiotherapy and further can experience a DR or Death.

The DR and Death health states are 2 absorbing states considered in the analysis, therefore there are no modelled cycle-by-cycle transitions for the probabilities of remaining in DR or Death after experiencing DR. Instead, for the DR health state, survival in the metastatic setting uses external data in the form of extrapolated first-line mUC literature Kaplan-Meier curves. This approach was used to avoid a tunnel state structure and to appropriately model outcomes in the first-line mUC setting and is in line with the modelling approach taken in the cost-effectiveness analysis of adjuvant dabrafenib + trametinib submission for resected BRAF V600 mutation-positive melanoma (TA544).[124]

Figure J-1. Overview of the 4-health-state model



Arrows represent possible transition probabilities in the semi-Markov model; DR and Death health states are absorbing states.

P(DF|DF) = Probability of staying in DF; P(LR|DF) = Probability of moving from DF to LR; P(LR|LR) = Probability of staying in LR; P(DR|DF) = Probability of moving from DF to DR; P(DR|LR) = Probability of moving from LR to DR; P(Death|DF) = Probability of death from DF; P(Death|LR) = Probability of death from LR.

The number of patients occupying each state in the model is derived from the Markov process using the transition probabilities briefly described below:

- The proportion of patients staying in DF health state is estimated by DFS, estimated using patient-level data from the CheckMate-274 trial with both standard parametric and spline parametric survival curves fitted to the observed data to find the best-fitting model extrapolations from baseline (time 0) or from 12 months after randomisation.
- The transition probabilities from DF health state were estimated by calculating the risk of leaving the DF health state from the DFS endpoint.
- The risk of leaving the DF health state was further split into LR, DR, and death based on the observed total number of first events in the trial. Scenarios are tested using different methodologies for defining the split of transitions from DF health state (see Section 8.1.8 of the dossier).
- Transitions from the LR health state are estimated by parametric fitting of a LR survival curve using pooled data from both treatment arms of CheckMate-274, which was used to determine the proportion of patients staying in and at risk of leaving the LR health state.
- The risk of leaving the LR health state was split into DR and Death based on the proportions of DR and Death events in patients who had received either nivolumab or placebo and experienced a LR in CheckMate-274.
- No transition probabilities are directly applied to the DR health state, as this is modelled as an absorbing health state, with costs and outcomes informed by external first-line mUC literature data.

Appendix J.1.1.1 describes calculations of transition probabilities between the different health states in detail.

Appendix J.1.1 Transition probabilities in 4-health-state model

In the 4-health-state model, DF, LR, DR, and Death were modelled using a semi-Markov approach. Appendix J.1.1.2 and Appendix J.1.1.3 present the transition probabilities for the DF and LR health states. Note that no transition probabilities directly apply to the DR health state, as this is modelled as an absorbing health state aligned with the 3-health-state model, with costs and outcomes based on literature survival data.

Appendix J.1.1.1 Transitions from Disease-Free (DF) health state

DFS curves inform the probability of patients staying in the DF health state, while all other patients move out of DF to other health states. Since OS data or other identifiers of death events are not available from CheckMate-274, assumptions are made to split the transition from DF state across the others health states (LR, DR, and Death).

The initial DFS curves for each treatment were derived from the extrapolations of the patient-level DFS data from CheckMate-274 (see Section 8.3.1 in the dossier). These curves inform the total number of LYs in the DF state and the probability of staying in DF state in each cycle.

The transition probabilities from the DF health state are detailed below:

- The probability of remaining Disease Free (DF):

$$P(DF|DF) = \left[\frac{(DF\ Survival)_{t+1}}{(DF\ Survival)_t}\right]$$

- The probability of transitioning from Disease Free (DF) to Local Recurrence (LR):

$$P(LR|DF) = [1 - P(DF|DF)] * (\%\ pts\ with\ LR_{CM-274})$$

- The probability of transitioning from Disease Free (DF) to Distant Recurrence (DR):

$$P(DR|DF) = [1 - P(DF|DF)] * (\%\ pts\ with\ DR_{CM-274})$$

- The probability of death from Disease Free (DF):

$$P(Death|DF) = [1 - P(DF|DF)] * (\%\ pts\ Died_{CM-274})$$

Distribution of events from DF health state

Transitions out of DF state are obtained from the modelled DFS curve to which relative proportions of events (%LR, %DR, and %death) are applied to estimate proportion of patients transitioning to those health states.

Table J-1 shows the number of first events (recurrences and deaths) of ITT population from DFS as observed in CheckMate-274 across both the nivolumab and placebo arms. The distribution of first events for each treatment and both treatments pooled together is further calculated using the methodology given below.

- **Proportion of LR recurrence** (*% pts with LR_{CM-274}*): this is calculated as the sum of local non-urothelial, urothelial non-invasive, and urothelial invasive events divided by the total events from DFS

$$(\%\ pts\ with\ LR_{CM-274}) = \frac{(Local\ non-urothelial) + (Urothelial\ non-invasive) + (Urothelial\ invasive)}{Total\ DFS\ events}$$

- **Proportion of DR recurrence** (*% pts with DR_{CM-274}*): this is calculated as the total distant recurrence events as a proportion of total events from DFS

$$(\%\ pts\ with\ DR_{CM-274}) = \frac{Distant\ recurrence\ from\ DFS\ events}{Total\ DFS\ events}$$

- **Proportion of death** (*% pts with Died$_{CM-274}$*): this this is calculated as death events from DFS as a proportion of the total events from DFS

$$(\%\ pts\ Died_{CM-274}) = \frac{Death\ from\ DFS\ events}{Total\ DFS\ events}$$

Table J-1. Distribution of patients from DFS (ITT CheckMate-274)

Events (n)	Nivolumab	Placebo	Total
[redacted]			

DFS = disease-free survival; DR = Distance Recurrence; ITT = intention to treat; LR = Local Recurrence.
Sources: CheckMate-274 Table S.5.26.1; BMS data on file (2021)[75]

The distribution of the first events in the entire trial (pooled data from both arms) is used in estimating the transitions from the DF state in the CEM base case to provide a conservative scenario. However, the model allows the functionality to use separate distributions of events for both the arms as suggested by the experts in the ad-board.

Similar to the approach used in the adjuvant melanoma CEM for nivolumab (NICE TA558), the distribution of first recurrent events is assumed to be constant over time in the base case. However, following feedback from the VAB on 9 June 2021, flexibility is built into the model to allow for transitions to vary over time up to year 5 in the model where patients remaining in the DF health state are considered to be functionally cured and no longer at risk of experiencing a recurrence or dying of MIUC and all patients are assumed to follow general population mortality.

As an alternative option to the CheckMate-274 trial data, the distribution of events from DF from the first year of the model to year 5 can be entered separately. For this option the distribution for the first year is populated with inputs from CheckMate-274 and transitions for years 1-5 are populated by findings from Mitra et al. (2012)[125]. The user can update these numbers to apply either a linear decrease in patients experiencing recurrence using the data from Mitra et al. (2012)[125] or can populate tables with local clinical data, if available.

Yearly proportion of transitions from DF health state to LR, DR, or Death from Mitra et al. (2012)[125]

Annual distribution of local and distant disease recurrence at different sites from years 0-5 was sourced from the publication. The proportion of local or distant recurrence to the total of local and distant recurrence was further estimated. Note the events with combined local and distant recurrence or unknown were not counted

in the total recurrence. Year-on-year change for LR and DR was estimated and applied on the starting distribution of the LR and DR events observed in the CheckMate-274.

Appendix J.1.1.2 Transitions from Local Recurrence (LR) survival

Under the 4-health-state model structure the transition probabilities applicable to the LR health state are the probability of transitioning to the DR health state and the probability of dying given a patient is in the LR health state. The methodology of estimating the transitions from the LR health state is similar to that used to estimate transitions from DR health state. Transitions from the LR health state are estimated by construction of a LR survival curve which determined the proportion of patients staying in the LR health state and a distribution was used to assign the remaining patient to the transitions of LR to DR and LR to Death health states.

The transition probabilities for the LR health state are detailed below:

- The probability of staying in Local Recurrence (LR) state:

$$P(LR|LR) = \left[\frac{(Survival\ from\ LR)_{t+1}}{(Survival\ from\ LR)_t}\right]$$

- The probability of transitioning from Local Recurrence (LR) to Distant Recurrence (DR):

$$P(DR|LR) = [1 - P(LR|LR)] * (\%\ pts\ with\ DR\ after\ LR_{CM-274:\ Survival\ from\ LR})$$

- The probability of death from Local Recurrence (LR):

$$P(Death|LR) = [1 - P(LR|LR)] * (\%\ pts\ Died\ after\ LR_{CM-274:\ Survival\ from\ LR})$$

The "survival from LR" curves were derived from extrapolations of the patient-level data from CheckMate-274 after pooling data of both treatment arms. Parametric fitting of the "survival from LR" curve from CheckMate-274 (pooled treatment arms) was done using standard parametric models and the exponential model was chosen for extrapolations (see Appendix J.1.2).

Distribution of events from LR health state

To generate the P(DR|LR) and P(Death|LR), the total number of "DR events" and "Death events" used in the construction of the Kaplan-Meier curve was used to spread the overall probability of leaving LR state between the DR and Death states.

The proportion of events for patients in LR (either having a DR or Death event) are taken from the total LR events of the nivolumab and the placebo arm in CheckMate-274 equating to 21 total events from LR (Table J-2). Of these events, 7 were distant recurrences (33.3%) and the remaining 14 were deaths (66.7%). These proportions inform the LR transitions and are not treatment specific (i.e., identical for both treatment arms) in the model and are constant over time in the base-case analysis. Furthermore, as a conservative assumption, these proportions are also used when the "PD-L1 ≥ 1%" population is selected because of the low event numbers from LR observed in the tumour cell PD-L1 expression ≥ 1% subgroup in CheckMate-274.

Table J-2. Modelled survival from LR endpoint events from CheckMate-274 ITT population

Events (n) from local recurrence	Nivolumab (n = 25)	Placebo (n = 34)	Total (n = 59)
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]			
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]

DR = Distant Recurrence; LR = Local Recurrence.

Source: CheckMate-274

Appendix J.1.1.3 Transitions from Distant Recurrence (DR) health state

Under the 4-health-state model structure patients can move into the DR health state from both the DF and LR health states. The DR health state was modelled as an "absorbing/non-transient health state"—that is, transitions are not modelled in a "cycle-by-cycle" manner but rather calculated separately from the rest of the model aligned with the modelling of RD in the 3-health-state model.

Appendix J.1.1.4 Cost calculations in the 4-health-state model

The key difference regarding costs between the 3- and 4-health-state model is that patients in the LR health state are assumed only to receive surgery and/or radiotherapy whereas patients in the DR health state are assumed to receive only first-line/subsequent systemic anticancer therapy. This assumption is supported by feedback from clinical experts from the VAB.[108] Therefore, total surgery and radiotherapy-related costs are applied to patients who transition to the LR health state at each cycle and treatment costs (acquisition, administration and monitoring cost) of subsequent treatment are applied as one-time costs when patients enter the DR health state.

Costs of surgery and radiotherapy were applied to LR patients based on the proportions of patients receiving surgery and radiotherapy in CheckMate-274 (Table J-3) as:

$$\%\ receiving\ surgery\ and\ radiotherapy = \frac{Overall\ \#\ of\ patients\ that\ received\ surgery\ \&\ radiotherapy}{Total\ number\ of\ LR\ events\ within\ DFS}$$

$$\%\ receiving\ subsequent\ therapy = \frac{Overall\ \#\ of\ patients\ that\ received\ subsequent\ therapy}{Total\ number\ of\ DR\ events\ within\ DFS}$$

Table J-3. Proportion of patients receiving subsequent surgery and radiotherapy treatment

	ITT		Tumour cell PD-L1 expression ≥ 1%	
	Nivolumab	Placebo	Nivolumab	Placebo
DR events (n)	110	134	41	54
LR events (n)	49	65	10	25
Subsequent surgery proportions				
Subjects who received subsequent surgery (n)	7	5	1	2
Weighted proportion of LR patients receiving surgery (used in 4HS)	14.3%	7.7%	10.0%	8.3%
Weighted proportion of LR and DR patients receiving surgery (used in 3HS)	4.4%	2.5%	2.0%	2.6%
Subsequent radiotherapy proportions				
Subjects who received subsequent radiotherapy (n)	7	6	2	3
Weighted proportion of LR patients receiving radiotherapy (used in 4HS)	14.3%	9.2%	20.0%	12.5%
Weighted proportion of LR and DR patients receiving radiotherapy (used in 3HS)	4.4%	3.0%	4.0%	3.9%

3HS = 3-health state; 4HS = 4-health state; DR = Distant Recurrence; ITT = intention to treat; LR = Local Recurrence; PD-L1 = programmed death-ligand 1.

Source: CheckMate-274

Appendix J.1.2 Survival from LR: CheckMate-274

A Kaplan-Meier curve for survival from LR was constructed using patient-level data from CheckMate-274. Data from the 2 treatment arms of the ITT population were pooled due to the low number of events in the 19 May 2021 database relock (with data cutoff on 1 February 2021) for this population when stratified by treatment. The following steps were performed to identify patients who experienced LR and were at risk of either DR or Death.

- A total of 151 patients were identified with LR using the LR DFS endpoint.
- Patients who had a LR event first and then a DR or Death were included whereas those experiencing simultaneous occurrences of LR and DR as a first event were excluded.
  - 5 patients were censored as they were censored for DR just before a LR event.
  - 87 patients had "time to LR" = "time to DR," of these 37 had both a DR and LR event at the same time; and the remaining 50 had a LR event and were censored for DR at the same time.
- At the end, 59 patients ([151 – 5] – 87 = 59) were identified for plotting Kaplan-Meier curve from LR health state.
- The specific number of "Death" and "DR" events from LR were informed by looking at the DMFS of the 59 patients that informed the Kaplan-Meier curve. Within DMFS, "death" and "disease at baseline" were censored as these are considered events within DMFS.

Parametric fitting of the "survival from LR" curve from CheckMate-274 (pooled treatment arms) was done using standard parametric models. Table J-4 shows AIC and BIC values of the standard parametric models fitted to the 'survival from LR' Kaplan-Meier curve. Exponential model was only 2.5+ and 0.5+ points more

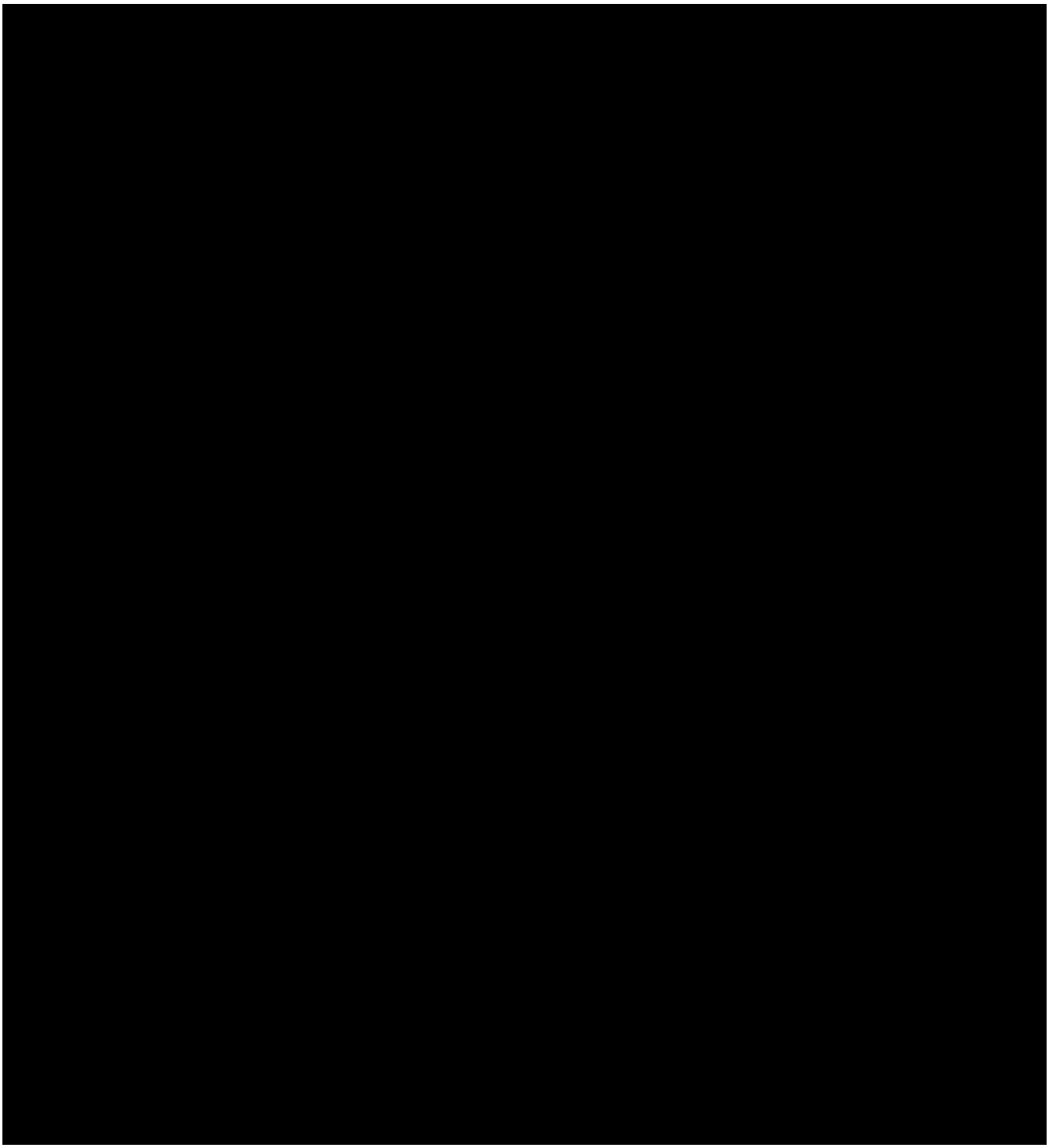
than the lowest AIC and BIC values observed with the log-normal model and therefore provides similar statistical fit to other models.

Spline models were not used, to avoid the risk of over-fitting due to the limited number of events subsequent to a LR observed in CheckMate-274. Parametric extrapolations using standard parametric models fitted to the "survival from LR" endpoint from CheckMate-274 are given in Figure J-2 and Figure J-3 for 60 and 240 months, respectively. Corresponding hazard plots are given in Figure J-4 and Figure J-5 for short- and long-term extrapolations.

The exponential distribution was chosen for the extrapolation of the "survival from LR" curve due to the following reasons:

- It is only 2.5+ and 0.5+ points more than the lowest AIC and BIC values observed with the log-normal model and therefore provides similar statistical fit to other models.
- It implies constant transition probabilities over time, which is desirable given a proportion of patients enter LR health state in each cycle and it helps to keep the memoryless structure of the Markov model.
- It helps to avoid tunnel states as patients transition to and from LR health state and therefore does not further complicate the model.

It shall be noted though that Figure J-4 and Figure J-5 show poor fit of the exponential model to the observed hazards compared with other parametric models.



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[redacted]

Table J-4. Statistical fits (AIC and BIC values) and mean survival times of best-fitting distribution curves for "survival from LR"

Distribution	AIC	BIC	Rank (AIC)	Rank (BIC)	Mean (months)[a] Time horizon of 40.3 months
Log-normal	175.82	179.98	1	1	18.81
Gompertz	176.4933	180.6484	2	3	19.61
Log-logistic	176.7351	180.8902	3	4	18.48
Generalised gamma	177.5703	183.803	4	6	19.31
Exponential	178.3842	180.4618	5	2	19.02
Weibull	179.1542	183.3093	6	5	19.15
Gamma	179.6517	183.8068	7	7	19.04

AIC = Akaike information criterion; BIC = Bayesian information criterion.

[a] Mean survival from LR was 20.08 months from Kaplan-Meier curve from CheckMate-274.

Source: CheckMate-274

Appendix K. Estimation of cost of subsequent therapy

As presented in Section 8.6.6, costs of RD were modelled as one-off costs in the base-case analysis with alternative options available in the model. Table K-1 presents the acquisition, monitoring, and administration cost of each subsequent treatment included for calculation of treatment costs regardless of approach selected.

Table K-1. Dosing details of included subsequent treatments

Regimen	Treatment	Pack/ vial size (mg)	Cost per vial/pack (DKK)	Dose	Source
Gemcitabine + cisplatin	Cisplatin	10		70 mg/m^2 Q4W	Laegemiddelstyrelsen (Danish Medicines Agency), Apotekets indkøbspris, Cisplatin[126]
		50	100.00		
		100	200.00		
	Gemcitabine	200		1,000 mg/m^2 Q1.3W	Laegemiddelstyrelsen (Danish Medicines Agency), Apotekets indkøbspris, Gemcitabin[126]
		1,000			
		2000	1200.00		
MVAC	Methotrexate	10	350.00	30 mg/m^2 Q1.3W	Laegemiddelstyrelsen (Danish Medicines Agency), Apotekets indkøbspris, Methotrexat[126]
		15			
		20			
		25	125.00		
		30			
	Vinblastine	10	215.00	3 mg/m^2 Q1.3W	Laegemiddelstyrelsen (Danish Medicines Agency), Apotekets indkøbspris, Velbe (Vinblastin)[126]
	Adriamycin	10		30 mg/m^2 Q4W	Laegemiddelstyrelsen (Danish Medicines Agency), Apotekets indkøbspris, Adriamycin[126]
		50	521.69		
	Cisplatin	10		70 mg/m^2 Q4W	Laegemiddelstyrelsen (Danish Medicines Agency), Apotekets indkøbspris, Cisplatin[126]
		50	100.00		
		100	200.00		

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Regimen	Treatment	Pack/ vial size (mg)	Cost per vial/pack (DKK)	Dose	Source
HD-MVAC	Methotrexate	10	350.00	30 mg/m^2 Q2W	Laegemiddelstyrelsen (Danish Medicines Agency), Apotekets indkøbspris, Methotrexat[126]
		15			
		20			
		25	125.00		
		30			
	Vinblastine	10	215.00	3 mg/m^2 Q2W	Laegemiddelstyrelsen (Danish Medicines Agency), Apotekets indkøbspris, Velbe (Vinblastin)[126]
	Adriamycin	10		30 mg/m^2 Q2W	Laegemiddelstyrelsen (Danish Medicines Agency), Apotekets indkøbspris, Adriamycin[126]
		50	521.69		
	Cisplatin	10		70 mg/m^2 Q2W	Laegemiddelstyrelsen (Danish Medicines Agency), Apotekets indkøbspris, Cisplatin[126]
		50	100.00		
		100	200.00		
	G-CSF	0.3		1.7 mg/m^2 Q2W	
Gemcitabine + carboplatin	Carboplatin	50	84.00	400 mg/m^2 Q3W	Laegemiddelstyrelsen (Danish Medicines Agency), Apotekets indkøbspris, Carboplatin[126]
		150	203.00		
		450			
		600			
	Gemcitabine	200		1,000 mg/m^2 Q1.5W	Laegemiddelstyrelsen (Danish Medicines Agency), Apotekets indkøbspris, Gemcitabin[126]
		1,000			
		2,000	1200.00		
Pembrolizumab	Pembrolizumab	100	23,204.61	200 mg Q3W	Laegemiddelstyrelsen (Danish Medicines Agency), Apotekets indkøbspris, Keytruda (Pembrolizumab)[126]
Atezolizumab	Atezolizumab	1,200	31,141.55	1,200 mg Q3W	Laegemiddelstyrelsen (Danish Medicines Agency), Apotekets indkøbspris, Tecentriq (Atezolizumab)[126]
Avelumab	Avelumab	200	6,816.95	800 mg Q2W	Laegemiddelstyrelsen (Danish Medicines Agency), Apotekets indkøbspris, Bavencio (Avelumab)[126]

G-CSF = granulocyte colony-stimulating factor; HD-MVAC = high-dose mitoxantrone, vinblastine, and CCNU (lomustine); MVAC = mitoxantrone, vinblastine, and CCNU (lomustine) ; Q2W = every 2 weeks; Q3W = every 3 weeks; Q4W = every 4 weeks.

Table K-2 presents the duration of therapy by subsequent treatment included.

Table K-2. Duration of subsequent treatments

Treatment	Duration of therapy (months)	Source
Gemcitabine + cisplatin	3.75	Bellmunt et al. (2012)[76]
MVAC	4.83	Sternberg et al. (2006)[127] EORTC 30924
MVAC-HD	2.76	Sternberg et al. (2006)[127] EORTC 30924
Gemcitabine + carboplatin	3.20	De Santis et al. (2012)[77]
Pembrolizumab	8.10	KEYNOTE-361 Appendix Table S4[78]
Atezolizumab	12.90	NICE TA739 Atezolizumab Assessment Report, p.11[128]
Avelumab	11.45	NoMA submission for avelumab[60]

MVAC-HD = high-dose mitoxantrone, vinblastine, and CCNU (lomustine); NICE = National Institute for Health and Care Excellence; NoMA = Norwegian Medicines Agency.

Table K-3 presents the administration cost by subsequent treatment included.

Table K-3. Administration costs of subsequent treatments

Treatment	Frequency per week	Cost per administration (DKK)	Source
Gemcitabine + cisplatin	1.00	2,038.00	DRG Tariffs 2022 (DRG11MA98)[65]
MVAC	1.00	2,038.00	
MVAC-HD	1.00	2,038.00	
Gemcitabine + carboplatin	1.00	2,038.00	
Pembrolizumab	1.00	2,038.00	
Atezolizumab	1.00	2,038.00	

MVAC-HD = high-dose mitoxantrone, vinblastine, and CCNU (lomustine).

Table K-4 presents the monitoring costs of subsequent treatments. These costs reflect treatment-specific resource use such as labs and scans that are required to ensure patients are tolerating the treatment well. The monitoring costs are based on the Danish-specific costs from 2022, alternatively adjusted for 2022 inflation rate.

Table K-4. Monitoring costs per included subsequent treatment

Monitoring cost	Frequency per week	Source	Unit cost (DKK)	Source
Cisplatin + gemcitabine				
Outpatient visit	1.00	Expert input BMS data on file (2021)[108]	2,910.00	DRG Tariffs 2022 (DRG07MA98)[65]
Hepatic function test	1.00		15.37	Laboratoriemedicinske vejledninger (2021)[109] (NPU19651)
Renal function	1.00		15.37	Laboratoriemedicinske vejledninger (2021)[109] (NPU18669)
CBC	1.32		15.37	Laboratoriemedicinske vejledninger (2021)[109], Blodprøve (NPU02593)
Total cost per 4 weeks			2,961.01	
MVAC				
Outpatient visit	1.00		2,910.00	DRG Tariffs 2022 (DRG07MA98)[65]

Monitoring cost	Frequency per week	Source	Unit cost (DKK)	Source
Hepatic function test	1.00	Expert input BMS data on file (2021)[108]	15.37	Laboratoriemedicinske vejledninger (2021)[109] (NPU19651)
Renal function	1.00		15.37	Laboratoriemedicinske vejledninger (2021)[109] (NPU18669)
CBC	1.32		15.37	Laboratoriemedicinske vejledninger (2021)[109], Blodprøve (NPU02593)
Total cost per 4 weeks			2,961.01	
HD-MVAC				
Outpatient visit	1.00	Expert input BMS data on file (2021)[108]	2,910.00	DRG Tariffs 2022 (DRG07MA98)[65]
Hepatic function test	1.00		15.37	Laboratoriemedicinske vejledninger (2021)[109] (NPU19651)
Renal function	1.00		15.37	Laboratoriemedicinske vejledninger (2021)[109] (NPU18669)
CBC	1.32		15.37	Laboratoriemedicinske vejledninger (2021)[109], Blodprøve (NPU02593)
Total cost per 4 weeks			2,961.01	
Carboplatin + gemcitabine				
Outpatient visit	1.00	Expert input BMS data on file (2021)[108]	2,910.00	DRG Tariffs 2022 (DRG07MA98)[65]
Hepatic function test	1.00		15.37	Laboratoriemedicinske vejledninger (2021)[109] (NPU19651)
Renal function	1.00		15.37	Laboratoriemedicinske vejledninger (2021)[109] (NPU18669)
CBC	1.32		15.37	Laboratoriemedicinske vejledninger (2021)[109], Blodprøve (NPU02593)
Total cost per 4 weeks			2,961.01	
Pembrolizumab				
Outpatient visit	1.00	Expert input BMS data on file (2021)[108]	2,910.00	DRG Tariffs 2022 (DRG07MA98)[65]
Hepatic function test	1.00		15.37	Laboratoriemedicinske vejledninger (2021)[109] (NPU19651)
Renal function	1.00		15.37	Laboratoriemedicinske vejledninger (2021)[109] (NPU18669)
Thyroid test	1.00		21.51	Laboratoriemedicinske vejledninger (2021)[109] (NPU03577)
Total cost per 1 week (model cycle)			2,962.24	
Atezolizumab				
Outpatient visit	1.00	Expert input BMS data on file (2021)[108]	2,910.00	DRG Tariffs 2022 (DRG07MA98)[65]
Hepatic function test	1.00		15.37	Laboratoriemedicinske vejledninger (2021)[109] (NPU19651)
Renal function	1.00		15.37	Laboratoriemedicinske vejledninger (2021)[109] (NPU18669)
Thyroid test	1.00		21.51	Laboratoriemedicinske vejledninger (2021)[109] (NPU03577)
Total cost per 4 weeks:			2,962.24	

CBC = complete blood count; GP = general practitioner; HD-MVAC = high-dose mitoxantrone, vinblastine, and CCNU (lomustine).

In addition to systemic anti-cancer subsequent treatment, the cost-effectivness model takes into account costs of subsequent surgery and radiotherapy (DKK 22,411.00 and DKK 2,733.00, respectively) as show in Table K-5. The costs are applied to RD patients based on the proportions of patients receiving surgery and radiotherapy in CheckMate-274 (see Table K-6).

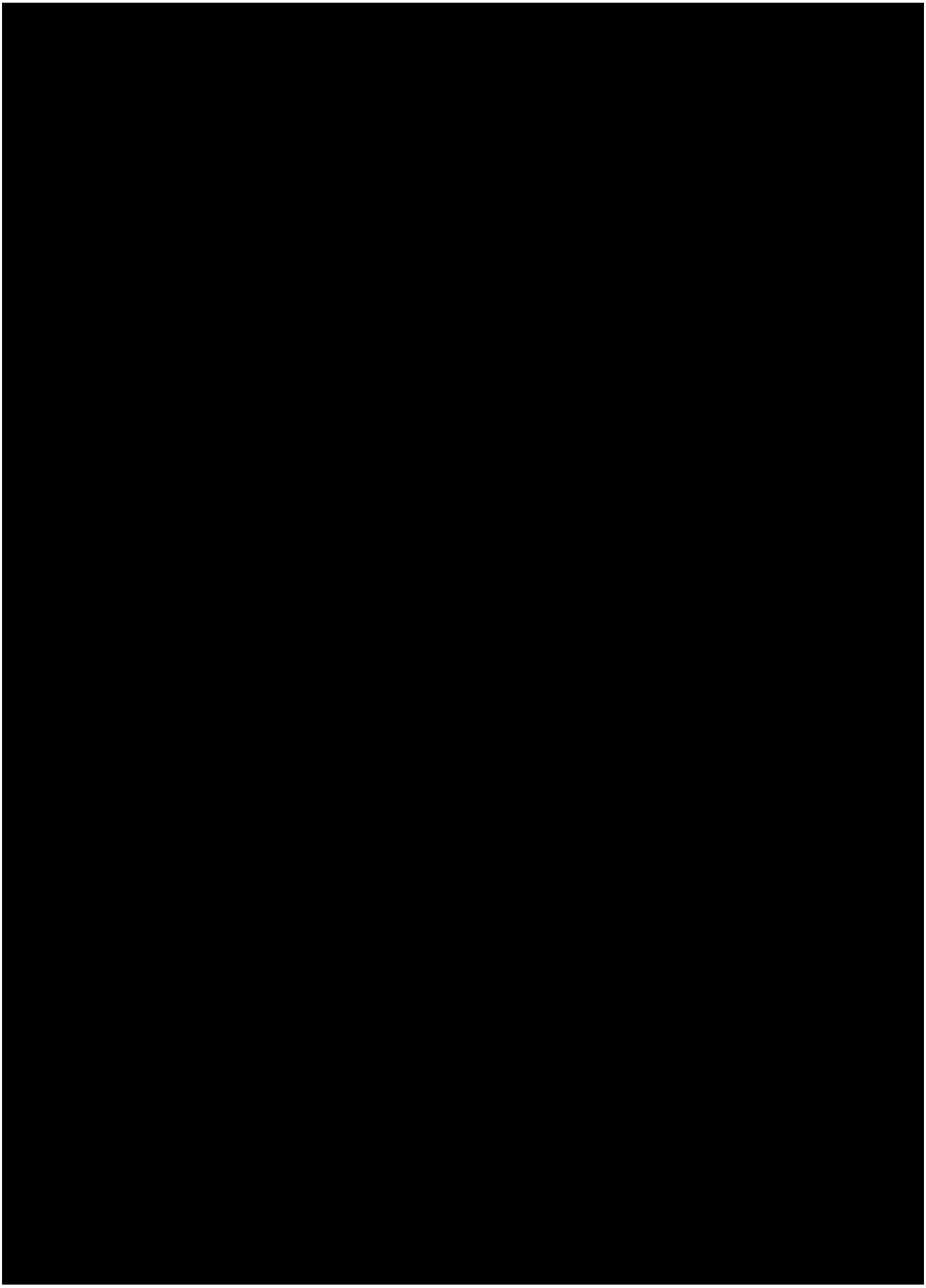
Table K-5. Surgery and radiotherapy costs by unit

Resource	Unit cost (DKK)	Source
Surgery	22,411.00	DRG Tariffs 2022 (DRG11MP17)[65]
Radiotherapy	2,733.00	DRG Tariffs 2022 (DRG27MA08)[65]

Table K-6. Proportion of patients receiving subsequent surgery and radiotherapy treatment

	Nivolumab	Placebo
Recurrence events (n)	51	79
Subsequent surgery proportions		
Subjects who received subsequent surgery (n)	1	2
Weighted proportion of recurred patients receiving surgery	1.96%	2.53%
Subsequent radiotherapy proportions		
Subjects who received subsequent radiotherapy (n)	2	3
Weighted proportion of recurred patients receiving radiotherapy	3.92%	3.80%

Source: CheckMate-274 CSR[57]



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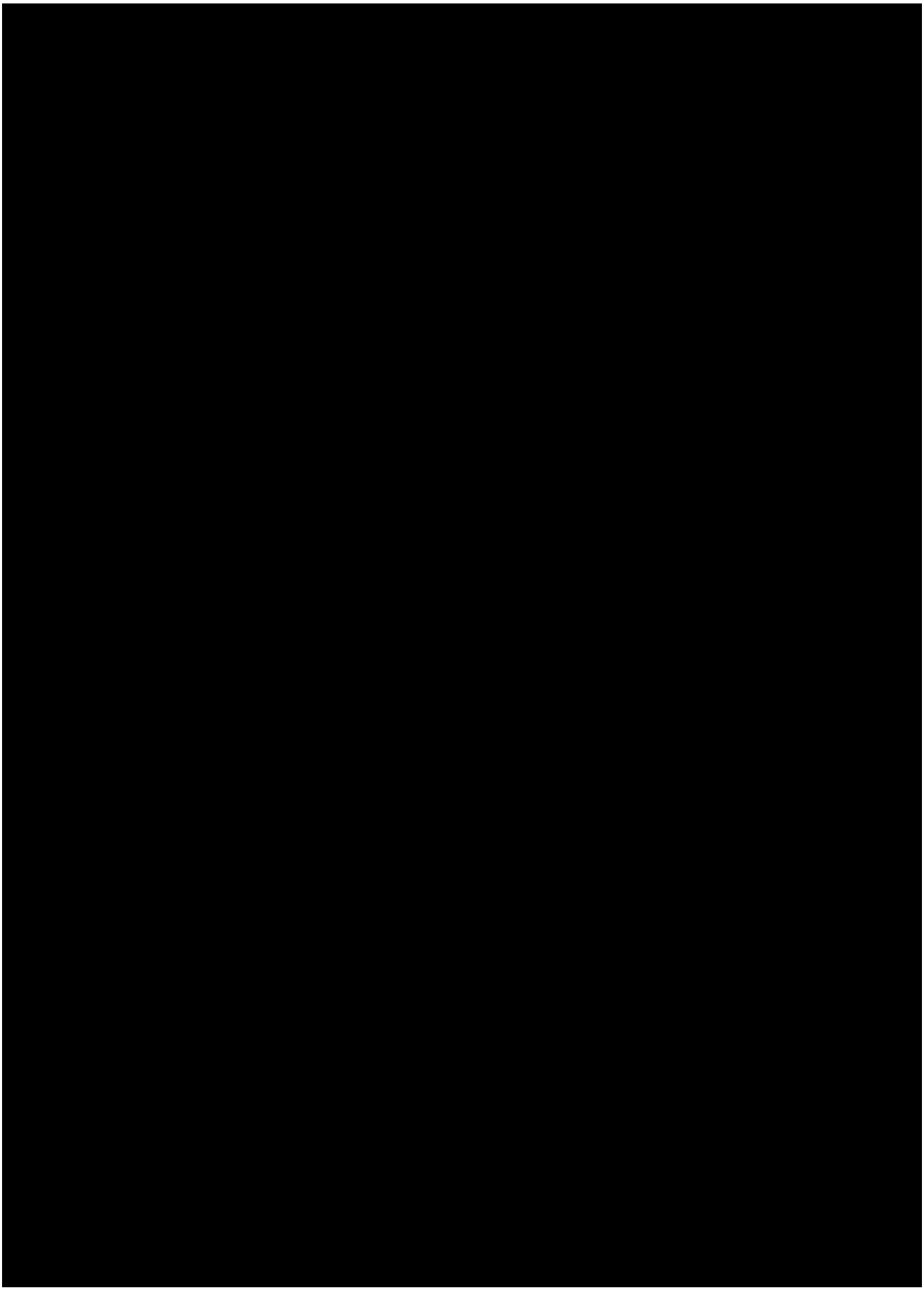

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