Medicinrådet

Bilag til Medicinrådets anbefaling vedrørende nivolumab i kombination med kemoterapi til behandling af neo-adjuverende behandling af NSCLC

Vers. 1.0

Bilagsoversigt

1. Ansøgers notat til Rådet vedr. nivolumab i kombination med kemoterapi
2. Forhandlingsnotat fra Amgros vedr. nivolumab i kombination med kemoterapi
3. Ansøgers endelige ansøgning vedr. nivolumab i kombination med kemoterapi

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Virum, 23. oktober 2023

Til Medicinrådet

Bristol Myers Squibbs tilbagemelding på udkastet til vurdering af nivolumab i kombination med kemoterapi til neoadjuverende behandling af ikke-småcellet lungekræft.

Sigtet med denne neoadjuverende immunterapeutiske behandling er at sætte ind med blokering af PD-1 signalvejen, mens primær tumor stadig er til stede, for at få størst mulig effekt på tumor samt mikrometastaser gennem en kort eksponering.

CheckMate 816 viser, at risikoen for tilbagefald halveres med neo-adjuverende behandling med nivolumab + kemoterapi, ift. neoadjuverende kemoterapi alene, for patienter med stadie IIB-IIIB(N2) NSCLC og PD-L1 ekspression ≥ 1% (EFS HR 0,49; 95% CI 0,29 – 0,83).

Denne halvering i risikoen for tilbagefald med tre serier af immunterapi reducerer risikoen for metastatisk sygdom (TTDM HR 0,40; 95% CI 0,22 – 0,72), og dermed omkostningerne forbundet med behandling af metastatisk sygdom, og forlænger overlevelsen markant (OS HR 0,43; 95% CI 0,22 - 0,83).

Neo-adjuverende behandling med nivolumab + kemoterapi er derfor en yderst omkostningseffektiv behandling. Det er BMS's forståelse, at Medicinrådet og BMS er enige om dette forhold, hvorfor indikationen er behandlet som en fast-track evaluering af immunterapeutiske indikationer.

I den forbindelse ønsker BMS at takke for muligheden for at være med til at afprøve Medicinrådets fast-track evaluering af immunterapeutiske indikationer.

Konkomitant kemoradioterapi

Bristol Myers Squibb bemærker, at Medicinrådet omtaler konkomitant kemoradioterapi som dansk klinisk praksis for en ukendt andel af de stadie IIIA (TNM version 7) patienter, der er indrulleret i CheckMate 816. Vi anerkender, at vurderingen af hvorvidt en patient er operabel er en kompleks multidisciplinær team (MDT) beslutning, som kan variere mellem lande.

Sigtet med CheckMate 816 har været at afprøve neoadjuverende nivolumab + kemoterapi til den gruppe af stadie IIIA (TNM version 7) patienter, hvor kirurgi er intenderet. Populationen af patienter med stadie III sygdom hvor kirurgi *ikke* er intenderet, har BMS indrulleret i et separat studie (CheckMate-73L), og heri er komparator konkomitant kemoradioterapi, med mulighed for efterfølgende behandling med durvalumab, som det er dansk klinisk praksis.

Bristol Myers Squibb henstiller til, at Rådet er opmærksomme på det potentielle skred i **P**I**C**O diskussionen ifm. denne vurdering og at man alene forholder sig til anbefalingen af nivolumab + kemoterapi til den andel af patienter hvor operation er intenderet, og derfor er kemoradioterapi *ikke* en komparator for denne patientgruppe i klinisk praksis.

Genbehandling med immunterapi efter neo-adjuverende nivolumab + kemoterapi.

BMS ønsker at understrege, at der ikke er evidens for, at tre serier nivolumab i kombination med kemoterapi skulle reducere effekten af genbehandling mere end de 12 måneders atezolizumab behandling, som i dag anvendes til en delmængde af patienterne. I både vurderingen af atezolizumab, samt den nærværende vurdering, gøres det dog også klart, at:

"Beslutning om eventuel genbehandling er en lægefaglig vurdering, som bør forudgås af ny PD-L1-analyse"

Adjuverende immunterapi efter neoadjuverende nivolumab + kemoterapi

Medicinrådet diskuterer, hvorvidt patienter med PD-L1>50% kunne være kandidater til immunterapi post-operativt, og beskriver, hvorledes indikationen så ville kræve foregående adjuverende kemoterapi.

På dette års ESMO-konference blev data fra det peri-operative studie CheckMate 77T præsenteret. CheckMate 77T har undersøgt neo-adjuverende behandling med nivolumab + kemoterapi efterfulgt af adjuverende nivolumab og BMS ser frem til diskutere dataene med de europæiske myndigheder og forhåbentligt sidenhen med Medicinrådet.

Men først og fremmest ser BMS frem til Medicinrådets anbefaling vedrørende neo-adjuverende nivolumab + kemoterapi (CheckMate 816). En anbefaling, som vi forventer, vil understrege den kliniske og sekundært den økonomiske værdi af, at bringe immunterapien i spil så tidligt som muligt med kurativt sigte.

Med venlig hilsen,

Anders Thelborg
Adm. direktør
Bristol Myers Squibb, Denmark

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30.10.2023

DBS/INK

Forhandlingsnotat

Dato for behandling i Medicinrådet	22. november 2023
Leverandør	BMS
Lægemiddel	Opdivo (nivolumab)
Ansøgt indikation	Nivolumab i kombination med kemoterapi til neoadjuverende behandling af ikke-småcellet lungekræft
Nyt lægemiddel / indikationsudvidelse	Indikationsudvidelse (fast-track)

Prisinformation

Amgros har følgende pris på Opdivo (nivolumab):

Tabel 1: Forhandlingsresultat

Lægemiddel	Styrke	Pakningsstr.	AIP (DKK)	Nuværende SAIP (DKK)	NY Pris pr. 01.01.2024 SAIP (DKK)	Rabatprocent ift. AIP
Opdivo	100 mg/10 ml	1 stk.	8.715,54	[redacted]	[redacted]	[redacted]
Opdivo	120 mg/12 ml	1 stk.	10.458	[redacted]	[redacted]	[redacted]
Opdivo	240 mg/24 ml	1 stk.	20.917	[redacted]	[redacted]	[redacted]
Opdivo	40 mg/4 ml	1 stk.	3.508,46	[redacted]	[redacted]	[redacted]

Amgros har en aftale på Opdivo, som er en del af et dynamisk udbud sammen med Keytruda (pembolizumab) og Tecentriq (atezolizumab). Amgros har afsluttet et udbud med aftalestart d. 01.01.2024. [redacted]

Konkurrencesituationen

Opdivo i kombination med kemoterapi er den eneste immunterapi til neoadjuverende behandling af ikke-småcellet lungekræft.

Tabel 2: Lægemiddeludgift pr. patient for behandling med Opdivo i 3 cykler

Lægemiddel	Styrke	Paknings størrelse	Dosering	Pris pr. pakning Pr.1.1.2024 (SAIP, DKK)	Lægemiddeludgift for 3 cyklusser (SAIP, DKK)
Opdivo	100 mg/10 ml	1 stk.	Max. 4,5 mg/kg* hver 3. uge i 3 cykler	[redacted]	[redacted]

*Patientvægt 72 kg

Status fra andre lande

Tabel 4: Status fra andre lande

Land	Status	Link
Norge	Under vurdering	Link til vurdering
England	Anbefalet	Link til anbefaling

Konklusion

[redacted] Der kan komme yderligere prisjusteringer indenfor immunterapierne, når de næste indikationer, som indeholder store patientpopulationer, bliver vurderet i Medicinrådet.

Application for the assessment of nivolumab plus chemotherapy for the neoadjuvant treatment of resectable non-small cell lung cancer at high risk of recurrence in adult patients whose tumours express PD-L1 ≥1%

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1 Basic information

Contact information	
Name	Lars Oddershede
Title	Market Access Manager | Market Access
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Overview of the pharmaceutical	
Proprietary name	OPDIVO plus platinum doublet chemotherapy
Generic name	Nivolumab plus platinum doublet chemotherapy
Marketing authorization holder in Denmark	Bristol Myers Squibb
ATC code	L01XC17
Pharmacotherapeutic group	Antineoplastic agents, monoclonal antibodies
Active substances	Nivolumab plus platinum doublet chemotherapy
Pharmaceutical form	Concentrate for solution for infusion
Mechanism of action	Nivolumab is a human immunoglobulin G4 (IgG4) monoclonal antibody (HuMAb), which binds to the programmed death-1 (PD-1) receptor
Dosage regimen	Non-squamous non-small cell lung cancer (NSCLC) Nivolumab 360 mg every 3 weeks (30-minute IV infusion), for three cycles Chemotherapy Pemetrexed at a dose of 500 mg/m^2 (10 minutes IV infusion) plus Cisplatin at a dose of 75 mg/m^2 (120 minutes IV infusion) every 3 weeks, for three cycles Squamous NSCLC Nivolumab 360 mg every 3 weeks (30-minute IV infusion), for three cycles Chemotherapy Gemcitabine at a dose of 1000 mg/m^2 or 1250 mg/m^2 (30 minutes IV infusion) on day 1 and day 8 of each cycle of treatment plus cisplatin at a dose of 75 mg/m^2 (120 minutes IV infusion) every 3 weeks, for three cycles Any histology Nivolumab 360 mg every 3 weeks (30-minute IV infusion), for three cycles Chemotherapy Paclitaxel 175 or 200 mg/m^2 (180 minutes IV infusion) plus carboplatin AUC 5 or 6 (30 minutes IV infusion) every 3 weeks, for three cycles
Therapeutic indication relevant for assessment (as defined by the European Medicines Agency, EMA)	OPDIVO in combination with platinum-based chemotherapy is indicated for the neoadjuvant treatment of resectable non-small cell lung cancer at high risk of recurrence in adult patients whose tumours express PD-L1 ≥1% Further selection criteria are described in section 5.3 of the present document.
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 (PFS) and overall survival (OS) 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 (NSCLC)

Overview of the pharmaceutical	
	OPDIVO in combination with ipilimumab and 2 cycles of platinum-based chemotherapy is indicated for the first-line treatment of metastatic non-small cell 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 (MPM) OPDIVO in combination with ipilimumab is indicated for the first-line treatment of adult patients with unresectable malignant pleural mesothelioma. Renal cell carcinoma (RCC) 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 (cHL) OPDIVO as monotherapy is indicated for the treatment of adult patients with relapsed or refractory classical Hodgkin lymphoma after autologous stem cell transplant (ASCT) and treatment with brentuximab vedotin. Squamous cell cancer of the head and neck (SCCHN) 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 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. Mismatch repair deficient (dMMR) or microsatellite instability-high (MSI-H) colorectal cancer (CRC) 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 (OSCC) 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%. 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 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. Adjuvant treatment of oesophageal or gastro-oesophageal junction cancer (OC or GEJC) 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. Gastric, gastro oesophageal junction (GEJ) or oesophageal adenocarcinoma

Overview of the pharmaceutical	
	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 (CPS) ≥ 5.
Will dispensing be restricted to hospitals?	Yes
Combination therapy and/or co-medication	Yes, nivolumab plus chemotherapy
Packaging – types, sizes/number of units, and concentrations	Nivolumab (10 mg/mL): Single-use vials 40 mg/4 mL 100 mg/10 mL 120 mg/12 mL 240 mg/24 mL
Orphan drug designation	No

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2 Abbreviations

Abbreviation	Description of abbreviation
1L	First line
2L	Second line
AACR	American Association for Cancer Research
AE	Adverse event
AFT	Accelerated failure time
AIC	Akaike's Information Criteria
AJCC	American Joint Committee on Cancer
ALAT	Alanine aminotransferase
ALK	Anaplastic lymphoma kinase
ASAT	Aspartate transaminase
AUC	Area under the curve
BIC	Bayesian Information Criteria
BICR	Blinded independent central review
BIPR	Blinded independent pathological review
BL	Baseline
BMS	Bristol Myers Squibb
BSA	Body surface area
BSC	Best supportive care
CADTH	Canadian Agency for Drugs and Technologies in Health
CE	Cost-effectiveness
CEAC	Cost-effectiveness acceptability curve
CEM	Cost-effectiveness model
CG	Collaborative group
CHMP	Committee for Medicinal Products for Human Use
ChT	Chemotherapy
CI	Confidence interval
CM-816	CheckMate-816
CMH	Cochran Mantel-Haenszel
COVID-19	Coronavirus Disease 2019
CRF	Case report form
cRR	Clinical response rate
CRT	Chemoradiotherapy
CT	Computed tomography
CTCAE	Common Terminology Criteria for Adverse Events
ctDNA	Circulating tumour DNA
CTLA	Cytotoxic T lymphocyte-associated antigen
cTNM	Clinical tumour-node-metastasis based staging
DFS	Disease-free survival
DKK	Danish Kroner
DLCG	Danish Lung Cancer Group
DLCR	Danish Lunge Cancer Registry
DM	Distant metastasis
DMC	Danish Medicines Council (Medicinrådet)
DRG	Diagnosis Related Groups
DSA	Deterministic sensitivity analysis
DSU	Decision Support Unit
ECOG	Eastern Cooperative Oncology Group
EF	Event-free
EFS	Event-free survival
EGFR	Epidermal growth factor receptor

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Abbreviation	Description of abbreviation
EMA	European Medicines Agency
EQ-5D-3L	EuroQoL Five-Dimension, Three-Level
EQ-5D-5L	EuroQoL Five-Dimension, Five-Level
ESMO	European Society for Medical Oncology
EU	European Union
FDA	Food and Drug Administration
HAS	Haute Autorité de Santé
HR	Hazard ratio
HRQoL	Health-related quality of life
HSUV	Health state utility values
HTA	Health Technology Assessment
IASLC	International Association for the Study of Lung Cancer
ICER	Incremental cost effectiveness ratio
IHC	Immunohistochemistry
INHB	Incremental net health benefit
IPD	Individual patient level data
IPI	Ipilimumab
IQR	Interquartile range
ISPOR	International Society for Pharmacoeconomics and Outcomes Research
ITT	Intent-to-treat
IV	Intravenous
KM	Kaplan-Meier
KN	KEYNOTE
LACE	Lung Adjuvant Cisplatin Evaluation
LR	Locoregional recurrence
LS	Least squares
LY	Life years
MA	Meta-analysis
MDT	Multi-disciplinary team
MedDRA	Medical Dictionary for Regulatory Activities
MMRM	Mixed model for repeated measures
MPR	Major pathologic response
MRI	Magnetic resonance imaging
MRU	Medical resource use
MST	Median survival time
NA	Not available
NE	Not estimable
NICE	National Institute for Health and Care Excellence
NIVO	Nivolumab
NR	Not reached
NSCLC	Non-small cell lung cancer
NSQ	Non-squamous
OR	Odds ratio
ORR	Overall response rate
OS	Overall survival
PBAC	Pharmaceutical Benefits Advisory Committee
pCR	Pathologic complete response
PD	Progressive disease
PD-1	Programmed cell death ligand 1
PDC	Platinum-double chemotherapy
PD-L1/2	Programmed death ligand 1/2
PFS	Progression-free survival

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Abbreviation	Description of abbreviation
PH	Proportional hazard
PPP	Pharmacy purchase price
PRO	Patient reported outcome
PS	Performance status
PSA	Probabilistic sensitivity analysis
pTNM	Pathological Tumor-Node-Metastasis staging
Q2W	Every 2 weeks
Q3W	Every 3 weeks
QALY	Quality adjusted life years
RCT	Randomised controlled trial
RDI	Relative dose intensity
RECIST	Response Evaluation Criteria In Solid Tumours
RFS	Recurrence-free/relapse-free survival
RT	Radiotherapy
RVT	Residual viable tumour cells
SAE	Serious adverse event
SCLC	Small cell lung cancer
SD	Standard deviation
SE	Standard error
SLR	Systematic literature review
SLV	Statens legemiddelverk
SmPC	Summary of product characteristics
SQ	Squamous
TC	Tumour cells
TMB	Tumour mutation burden
TNM	Tumour-node-metastasis cancer staging system
TRAE	Treatment-related adverse events
TRSAE	Treatment related serious adverse event
TTD	Time-to-treatment discontinuation
TTDM	Time to death or distant metastases
UK	United Kingdom
US	United States
VAS	Visual analogue score
VAT	Value added tax
VATS	Video-assisted thoracoscopic surgery

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3 Tables and figures

List of figures

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4 Summary

Population

Lung cancer is the leading cause of death among all cancers in Denmark, with a 5-year survival of nearly 30%. The lung cancer histological subtype, non-small cell lung cancer (NSCLC), accounts for 80% of all lung cancer cases (1).

There is a higher survival probability with diagnosis of earlier stages of lung cancer—stage II and stage III disease (TNM version 8). Patients with newly diagnosed non-metastatic NSCLC are treated with curative intent to the extent possible. Patients that are considered resectable are preferably treated with surgery. Postoperative (adjuvant) treatment with platinum-doublet chemotherapy (PDC) can also be recommended for patients with NSCLC in stages II-III (TNM version 8). The Danish treatment guidelines further recommend that patients with NSCLC who are evaluated to be candidates for minimal invasion surgery can be considered for preoperative (neoadjuvant) treatment with PDC (2).

Patients eligible for neoadjuvant treatment with nivolumab in combination with PDC are adults with resectable NSCLC at high risk of recurrence in adult patients whose tumours express PD-L1 ≥ 1%. The indication has specified selection criteria to determine a high risk of recurrence and is reflective of a patient population with tumour PD-L1 expression ≥ 1% and stage II-IIIA (TNM version 7, equivalent to stages IIB-IIIB N2 in TNM version 8). In Denmark, this population is estimated to be around 160 patients per year.

Intervention

Nivolumab is a human immunoglobulin type 4 (IgG4), programmed death-1 (PD-1) receptor-blocking monoclonal antibody that prevents inactivation and ability of T cells to attack the tumour (3, 4). Nivolumab, thereby, restores normal T cell antitumour function. Evidence has indicated when adding a PD-1 receptor blocking immunotherapy agent—such as nivolumab—in the neoadjuvant setting, the agent is expected to be particularly effective for eliminating micro-metastases of the primary tumour (5). Additionally, the immune-mediated effects of chemotherapy suggest that combining chemotherapy with immunotherapy is likely to further enhance the anti-tumour effects of immunotherapy (5). Nivolumab is administered in combination with PDC (pemetrexed and cisplatin), hereafter referred to as nivolumab plus PDC, every 3 weeks for a total of three cycles.

The efficacy of nivolumab plus PDC was studied in a phase 3 clinical trial, CheckMate 816. Neoadjuvant treatment with nivolumab plus PDC was compared with neoadjuvant PDC alone in patients with resectable, non-metastatic NSCLC (TNM version 7, stage IB (≥4cm), stage II, or stage IIIA) (6, 7).

Comparator

In the Danish treatment setting, the most relevant comparator for neoadjuvant treatment with nivolumab plus PDC is adjuvant PDC treatment.

Based on the current literature, adjuvant and neoadjuvant PDC have shown to provide similar clinical efficacy in patients with early-stage NSCLC (8, 9). Thus, the current application uses the direct comparison in CheckMate 816 where the comparator of neoadjuvant PDC will be used as a proxy for adjuvant PDC, which is in line with the Danish treatment guidelines that are in agreement with the equivalence statement (10).

Outcomes

Results from key outcomes are summarised in Table 1 and include event free survival (EFS), overall survival (OS), time to distant metastasis (TTDM) and surgical outcomes. At the latest data cut (October 2022; median follow-up time of

41.1 months, minimum follow-up of 32.9 months), nivolumab plus PDC demonstrated clinically meaningful improvement in EFS over PDC alone, both for patients with PD-L1 expression ≥ 1% and stage II – IIIA (TNM version 7) and for all-comers. In patients with PD-L1 expression ≥ 1%, stage II – IIIA (TNM version 7) median EFS was not reached for patients treated with nivolumab plus PDC while a median EFS of 26.71 months was reported for the PDC alone group (HR: 0.49; 95% CI: 0.29–0.83) (11). Overall, the outcomes for patients with PD-L1 expression ≥ 1% and with stage II-IIIA (TNM version 7) are similar to outcomes for patients with tumour PD-L1 expression ≥1% for all stages in CheckMate 816 (Table 1).

Table 1: Summary of efficacy data for CheckMate 816

	Nivolumab plus PDC (N=179)	PDC alone (N=179)	HR
Primary outcomes (October 2022)			
Median EFS[a], months **ITT Population**	NR (95% CI: 31.57–NR)	21.06 (95% CI: 14.75–42.09)	HR: 0.68 (95% CI: 0.49–0.93)
36-month EFS rate, % **ITT Population**	57%	43%	
Median EFS[a], months **Patients with PD-L1 ≥ 1%**	NR (95% CI: 44.42–NR)	26.71 (95% CI: 13.40–NR)	HR: 0.46 (95% CI: 0.28–0.77)
Median EFS[a], months **Patients with PD-L1 ≥ 1% and with stage II-IIIA (TNM version 7)**	NR (95% CI: 44.42–NR)	26.71 (95% CI: 13.40–NR)	HR: 0.49 (95% CI: 0.29–0.83)
Secondary outcomes (October 2022)			
Median OS, months **ITT Population**	NR (95% CI: NR–NR)	NR (95% CI: 46.8–NR)	HR: 0.62 (95% CI: 0.42–0.90)
36-month OS rate, % **ITT Population**	78.0%	64.0%	
Median OS, months **Patients with PD-L1 ≥ 1% and with stage II-IIIA (TNM version 7)**	NR (95% CI: NR-NR)	NR (95% CI: NR-NR)	HR: 0.43 (95% CI: 0.22–0.83)
Median TTDM[c], months **ITT Population**	NR (95% CI: 48.59–NR)	34.3 (95% CI: 23.65–NR)	HR: 0.55 (95% CI: 0.39–0.78)
Median TTDM[c], months **Patients with PD-L1 ≥ 1% and with stage II-IIIA (TNM version 7)**	NR (95% CI: 44.42–NR)	NR (95% CI: 18.83–NR)	HR: 0.40 (95% CI: 0.22–0.72)
Exploratory outcome: surgical outcomes (October 2021)			
Patients with definitive surgery[d], % **ITT Population**	83.2%	75.4%	
Patients with delayed surgery[e,f], % **ITT Population**	20.8%	17.8%	
Median length of surgery delay, weeks (IQR) **ITT Population**	2.0 (0.6–3.0)	2.4 (1.0–3.7)	

Abbreviations: BIPR, Blinded independent pathological review; CI, Confidence interval; EFS, Event-free survival; HR, Hazard ratio; ITT, Intent-to-treat; IQR, Inter-quartile range; MPR, Major pathological response; NR, Not reached; OR, Odds ratio; OS, Overall survival; pCR, Pathological complete response; PDC, Platinum-doublet chemotherapy; TTDM, Time to death or distant metastases.
Notes:
[a] Per BICR (Primary endpoint) and based on Kaplan-Meier Estimates
[b] Significance boundary for OS was not crossed at this interim analysis
[c] Per BICR; (Secondary endpoint) and based on Kaplan-Meier Estimates
[d] Definitive surgery was not reported in two patients in the nivolumab plus PDC group and seven in the PDC alone group.
[e] Time from last dose to neoadjuvant surgery >6 weeks.
[f] Denominator based on patients with definitive surgery (N=149 in the nivolumab plus PDC group, N=135 in the PDC alone group).
Reference: (11-13)

Nivolumab plus PDC as a neoadjuvant therapy was generally well tolerated, having a similar incidence of treatment-related AEs, surgery-related AEs, AEs leading to discontinuation, and serious AEs (SAEs) compared with neoadjuvant PDC alone (13).

Health economic evaluation

A three health-state Markov model was developed to evaluate the incremental cost-effectiveness of neoadjuvant treatment with nivolumab plus PDC versus adjuvant PDC alone in adult patients newly diagnosed with histologically confirmed resectable, non-metastatic NSCLC with PD-L1 expression ≥ 1%, stage II – IIIA (TNM version 7). The model considers all disease stages included in the population studied in CheckMate 816 (stage IB – IIIA, TNM version 7)—whilst the EMA population criteria is restricted to stages II – IIIA (TNM version 7)—as the number of patients and baseline characteristics are similar and no major differences in outcomes have been observed.

The results from the cost-effectiveness analysis show that neoadjuvant treatment with nivolumab plus PDC is associated with an expected gain of 1.72 LYs and 1.52 QALYs compared with neoadjuvant PDC alone. The use of nivolumab plus PDC resulted in incremental costs of -40 996 DKK compared to neoadjuvant PDC, resulting in nivolumab plus PDC dominating treatment with PDC alone. Results of the economic analysis demonstrated that nivolumab plus PDC delivers a significant survival benefit over PDC alone while saving costs over a lifetime horizon.

5 The patient population, the intervention and choice of comparator

5.1 The medical condition and patient population

In Denmark, lung cancer is one of the most frequent cancer types. There are two subtypes of lung cancer, non-small cell lung cancer (NSCLC) and small cell lung cancer (SCLC). A total number of 4973 patients were registered with lung cancer in 2021, of which approximately 80% have NSCLC (1). Although lung cancer was historically more frequently diagnosed among men, in 2021, 51.8% of patients were women; the ratio has been gradually, but constantly, rising in the recent years (1).

Even though much progress has been made in optimizing the treatment of NSCLC, survival for patients with lung cancer is generally poor. Lung cancer is the highest leading cause of death among all cancers, accounting for almost 22% of cancer related mortality in 2020, and caused 1690 deaths among each group of men and women (14).

5.1.1 Survival by disease stage

The American Joint Committee on Cancer (AJCC) tumour-node-metastasis (TNM) staging system categorises patients with NSCLC into the stages of the disease which predict survival outcomes (further details in Appendix K). Clinical TNM (cTNM) staging involves primary clinical and imaging-based examination of the tumour and nodes, but pathological TNM (pTNM) staging is provided by the pathological examination of tumour following the surgical resection. Not all the patients grouped based on the cTNM staging are eligible for curative treatment, including factors beyond tumour classification. This is reflected in the lower survival probability of patients based on cTNM compared to patients based on the pTNM, who have undergone surgery with curative intent (Table 1). As such, stage per pTNM can be the more relevant indicator of OS for patients diagnosed with resectable, non-metastatic disease eligible for surgery.

Further, the differences in overall survival (OS) probability among the TNM based stages of the disease are associated with the extent of the disease at the time of diagnosis. Based on the data for cTNM staging reported in the Danish Lung Cancer Registry (DLCR) report, among the diagnosed lung cancer patients, 33.7% of the patients had stages IA-IIB, 8.4% had stage IIIA, and 55.9% of the patients had stages IIIB-IVB (TNM version 8) (1). Also, the same report showed that the 1-, 2-, and 5 years OS rates of NSCLC patients treated with curative oncologic treatments are 83.5%, 66.9%, and 32.8%, respectively. However, for patient treated with palliative care, the 1-, 2-, and 5-year OS rates drop to 42.7%, 23.1%, and 5.3%, respectively (1). The registry also reported that patients treated with adjuvant therapy (after surgery) have 1-, 2-, and 5 year OS rates of 91.4%, 80.6%, and 47.8% respectively (patients diagnosed in 2020, 2019, and 2016) (1). Table 2 shows 1-year overall survival rates of the Danish patients with lung cancer divided by different TNM staging groups (TNM version 8) (1), which further shows that patient with early stages of lung cancer show higher probability of survival when compared with later stages of lung cancer, both for cTNM and pTNM. The decrease in OS with increasing stage of disease reflects an increase in the risk of disease progression or recurrence.

Table 2: Survival probability of Danish patients diagnosed with different cTNM and pTNM stages of lung cancer (TNM version 8)

	IA	IB	IIA	IIB	IIIA	IIIB	IIIC	IVA	IVB
1-year survival rate in 2020, % (Based on cTNM staging)	92.5	87.4	74.5	80.5	68.4	58.4	50.4	46.7	25.7
1-year survival rate in 2020, % (Based on pTNM) staging)	95.4	95.1	86.9	92.9	87.0	90.9	50.0	75.0	76.5

Abbreviation: cTNM, Clinical tumour-node-metastasis based staging; pTNM, Pathological Tumour-Node-Metastasis staging
Notes: Bolded values reflect stages of patients who would be eligible for neoadjuvant treatment with nivolumab plus PDC.
Reference: (1)

5.1.1.1 Surgery rates

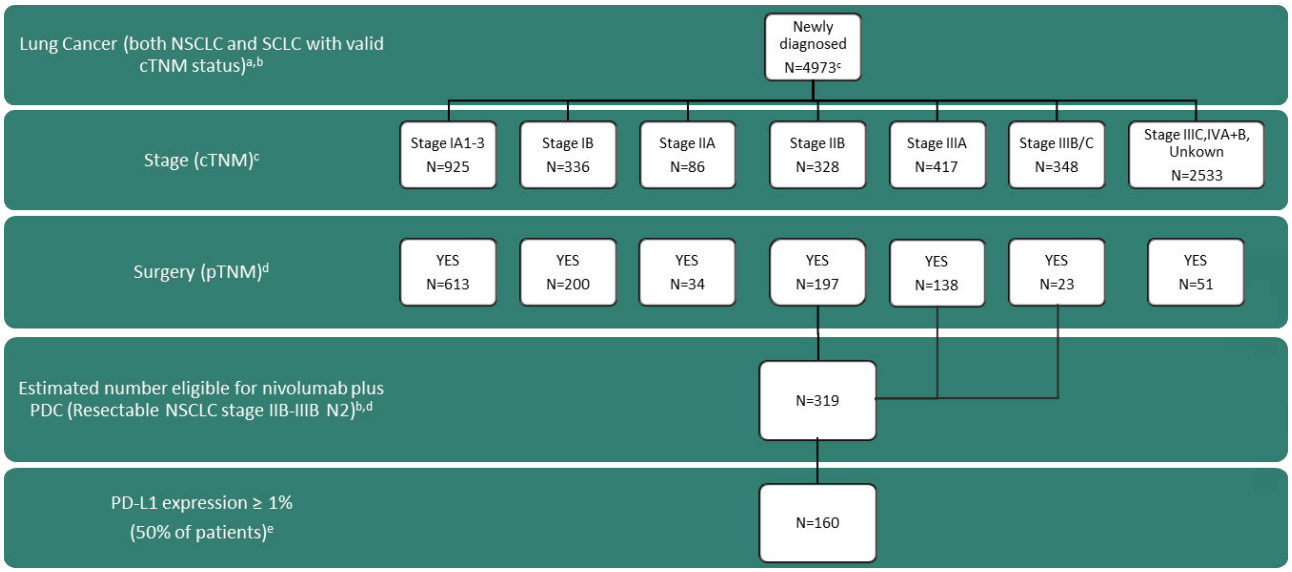
Surgery is the preferred treatment for all patients with resectable disease and who are able to tolerate surgery (15, 16). In Denmark, when patients are diagnosed with NSCLC, an overall evaluation by medical multi-disciplinary team (MDT)

is conducted to determine whether the disease is amenable to resection and whether the patient is deemed operable. The general consensus across guidelines is that surgery should be offered to all patients with disease amenable to surgery (16). Therefore, patients with stage I and II NSCLCs (TNM version 8) are treated primarily with curative surgery. In 2021, 1256 patients out of 4973 lung cancer patients (28.6%) in Denmark received lung cancer surgery (1). In 2021, minimally invasive techniques (i.e., video-assisted thoracoscopic surgery (VATS)) were accounted for 81.2% of lung cancer surgeries that were performed in Danish patients (1). The rates of using VATS surgery varied in different regions of the country ranging from 71% to 95% of all types of lung surgeries (1). Non-radically operated patients, with residual macroscopic or microscopic disease, may be offered a combination of adjuvant radiation therapy and medical oncology treatment.

5.1.2 Patient populations relevant for this application

It is estimated that approximately 160 Danish patients with resectable, non-metastatic, PD-L1 expression ≥ 1% NSCLC stages IIB-IIIB N2 (TNM version 8, equivalent to stage II-IIIA TNM version 7) are eligible to receive nivolumab plus PDC in the neoadjuvant setting. Figure 1 below shows the patients flow diagram in Denmark and illustrates how the number of eligible patients is estimated.

Figure 1: Patient flowchart for neoadjuvant NSCLC with PD-L1 expression ≥ 1% (IIB—IIIB N2, TNM version 8) in Denmark



Abbreviations: NSCLC, Non-small cell lung cancer; PDC, Platinum-double chemotherapy; SCLC, Small cell lung cancer
Notes:
[a] In 2021, 5004 lung cancer patients were diagnosed in Denmark of which 4100 cases were diagnosed with NSCLC. Source: Årsrapport 2021 – Dansk lunge cancer register – numbers from national pathology registry 2021, Tabel 5.3 page 57
[b] In 2021, 1256 Danish patients with lung cancer received surgery of which 1130 (i.e., 90%) were diagnosed with NSCLC. Source: Årsrapport 2021 – Dansk lunge cancer register – numbers from national pathology registry 2021, Tabel 7.2.6 page 126
[c] Årsrapport 2021 - Dansk lunge cancer register – numbers from national pathology registry 2021, Tabel 7.1.5.1 page 94, cTNM stadie I abslute tall
[d] Årsrapport 2021 – Dansk lunge cancer register – numbers from national pathology registry 2021, Tabel 7.2.4.2 page 113 pTNM – afdelinger, rad for "Denmark"
[e] Proportion of PD-L1 expressing population was sourced from publication by Forde 2022 (13)
Reference: (1, 17)

Table 3 provides the estimated number of Danish patients with resectable, non-metastatic, PD-L1 expression ≥ 1% NSCLC stages IIB-IIIB N2 (TNM version 8, equivalent to stage II-IIIA TNM version 7), who will be eligible to receive nivolumab plus PDC in the neoadjuvant setting in the period of time from Year 1 to Year 5. Of the approximately 160 Danish patients who were estimated to be eligible for neoadjuvant treatment annually, it is assumed that 75% of the patients (i.e., 120 patients) will accept and receive the treatment (18, 19).

Table 3: Estimated number of patients eligible for neoadjuvant treatment for NSCLC, PD-L1 expression ≥ 1% with nivolumab plus PDC in Denmark

Year from approval	Year 1	Year 2	Year 3	Year 4	Year 5
Number of patients in Denmark who are expected to use the nivolumab plus PDC in the coming years	120	120	120	120	120

Abbreviations: NSCLC, Non-small cell lung cancer; PDC, Platinum-double chemotherapy; TNM, Tumour-node-metastasis

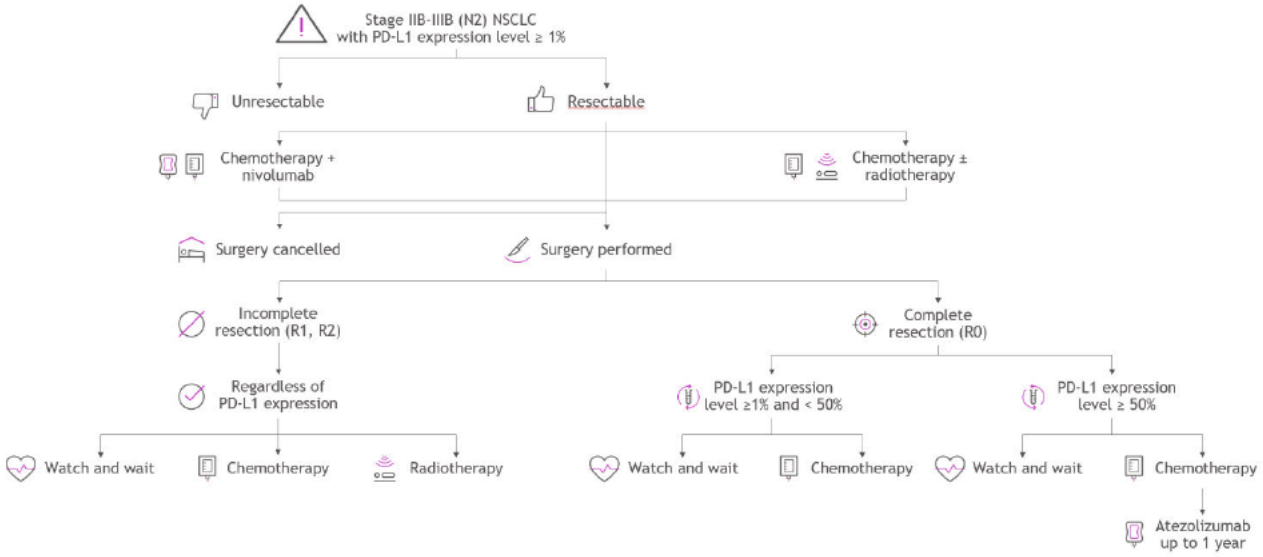
5.2 Current treatment options and choice of comparator

5.2.1 Danish treatment guideline

The Danish Lung Cancer Group's (DLCG) publishes the national guidelines for the treatment of lung cancer, with the latest update published in November 2022 (2).

According to the guidelines, management of NSCLC can involve a combination of surgery, radiotherapy (RT), platinum doublet chemotherapy (PDC), and chemoradiotherapy (CRT). Cure is the ultimate goal of therapy for resectable, non-metastatic disease, but can require a long duration of follow-up for patients receiving treatment and is influenced by subsequent therapies given following disease relapse. Figure 2 provides an overview of the proposed treatment pathway for patients diagnosed with NSCLC. Figure 2 considers that nivolumab plus PDC will become an option for neoadjuvant treatment of patients with resectable, PD-L1 expression ≥ 1%, non-metastatic NSCLC stages IIB-IIIB N2 (TNM version 8), as well as the possibility of patients with PD-L1 expression level >50% receiving adjuvant immunotherapy after adjuvant chemotherapy. This reflects atezolizumab as a potential adjuvant treatment option following complete resection and PDC for adult patients with NSCLC with a high risk of recurrence whose tumours have PD-L1 expression on ≥ 50% of tumour cells (TC) and who do not have EGFR mutant or ALK-positive NSCLC. Atezolizumab as post-adjuvant PDC treatment has recently (March 2023) been recommended by the Danish Medicines Council (DMC) (20), but this is not yet reflected in the latest clinical guidelines released in November 2022 (2). Due to notable differences between the market authorisation studies investigating atezolizumab and nivolumab plus PDC and their resulting EU labels, atezolizumab is not a suitable comparator in this submission. Please see Appendix O for further details.

Figure 2: Proposed algorithm of treatment options for newly diagnosed non-metastatic NSCLC with PD-L1 expression level ≥ 1% (TNM version 8)



Abbreviations: NSCLC, non-small cell lung cancer; PD-L1, Programmed cell death ligand 1; R, Resection

Reference: BMS developed the figure based on the national guidelines for the treatment of lung cancer (2) and assessment for atezolizumab (Tecentriq) by the Danish Medicines Council (20).

5.2.1.1 Surgery

Treatment options for patients with newly diagnosed non-metastatic NSCLC consider both the stage of disease and whether the tumour is resectable. Patients with non-metastatic NSCLC are treated with curative intent, e.g., surgery, to the extent possible (Figure 2).

As mentioned, in Denmark, the MDT team conducts the final assessment of patients with NSCLC and decides if patients are operable (2). Patients with NSCLC in stages I and II (TNM version 8) are assessed regarding lung and cardiac functionality (2). When postoperative lung function is less than 40%, the patients are not eligible for surgery. Also, the status of cardiac functionality would assess potential risks of possible cardiac interventions or optimization prior to surgery. The patients with NSCLC patients are also strictly recommended to avoid smoking and alcohol consumption.

The majority of resectable lung cancer patients receive minimal invasive surgery via the endoscopic-technique, video-assisted thoracoscopic surgery (VATS). The dominating type of surgery is lobectomy (83%) and a small number of patients receive pneumonectomy (<2%) (1). The number of patients receiving multimodal treatment is low and decreasing (21, 22).

According to the Danish Lung Cancer Registry report in 2021 (1), there is considerable variation between the national hospitals regarding the timeframe from diagnosis of lung cancer to surgery as the first-line (1L) of treatment. Moreover, more than one third of patients with stage I-II NSCLC (TNM version 8) wait more than 90 days from diagnosis to surgery as the 1L of treatment (1). See Table 4 for an overview of the recommended processing times from the time of referral to the time of surgery (23), and the actuals (1).

Table 4: Overview of course times for lung cancer

		Danish Health Authorities recommended timelines	Observed timelines in registry
Referral			
Time from received referral to first meeting at the oncology department		6 calendar days	
Investigation			
Time from first meeting at the oncology department to the finalisation of the investigation		24 calendar days	Patients receiving no treatment: 73.6% within 30 days Patients receiving any treatment: 72.5% within 30 days Patients receiving surgery: 60.6% within 30 days
Treatment initiation			
Time from the finalisation of the investigation to treatment initiation	Surgical treatment Medical treatment Radiation therapy	14 calendar days 11 calendar days 15 calendar days	
Total timeline			
Time from received referral to treatment initiation	Surgical treatment Medical treatment Radiation therapy	44 calendar days 41 calendar days 45 calendar days	From *diagnosis*: 61.5% within 90 days (Stage I-II NSCLC patients)

Note: NSCLC stages refer to TNM version 8.
References: (1, 23)

Surgery is the preferred treatment for all patients with resectable disease who are able to tolerate surgery (15, 16). However, data from the Danish lung cancer registry have shown that up to 40% of operated patients experience relapse of the disease and there is a need for further options to decrease this number (24).

5.2.1.2 Adjuvant and neoadjuvant treatment

After surgery, patients with stage I-III (TNM version 8) NSCLC tumours can be assessed for postoperative RT or CRT (Figure 2). Patients with stage II-III disease (TNM version 8) should be considered for postoperative (adjuvant) treatment with PDC (cisplatin plus vinorelbine). The DLCG treatment guidelines further recommended that patients with NSCLC who are evaluated to be candidates for minimal invasion surgery can be considered for preoperative (neoadjuvant) treatment with PDC (cisplatin/carboplatin plus vinorelbine) (2).

In 2021, on a Danish national level, the share of resectable lung cancer patients receiving adjuvant treatment was 22%, while patients receiving neoadjuvant treatment with the current option in Denmark, CRT, was only 3.3% (1). The understanding is that neoadjuvant treatments has not been routinely used for the treatment of resectable NSCLC due to:

(1) Similar effectiveness between neoadjuvant and adjuvant treatment, as supported by the meta-analyses by Lim and colleagues from 2009 (8) as well as within a randomised controlled trial (RCT) (9)
(2) Adjuvant chemotherapy has been considered easier to handle from an organisational perspective
(3) There is a larger number of evidence supporting the use of adjuvant therapy in patients with NSCLC (2)

However, neoadjuvant therapy may come with strategic treatment benefits and may be given with the goals of reducing the size of the tumour to facilitate resection, reducing the risk of recurrence post-surgery and, ultimately, prolonging survival. It is also the earliest opportunity to treat any micro-metastasis that are present. Also, from a practical standpoint, surgery can be delayed for non-disease related reasons and varies by regions. Therefore, neoadjuvant setting also provides an early treatment opportunity during potential lag time to surgery.

5.2.1.3 Treatment post-progression

For patients with NSCLC who progress to metastatic disease or are considered incurable, 1L palliative care would be considered. According to the DLCG guidelines, patients would be assessed for treatment options including thoracic palliative RT, chemotherapy, immunotherapy, depending on the patient's expression of PD-L1, the existence of activating mutations, or general health condition and performance status (2).

5.2.2 Choice of comparator

In the Danish treatment setting, the most relevant comparator for neoadjuvant treatment with nivolumab plus PDC is adjuvant PDC treatment. Based on the Danish treatment guidelines, combinations of cisplatin plus vinorelbine are recommended as adjuvant treatments. Carboplatin can be used to replace cisplatin in patients with intolerance to cisplatin, low general health condition, or with significant morbidities. Additionally, atezolizumab as a post-adjuvant PDC treatment has recently (March 2023) been recommended by the Danish Medicines Council (DMC) (20), but this is not yet reflected in the latest clinical guidelines released in November 2022 (2). As there were considerable differences between the market authorisation studies investigating atezolizumab and nivolumab plus PDC and their resulting EU labels, conducting a robust indirect treatment comparison (ITC) is not feasible. Please see Appendix O (section 27) for further details.

The pivotal trial, CheckMate 816, provides an in-trial comparison of neoadjuvant treatment with nivolumab plus PDC with neoadjuvant PDC. Based on the current literature, including a meta-analysis (8) and an RCT (9), adjuvant and neoadjuvant PDC were reported to have similar clinical efficacy in patients with resectable NSCLC (see Appendix N) (8,

9). Thus, the current application uses the direct comparison in CheckMate 816 where the comparator of neoadjuvant PDC will be used as a proxy for adjuvant PDC, which is in line with the Danish treatment guidelines that are in agreement with the equivalence statement (10).

Table 5 shows the chemotherapeutic agents which will be considered in the application.

5.2.3 Description of the comparator

An overview of adjuvant PDC in Danish clinical setting is presented in Table 5 (25). Cisplatin plus vinorelbine was one of the regimens used in the CheckMate 816 trial in the PDC alone treatment arm (6).

Table 5: Description of adjuvant PDC according to Danish treatment guidelines

Product description	
Active ingredient	Regimen 1: Cisplatin plus vinorelbine Regimen 2: Carboplatin plus vinorelbine
Pharmaceutical form	Concentrate for solution for infusion
Strength	Cisplatin 1 mg/ml Vinorelbin 10mg/ml Carboplatin 10 mg/ml
Recommended daily dose	Regimen 1: Cisplatin (75 mg/m^2 iv) on day 1 plus vinorelbine (30 mg/m^2 iv possibly 60 mg/m^2 po) on day 1 + day 8 Regimen 2: Carboplatin (900mg, AUC6) on the day 1 plus vinorelbine (30 mg/m^2 iv possibly 60 mg/m^2 po) on day 1 + day 8
Treatment length/criteria for termination of treatment	Every 3 weeks, for up to four cycles; within 6-8 weeks from the time of surgery
Requirements of diagnostics or other tests	N/A
Medically approved indication /-s	Please see summary of product characteristics (SmPC) for each product*

Abbreviations: iv, Intravenous; mg, Milligrams; ml, Millilitres; n/a, Not available; PDC, Platinum-double chemotherapy; SmPC, summary of product characteristics.
Adapted based on DLCG guideline 2022 (25); *SmPC available at Danish Medicines Agency and EMA (26-29).

5.3 The intervention

On 29 June 2023, the European Commission (EC) approved Opdivo (nivolumab) in combination with platinum-based chemotherapy for the neoadjuvant treatment of resectable NSCLC at high risk of recurrence in adult patients with tumour cell PD-L1 expression ≥1%.The selection criteria for patients with high risk of recurrence is reflective of a patient population with stage II-IIIA (TNM version 7): any patient with a tumour size ≥ 5 cm; any patient with N1 or N2 disease (regardless of primary tumour size); patients with multiple tumour nodules in either the same lobe or different ipsilateral lobes; patients with tumours that are invasive of thoracic structures; or tumours that involve the main bronchus; or tumours that are associated with atelectasis or obstructive pneumonitis that extends to the hilar region or involves the entire lung.

An overview of nivolumab plus PDC is presented in Table 6 below.

Table 6: Product description of nivolumab plus platinum-doublet chemotherapy

Product description	
Name of preparation/pharmaceutical	Nivolumab plus PDC
Active ingredient	Nivolumab plus PDC
Pharmaceutical form	Concentrate for solution for infusion
Strength	Nivolumab (10 mg/mL):

Product description	
	Single-use vials 40 mg/4 mL; 100 mg/10 mL; 120 mg/12 mL; 240 mg/24 mL
Recommended daily dose	Non-squamous NSCLC Nivolumab 360 mg every 3 weeks (30-minute IV infusion), for three cycles Chemotherapy Pemetrexed at a dose of 500 mg/m² (10 minutes IV infusion) plus Cisplatin at a dose of 75 mg/m² (120 minutes IV infusion) every 3 weeks, for three cycles Squamous NSCLC Nivolumab 360 mg every 3 weeks (30-minute IV infusion), for three cycles Chemotherapy Gemcitabine at a dose of 1000 mg/m² or 1250 mg/ m² (30 minutes IV infusion) on day 1 and day 8 of each cycle of treatment plus cisplatin at a dose of 75 mg/m² (120 minutes IV infusion) every 3 weeks, for three cycles Any histology Nivolumab 360 mg every 3 weeks (30-minute IV infusion), for three cycles Chemotherapy Paclitaxel 175 or 200 mg/m² (180 minutes IV infusion) plus carboplatin AUC 5 or 6 (30 minutes IV infusion) every 3 weeks, for three cycles
Should the intervention be used with other drugs?	No
Treatment length/criteria for termination of treatment	Nivolumab in combination with PDC every 3 weeks for three cycles
Required monitoring, under administration or during treatment period	Patients should be monitored continuously (at least up to 5 months after the last dose)
Requirements of diagnostics or other tests	Test to determine PD-L1 expression ≥1% to select patients according to label
Medically approved indications	See section 1

5.3.1 Mechanism of action

Nivolumab is a human immunoglobulin G4 (IgG4) monoclonal antibody, which binds to the programmed death-1 (PD-1) receptor and blocks its interaction with PD-L1/2. The PD-1 receptor is a negative regulator of T-cell activity that has been shown to be involved in the control of T-cell immune responses. Engagement of PD-1 receptor with the ligands PD-L1 and PD-L2, which are expressed in antigen presenting cells and may be expressed by tumours or other cells in the tumour microenvironment, results in inhibition of T-cell proliferation and cytokine secretion. Nivolumab potentiates T-cell responses, including anti-tumour responses, through blockade of PD-1 binding to PD-L1/2 ligands. In syngeneic mouse models, blocking PD-1 activity resulted in decreased tumour growth (30).

The current application concerns the indication for nivolumab in combination with PDC for the neoadjuvant treatment of resectable non-small cell lung cancer at high risk of recurrence in adult patients whose tumours have PD-L1 expression ≥ 1%, and with stage II – IIIA disease (TNM version 7). Evidence for the proof of concept of nivolumab in this setting comes from several different lines of study:

- Studies supporting the role of neoadjuvant chemotherapy in the management of resectable NSCLC
- Evidence for the importance of elimination of micro-metastases through neoadjuvant therapy for reducing the risk of relapse following surgery
- Evidence indicating that PD-(L)1 blockade provided by immunotherapy agents is expected to be particularly effective for eliminating micro-metastases, especially when used in presence of the primary tumour, i.e., in the neoadjuvant setting

- Evidence for immune-mediated effects of chemotherapy suggesting that combining chemotherapy with immunotherapy therapy is likely to further enhance the anti-tumour effects of immunotherapy

5.3.2 Pack size and price

The strength, pack size, and pharmacy purchase price (PPP) per pack for nivolumab are included in Table 7 below.

Table 7: The strength, pack size, and pharmacy purchasing price per pack in Denmark per May 2023.

Treatment	Strength	Pack size	Price per pack (PPP, DKK)
Nivolumab	10 mg/ml	4 ml	3508.46
	10 mg/ml	10 ml	8715.54
	10 mg/ml	12 ml	10 458.66
	10 mg/ml	24 ml	20 917.31

Abbreviations: PPP, pharmacy purchase price; DKK, Danish Kroner; VAT, Value added tax
Reference: (31)

6 Literature search and identification of efficacy and safety studies

BMS has not enclosed a systematic literature review (SLR) for this application, as the SLR is not expected to provide more relevant information than the direct clinical trial, CheckMate 816. The CheckMate 816 trial compares nivolumab plus PDC versus PDC in the neoadjuvant setting. Since the efficacy of PDC is expected to be similar in the adjuvant and neoadjuvant settings, the direct comparison from CheckMate 816 is used to assess the efficacy of nivolumab plus PDC versus PDC alone. Neoadjuvant PDC is considered a relevant proxy for the main Danish comparator: adjuvant PDC. As mentioned in Section 5.2.2, adjuvant and neoadjuvant PDC have already been shown to provide similar clinical efficacy in patients with resectable NSCLC (8, 9), which is acknowledged in the Danish treatment guideline (2). Because the neoadjuvant PDC treatment arm in CheckMate 816 is a known equivalent to the main comparator, adjuvant PDC, the SLR is redundant for this application.

A list of ongoing non-randomised studies on neoadjuvant therapy with nivolumab plus PDC is presented in Table 85 in Appendix L. In addition, the peri-operative trials NADIM (32) and NADIM II (33, 34) are listed here. The neoadjuvant part of the treatment mirrors the CheckMate 816 and therefore the outcomes up to and including the surgical outcomes could be considered supportive to this application. However, as the intervention in the NADIM trials also include adjuvant nivolumab, the EFS and OS results should be interpreted with caution, and the intervention differs for CheckMate 816.

7 Efficacy and safety

7.1 Efficacy and safety of nivolumab plus PDC compared to PDC alone for neoadjuvant treatment of patients with NSCLC

7.1.1 Relevant studies

7.1.1.1 CheckMate 816

In compliance with DMC submission template, the main study characteristics for CheckMate 816 are summarised in Appendix B.

7.1.1.1.1 Study design

CheckMate 816 is an ongoing, randomised, open-label, phase 3 trial of Nivolumab plus PDC versus PDC alone as neoadjuvant treatment for resectable (stage IB [≥4 cm], stage II, or stage IIIA, TNM version 7) NSCLC (6, 7). The trial was originally designed to compare nivolumab plus ipilimumab versus PDC. However, during the course of the study, external data from the KEYNOTE-021 study in metastatic NSCLC (35) and from a single-arm studies in resectable NSCLC, NADIM I (32) and NADIM II (33, 34), highlighted promising results with immunotherapy plus PDC. Both trials have shown that neoadjuvant nivolumab plus PDC provided a marked improvement in pCR compared to historical controls (32, 33). Therefore, a nivolumab plus PDC group was added to CheckMate 816 in 2017, as part of the primary analysis, along with nivolumab plus ipilimumab. In 2018, based on the evolving external data becoming available during the conduct of the study, a decision was made to close enrolment into the nivolumab plus ipilimumab group prematurely in order to accelerate enrolment to the nivolumab plus PDC group. BMS remained blinded to the study results while taking this decision. The primary analysis became nivolumab plus PDC vs PDC alone (contemporaneously randomised population) and the nivolumab plus ipilimumab group became exploratory with no formal comparison to either PDC alone or nivolumab plus PDC groups.

According to the final protocol, patients were thus randomised 1:1 to neoadjuvant nivolumab plus PDC or PDC alone (Figure 3). Eligible patients were stratified by PD-L1 expression (≥1% or <1%/not evaluable/indeterminate), disease stage (IB–II vs IIIA, TNM version 7), and gender (13).

[redacted]

Abbreviations: ALK, Anaplastic Lymphoma Kinase; BICR, blinded independent central review; BIPR, blinded independent pathological review; PDC, chemotherapy; ctDNA, circulating tumour DNA; ECOG, Eastern Cooperative Group; EFS, event-free survival; EGFR, epidermal growth factor receptor; IHC, immunohistochemistry; IPI, ipilimumab; MPR, major pathological response; NIVO, nivolumab; NSCLC, non-small cell lung cancer; NSQ, non-squamous; ORR, overall response rate; OS, overall survival; pCR, pathological complete response; PD-L1, programmed cell death protein ligand 1; Q2W,

every 2 weeks; Q3W, every 3 weeks; RT, radiotherapy; SAE, serious adverse event; SQ, squamous; TMB, tumour mutational burden; TNM, tumour-node-metastasis cancer staging system.
Notes:
[a] NCT02998528;
[b] Determined by the PD-L1 IHC 28-8 pharmDx assay (Dako).
[c] Included patients with PD-L1 expression status not evaluable and indeterminate.
[d] NSQ: pemetrexed + cisplatin or paclitaxel + carboplatin; SQ: gemcitabine + cisplatin or paclitaxel + carboplatin.
[e] Vinorelbine + cisplatin, docetaxel + cisplatin, gemcitabine + cisplatin (SQ only), pemetrexed + cisplatin (NSQ only), or paclitaxel + carboplatin.
[f] During the early stages of conducting the study, a decision was made to close enrolment into the nivolumab plus ipilimumab group prematurely in order to accelerate enrolment to the nivolumab plus PDC group. This arm of the trial is not part of the scope for the current dossier.
H Performed using tumour-guided personalized ctDNA panel (ArcherDX Personalized Cancer Monitoring)
Reference: (6)

Patients were randomised 1:1 to receive nivolumab plus PDC or PDC alone; both regimens were given in 3-week cycles up to a maximum of three cycles (see Table 77 in Appendix C for further details of the PDC). PDC doses could be reduced or delayed, or a specific drug could be discontinued, if necessary, for toxicity. The nivolumab dose could also be delayed but no dose modifications were permitted.

Following the completion of neoadjuvant treatment, patients were to undergo definitive surgery for NSCLC within 6 weeks of completing neoadjuvant treatment. Following definitive surgery, patients could receive up to four cycles of adjuvant PDC, with or without radiotherapy (RT), per institutional standard therapy and at the discretion of the investigator.

7.1.1.1.2 Assessment and endpoints

Baseline assessments were performed during the screening visit and included: collection of a tumour sample (unless already collected within 3 months), lymph node sampling, a positron emission tomography/CT scan and safety assessments. During and following the neoadjuvant treatment period, tumour assessments were performed using CT scans of the chest including adrenal glands and CT or MRI scans of other additional suspected/known sites of disease. The first tumour assessment was to occur 12 weeks (±7 days) after definitive surgery and further assessments were to be performed every 12 weeks (±7 days) for up to 2 years (104 weeks). Responses were determined by central review of scans. Tissue samples were collected from definitive surgical resection for pathological response assessments. Health related quality of life was to be assessed on day 1 of every treatment cycle and every 3 months after the third dose of neoadjuvant therapy for 1 year and then once every 6 months thereafter using the EuroQol-5 dimension/level 3.

The study had two independent primary endpoints, following the initial revisions to the protocol; EFS and pCR. Secondary endpoints included OS, MPR and TTDM. Definitions for the primary, secondary and key exploratory endpoints are summarised in Appendix B. Tumour mutational burden (i.e., the number of somatic mutations per million bases of interrogated genomic sequence in the tumour) and circulating tumour DNA (ctDNA) were also measured to assess their potential as predictive biomarkers.

7.1.1.1.3 Patients baseline characteristics

A total of 358 patients were randomised 1:1 to the two treatment groups. Baseline demographics and disease characteristics for all concurrently randomised patients were balanced across the treatment groups for the intention-to-treat (ITT), the PD-L1 expression ≥ 1% subgroup and the label population with PD-L1 expression ≥ 1% with stage II – IIIA (TNM version 7) (see Table 74, Table 75, and Table 76, respectively, in Appendix C for details of baseline characteristics). Patients with PD-L1 ≥ 1%, stage II – IIIA (TNM version 7) had a median age of 64.0 years and 65.5 years in the nivolumab plus PDC and the PDC alone groups, respectively; 72–77% were men. Fifty-six to 57% of patients were from Asia, and 69.1% and 65.1% of patients had stage IIIA (TNM version 7) disease in the nivolumab plus PDC and the PDC alone groups, respectively, at study entry. The majority of patients (72–73%) had an ECOG performance status of 0 and the remainder (27–28%) had a PS of 1. From 53% to 55% of patients had squamous cell carcinoma and approximately 90% of patients were current or former smokers.

7.1.1.1.4 Patient disposition

In total, in the ITT population, 176 patients (98%) in each group received neoadjuvant therapy. The rate of completion of the three cycles of neoadjuvant therapy was numerically greater in the nivolumab plus PDC group compared to the PDC group (93% and 85%, respectively). In both groups, a similar percentage of patients discontinued neoadjuvant therapy due to study drug toxicity (nivolumab plus PDC, 6%; PDC alone, 7%). One patient in the nivolumab group and two in the PDC group discontinued due to disease progression (1% in each group). Other reasons for not completing neoadjuvant treatment were mainly reported in the PDC alone group. Only one patient in nivolumab plus PDC group did not complete the treatment due to AE unrelated to study drug, while 13 patients in PDC alone group did not complete the treatment due to other reasons, which include AE unrelated to study drug, patient request to discontinue treatment, patient's withdrawal of consent, and patient no longer meeting study criteria (Table 8). Following definitive surgery, patients in each treatment arm may have received adjuvant chemotherapy, radiation, or both, per institutional standard and local clinical practice at the discretion of the investigator. Any subsequent therapy was received by 21.2% in the nivolumab plus PDC arm and 43.6% in the PDC alone arm; subsequent systemic therapy rates were 17.3% and 36.3%, respectively (Table 86). Reasons for the administration of adjuvant treatment to patients were not captured in the CheckMate 816 trial.

Table 8: Patient disposition in CheckMate 816, ITT population

	Nivolumab plus PDC (n=179)	PDC alone (n=179)
Patients who received neoadjuvant treatment, n (%)	176 (98.3)	176 (98.3)
Reason off neoadjuvant treatment[a], n (%)		
Completed (three cycles)	164 (93.2)	149 (84.7)
Study drug toxicity	10 (5.7)	12 (6.8)
Disease progression	1 (0.6)	2 (1.1)
Other[b]	1 (0.6)	13 (7.4)
Patients receiving adjuvant treatment[c], n (%)	35 (19.9)	56 (31.8)
Chemotherapy (≤four cycles) alone	21 (11.9)	39 (22.2)
Radiotherapy	9 (5.1)	12 (6.8)
Chemotherapy and radiotherapy	5 (2.8)	5 (2.8)

Abbreviations: AE, adverse event; ITT, Intent-to-treat; PDC, Platinum doublet chemotherapy
Database lock October 14, 2022; Minimum/median follow-up: 32.9/41.4 months.
Notes:
[a] Based on patients not continuing in the neoadjuvant treatment period (n = 176 in each arm)
[b] Other reasons include adverse event unrelated to study drug, patient request to discontinue treatment, patient withdrew consent, and patient no longer meeting study criteria
[c] Denominator based on patients receiving neoadjuvant treatment
Reference: (36) and Supplemental appendix table S2 (13).

7.1.2 Efficacy and safety – results per study

7.1.2.1 CheckMate 816

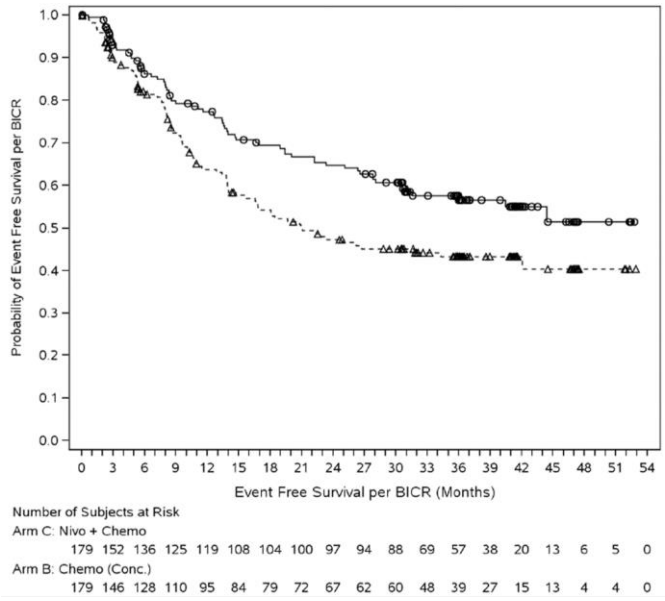
A summary of efficacy data for CheckMate 816 is presented in Appendix D. Results are focused on data from the latest data cut, October 2022 (median follow-up time of 41.1 months, minimum follow-up of 32.9 months); additional results are presented from the previous October 2021 data cut (median follow-up of 29.5 months, minimum follow-up of 21 months) when they were not captured in the October 2022 data cut disclosure.

Further, the EMA requested post-hoc, exploratory analyses during the late stages of the regulatory process, which resulted in the patient population restriction in PD-L1 expression ≥1% and stage II – IIIA disease (TNM version 7). As such, only limited analyses have been performed on the various primary, secondary, and other exploratory endpoints with respect to the patient population, and, thus, some endpoint analyses were unavailable (e.g., ORR and completeness of resection).

7.1.2.1.1 Event-free survival

In the ITT population, the addition of nivolumab to PDC was associated with a statistically significant and clinically meaningful increase in EFS, defined as the length of time from randomisation to any of the following events: any progression of disease precluding surgery, progression, or recurrence of disease (based on BICR assessment per RECIST 1.1) after surgery, or death due to any cause. Patients who did not undergo surgery for a reason other than progression were considered to have an event at RECIST 1.1 progression (based on BICR) or death. At the October 2022 data cut, the median EFS in the primary analysis population was not reached for nivolumab plus PDC treatment group while reported as 21.1 months for PDC alone group (hazard ratio [HR] 0.68, 95% confidence interval [CI] 0.49–0.93) (Figure 4). The EFS rates for nivolumab plus PDC and PDC alone were 77% versus 64% at 12 months, 65% versus 47% at 24 months, and 57% versus 43% at 36 months, respectively (12).

Figure 4: Primary endpoint: EFS[a,b,c,d,e] with neoadjuvant nivolumab plus PDC vs PDC alone in CheckMate 816, ITT population (October 2022)



Abbreviations: BICR, Blinded independent central review; Chemo, Chemotherapy; CI, confidence interval; EFS, Event-free survival; HR, Hazard ratio; ITT, Intent-to-treat; Mo, Months; NIVO, Nivolumab; NA, Not reached; PDC, Platinum doublet chemotherapy

Note:

[a] EFS was defined as the length of time from randomisation to any of the following events: any progression of disease precluding surgery, progression or recurrence of disease (based on BICR assessment per RECIST 1.1) after surgery, or death due to any cause. Patients who did not undergo surgery for a reason other than progression were considered to have an event at RECIST 1.1 progression (based on BICR) or death

[b] Hazard ratio (95% CI) for nivolumab plus PDC versus PDC alone group was 0.68 (0.49–0.93).

[c] Median EFS was not reached vs 21.06 months, for nivolumab plus PDC vs PDC alone group, respectively.

[d] The EFS rates for nivolumab plus PDC and PDC alone were 77% versus 64% at 12 months, 65% versus 47% at 24 months 57% (95% CI: 48-64) versus 43% (35-51) at 36 months.

[e] The number of events for nivolumab plus PDC was 69/179, median months and 95% CI: N.A. (31.57, N.A.), compared to PDC alone: 88/179, median months and 95% CI: 21.06 (14.75, 42.09).

Reference: (11)

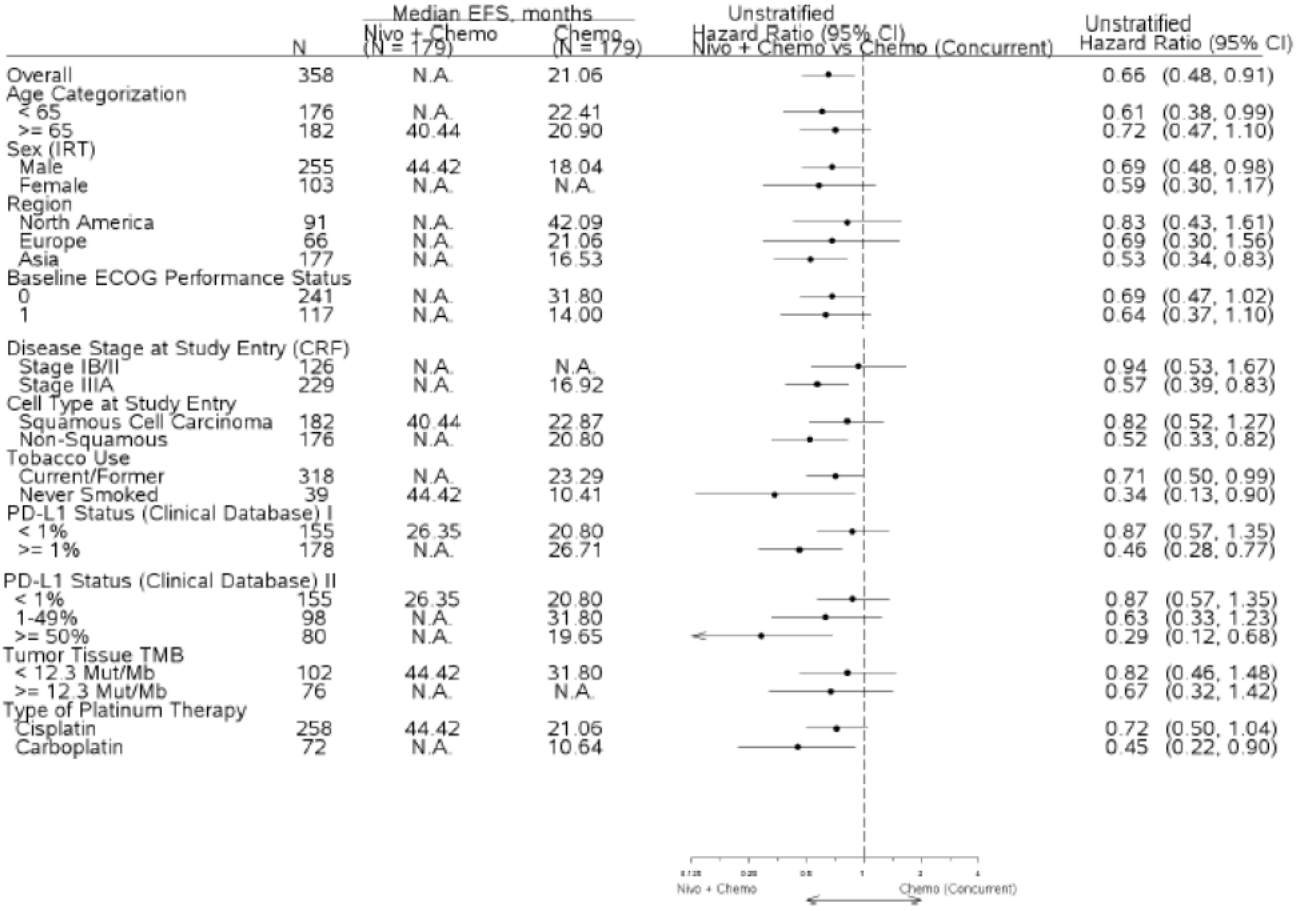
Although CheckMate 816 was not powered for subgroup analyses, at the October 2022 data cut, exploratory analysis of most key subgroups favoured nivolumab plus PDC (Figure 5). As the following EFS subgroup analyses are descriptive and exploratory in nature they should be interpreted with caution.

At the October 2022 data cut the magnitude of EFS benefit was greater in patients with stage IIIA disease (median EFS NR vs 16.9 months for nivolumab plus PDC vs PDC alone; HR: 0.57, 95% CI: 0.39–0.83) relative to stage IB–II disease (TNM version 7). Median EFS was not reached in either group (HR: 0.94, 95% CI: 0.53–1.67), although a lower proportion of events had been observed in the latter subgroup (see Figure 5 and Figure 55 in Section 28 Appendix P).

At the October 2021 data cut, exploratory analysis from CheckMate 816 shows an association between improvements in pCR and prolonged EFS (HR=0.13 for nivolumab plus PDC for patients who achieved pCR vs. those who did not), further supporting pCR as an early indicator of improvement of EFS and OS with longer follow-up. Notably, nearly two-thirds of patients in CheckMate 816 study had stage IIIA disease, representing a population with poor prognosis. Longer

follow-up may be needed to capture the clinical benefits of neoadjuvant therapy in patients with stage IB-II disease who have a more favourable prognosis (13).

Figure 5: EFS[a] with nivolumab plus PDC vs PDC alone in predefined patient subgroups in CheckMate 816 (October 2022)



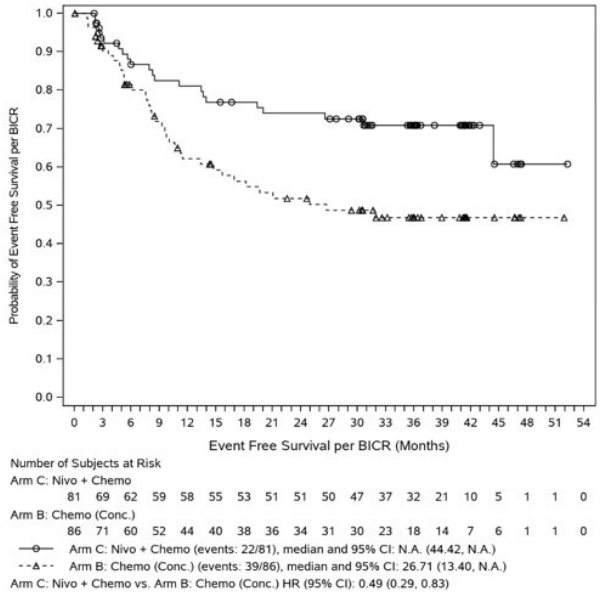
Abbreviations: BICR, Blinded independent central review; CI, confidence interval; ECOG PS, Eastern Cooperative Oncology Group performance-status score; HR, hazard ratio, mut/Mb, mutations per megabase; NR, not reached; PDC, Platinum doublet chemotherapy; PD-L1, programmed death ligand 1; RECIST, Response Evaluation Criteria in Solid Tumours; TMB, tumour mutational burden.
Note:
[a] EFS was per BICR and was defined as length of time from randomisation to any of the following events: any progression of disease precluding surgery, progression or recurrence of disease after surgery (based on BICR assessment per RECIST 1.1), progression without surgery, or death due to any cause; patients who received subsequent therapy were censored at the last evaluable tumour assessment on or prior to the date of subsequent therapy.
Reference: Figure 28 in the Assessment Report (11)

At the October 2022 data cut, the EFS benefit was also greater in patients with tumour PD-L1 expression ≥1% compared with PD-L1 expression <1%. Median EFS for patients with PD-L1 expression ≥1% was not reached vs 26.7 months (HR: 0.46, 95% CI: 0.28–0.77) and for patients with PD-L1 expression <1% was 26.4 vs 20.8 months (HR: 0.87, 95% CI: 0.57–1.35), for nivolumab plus PDC vs PDC alone, respectively. Similarly, the EFS benefits were greater in patients with PD-L1 expression ≥50% versus PD-L1 expression between 1% and 49% (see Figure 5 and Figure 56 in Section 28 Appendix P). Please note that the patients were only stratified by study design for PD-L1 <1% and PD-L1 ≥1% (12).

EFS in patients with tumour PD-L1 expression ≥1%, stage II – IIIA per TNM version 7

At the October 2022 data cut, the median EFS for patients with PD-L1 expression ≥1%, stage II – IIIA (TNM version 7), in the nivolumab plus PDC group was not reached (95% CI: 44.42–NA) vs 26.71 months (95% CI: 13.40–NA) in the PDC alone group (HR: 0.49, 95% CI: 0.29–0.83) (Figure 6) (11). See Section 29.1 Appendix Q for considerations in EFS outcomes between the tumour PD-L1 expression ≥1% for all stages vs stage II – IIIA (TNM version 7) patient populations.

Figure 6: EFS in patients with PD-L1 expression ≥1%, stage II – IIIA (TNM version 7) (October 2022)



Abbreviations: BICR, Blinded independent central review; Chemo, Chemotherapy; CI, confidence interval; EFS, event-free survival; HR, hazard ratio; Mo, months; NA, not available; Nivo, Nivolumab; PD-L1, programmed death ligand 1.

Notes:

* Statistical model for hazard ratio: unstratified Cox proportional hazard model. Symbols represent censored observations.

** The number of events for nivolumab plus PDC was 22/81, median months and 95% CI: N.A. (44.42, N.A.), compared to PDC alone: 39/86, median months and 95% CI: 26.71 (13.40, N.A.).

Source: (11)

7.1.2.1.2 EFS2

At the October 2022 data cut, in the ITT population, nivolumab plus PDC was associated with an improved EFS2 (defined as time from randomisation to objectively documented progression, per investigator assessment, after the next line of therapy or to death from any cause, whichever occurred first; patients without documented progression on the next line who started a second next line of subsequent therapy were considered to have had an event at the start of second next line of therapy), showing potential for long-term benefit (HR: 0.64, 95% CI: 0.45–0.91). The median EFS was not reached in either group (Figure 57) (11).

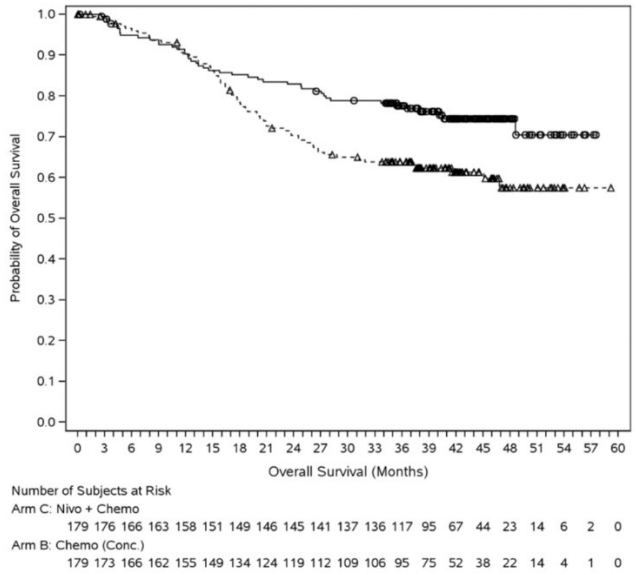
EFS2 in patients with tumour PD-L1 expression ≥1%, stage II – IIIA per TNM version 7

At the October 2022 data cut, the median EFS2 for patients with PD-L1 expression ≥1%, stage II – IIIA (TNM version 7) was not reached for either nivolumab plus PDC (95% CI: NA–NA) nor PDC alone (95% CI: 29.08–NA) groups (HR: 0.43, 95% CI: 0.22–0.83) (11).

7.1.2.1.3 Overall survival

At the October 2022 data cut, for the ITT population, a prespecified interim analysis for OS resulted in a HR of 0.62 (95% CI: 0.42–0.90), demonstrating an encouraging early trend in OS (at this prespecified interim analysis, OS did not cross the boundary of statistical significance [0.0124]). Median OS was not reached in both nivolumab plus PDC and PDC groups and the 3-year OS rates were 78% and 64%, respectively (Figure 7) (12). Continued follow-up is required for OS data to mature.

Figure 7: OS in CheckMate 816, ITT population (October 2022)

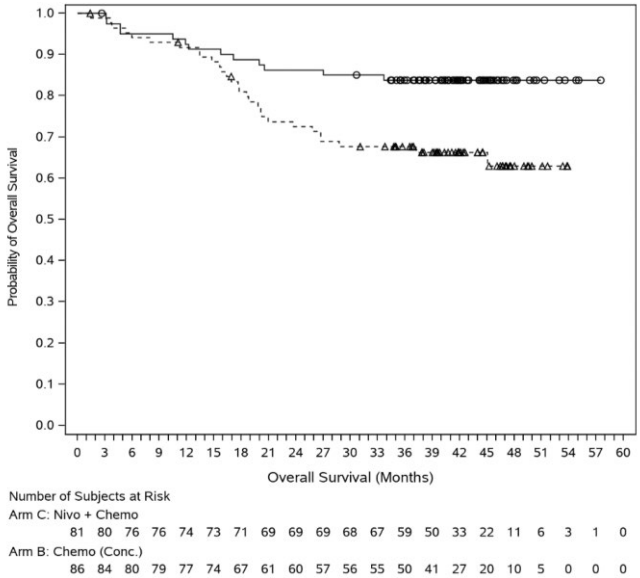


Abbreviations: CI, confidence interval; HR, hazard ratio; ITT, Intent-to-treat; Mo, months, N.A, Not available
Notes:
* OS rate for nivolumab plus PDC and PDC, respectively, following months: 12 months, 90% and 90%; 24 months, 83% and 70%; 36 months, 78% (95% CI: 71–83%) and 64% (95% CI: 56–70%).
** The number of events for nivolumab plus PDC was 44/179, median months and 95% CI: N.A., compared to PDC alone: 67/179, median months and 95% CI: N.A, (46.78, N.A.).
The stratified OS HR is: 0.62 (95% CI: 0.42, 0.90)
Reference: (11)

OS in patients with tumour PD-L1 expression ≥1%, stage II – IIIA per TNM version 7

At the October 2022 data cut, the median OS for patients with PD-L1 expression ≥1%, stage II – IIIA (TNM version 7) was not reached (95% CI: NA—NA) for neither nivolumab plus PDC or PDC alone groups (HR: 0.43, 95% CI: 0.22–0.83; Figure 8) (11). See Section 29.2 Appendix Q for considerations in OS outcomes between the tumour PD-L1 expression ≥1% for all stages vs stage II – IIIA (TNM version 7) patient populations.

Figure 8: OS in patients with PD-L1 expression ≥1%, stage II – IIIA (TNM version 7) (October 2022)

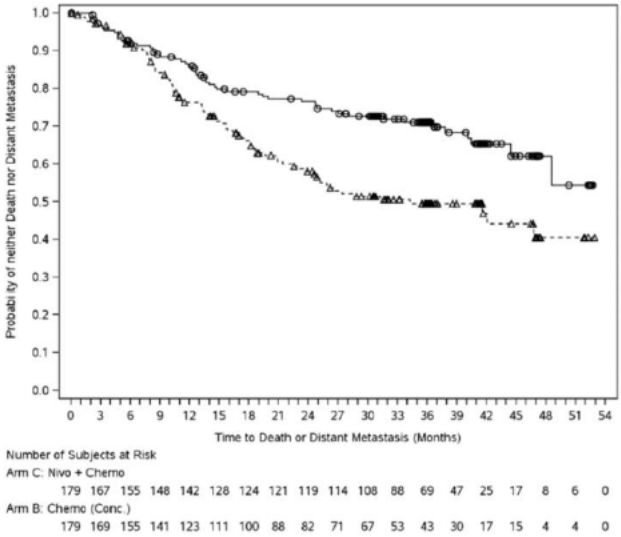


Abbreviations: BICR, Blinded independent central review; Chemo, Chemotherapy; CI, confidence interval; HR, hazard ratio; NA, not available; Nivo, Nivolumab; PD-L1, programmed death ligand 1; OS, Overall survival
Notes:
*Statistical model for hazard ratio: unstratified Cox proportional hazard model. Symbols represent censored observations.
** The number of events for nivolumab plus PDC was 13/81, median months and 95% CI: N.A., compared to PDC alone: 29/86, median months and 95% CI: N.A.
Source: (11)

7.1.2.1.4 Time to death or distant metastases

At the October 2022 data cut, for the ITT population, nivolumab plus PDC was associated with an increase in TTDM compared to PDC alone; median TTDM was not reached in the nivolumab plus PDC group versus 34.3 months in the PDC alone group (HR: 0.55, 95% CI: 0.39–0.78, Figure 9) (11).

Figure 9: TTDM[a,b,c,d] of nivolumab plus PDC vs PDC alone in CheckMate 816 , ITT population (October 2022)



Abbreviations: Chemo, Chemotherapy; CI, confidence interval; HR, hazard ratio; ITT, Intent-to-treat; mo, months; NIVO, nivolumab; NA, not reached; pCR, pathological complete response; PDC, Platinum doublet chemotherapy; TTDM, time to death or distant metastases

[a] Hazard ratio (95% C]) for nivolumab plus PDC versus PDC alone group was 0.55 (0.39–0.78).

[b] Median TTDM was not reached vs 34.3 months, for nivolumab plus PDC vs PDC alone group, respectively.

[c] The TTDM rates for nivolumab plus PDC and PDC alone were 86% versus 76% at 12 months, 77% versus 58% at 24 months 71% (95% CI: 63-77) versus 50% (41-57)at 36 months.

[d] The number of events for nivolumab plus PDC was 53/179, median months and 95% CI: N.A. (48.59, N.A.), compared to PDC alone: 82/179, median months and 95% CI: 34.27 (23.56, N.A).

Reference: (11)

TTDM in patients with tumour PD-L1 expression ≥1%, stage II – IIIA per TNM version 7

At the October 2022 data cut, the median TTDM for patients with PD-L1 expression ≥1%, stage II – IIIA (TNM version 7) was not reached for either nivolumab plus PDC (95% CI: 44.42–NA) nor PDC alone groups (95% CI: 18.83–NA) (HR: 0.40, 95% CI: 0.22–0.72) (11).

7.1.2.1.5 Objective response and downstaging

At the October 2021 data cut, for the ITT population, the radiographic objective response rate prior to definitive surgery was numerically higher with nivolumab plus PDC than with PDC alone (Table 9). Additionally, a numerically higher proportion of patients achieved radiographic downstaging (i.e., lower disease stage prior to surgery vs. baseline) in the nivolumab plus PDC group than in the PDC group (31% vs 24%, [redacted] (6).

Table 9: Objective response rate for patients treated with nivolumab plus PDC and PDC alone in CheckMate 816, ITT population (October 2022)

Patients, n (%)	Nivolumab plus PDC (n = 179)	PDC alone (n = 179)
Objective response rate (%)[ab]	96 (53.6)	67 (37.4)
Best overall response	96 (53.6)	67 (37.4)
Complete response	1 (0.6)	3 (1.7)
Partial response	95 (53.1)	64 (35.8)
Stable disease	70 (39.1)	88 (49.2)
Progressive disease	8 (4.5)	11 (6.1)
Not evaluable	1 (0.6)	1 (0.6)
Not reported	4 (2.2)	12 (6.7)

Abbreviations: CI, confidence interval; ITT, Intent-to-treat; NIVO, nivolumab; PDC, Platinum doublet chemotherapy
Notes:
[a] Objective response rate was assessed up to the presurgical scan.
[b] ORR rates 95% CI: NIVO plus PDC, 46-61; PDC alone, 30-45.
Reference: Supplemental appendix table S10 (13)

[redacted]

Abbreviations: ChT, chemotherapy; ITT, Intent-to-treat; NIVO, nivolumab
Note:
[a] Decrease in stage from baseline to presurgical scan
Reference: (6)

7.1.2.1.6 Surgical outcomes

Results for the ITT population from the October 2021 data cut show that neoadjuvant intervention with nivolumab plus PDC maintained the feasibility of surgery. Overall, a numerically higher proportion of patients underwent definitive surgery in the nivolumab plus PDC group compared to the PDC group (83% vs 75%, respectively, Table 10). Overall, the proportion of patients that had definitive surgery cancelled in the nivolumab plus PDC group was 16%, compared to 21% in the PDC group (Table 10). The reasons for cancellation were similar in the two groups with disease progression being the main reason, accounting for almost half of cancellations (Table 11). Rates of delayed definitive surgery were also similar in both groups (21% vs 18%) with the main cause being administrative reasons for the nivolumab plus PDC group (in more than half of patients) and AEs in the PDC group (more than a third of patients) (6).

Furthermore, minimally invasive surgery rates were 30% and 22%, and conversion from minimally invasive to open surgery rates were 11% and 16% for the nivolumab plus PDC group and PDC group, respectively. A numerically higher proportion of patients in the nivolumab group underwent lobectomy compared with the PDC group (77% vs 61% respectively) and fewer patients in the nivolumab group underwent pneumonectomy compared to the PDC group (complete removal of one lung, 17% vs 25%) (see Table 10) (6).

In addition, the rates of R0 resection (no microscopic disease) were 83% for the nivolumab plus PDC group and 78% for the PDC group, amongst patients undergoing surgery. The median number of lymph nodes dissected was similar between treatment groups (19.0, interquartile range [IQR]; 12–25 for nivolumab plus PDC and 18.5, IQR; 10–26 for PDC) (6).

The median duration of surgery was shorter for the nivolumab plus PDC group compared to the PDC group (185 vs 214 minutes, respectively). The length of hospital stay was also similar in both groups (median 10 days for both, Table 10), regardless of baseline disease stage (6).

Median (IQR) time from last neoadjuvant dose to definitive surgery was 5.3 (4.6–6.0) weeks with nivolumab plus PDC and 5.0 (4.6–5.9) weeks with PDC for all patients with definitive surgery.

Table 10: Surgical outcomes in CheckMate 816, ITT population (October 2022)

	Nivolumab plus PDC (N = 179)	PDC alone (N = 179)
Patients with definitive surgery[a] — no. (%)	149 (83.2)	135 (75.4)
Time from last neoadjuvant dose to definitive surgery — week	5.3 (4.6–6.0)	5.0 (4.6–5.9)
Median (IQR)		
Patients with cancelled definitive surgery — no. (%)	28 (15.6)	37 (20.7)
Disease progression	12 (6.7)	17 (9.5)
Adverse event	2 (1.1)	1 (0.6)
Other[b]	14 (7.8)	19 (10.6)
Patients with delayed surgery[c,d] — no. (%)	31 (20.8)	24 (17.8)
Administrative reason	17 (11.4)	1 (5.9)
Adverse event	6 (4.0)	1 (6.7)
Other	8 (5.4)	7 (5.2)
Length of delay in surgery — weeks		
Median (IQR)	2.0 (0.6–3.0)	2.4 (1.0–3.7)
Of patients with delayed surgery, proportion no. (%)		
with delay of[e]		
≤2 week	17 (54.8)	11 (45.8)
>2 and ≤4 weeks	8 (25.8)	8 (33.3)
>4 and ≤6 weeks	3 (9.7)	2 (8.3)
>6 weeks	3 (9.7)	3 (12.5)
Duration of surgery[f] — min		
Median (IQR)	185.0 (133.0–260.0)	213.5 (150.0–283.0)
Surgical approach[d] — no. (%)		
Thoracotomy	88 (59.1)	85 (63.0)
Minimally invasive[g]	44 (29.5)	29 (21.5)
Minimally invasive to thoracotomy	17 (11.4)	21 (15.6)
Type of surgery[d,h] — no. (%)		
Lobectomy	115 (77.2)	82 (60.7)
Sleeve lobectomy	2 (1.3)	10 (7.4)
Bilobectomy	3 (2.0)	4 (3.0)
Pneumonectomy	25 (16.8)	34 (25.2)
Other	24 (16.1)	21 (15.6)
Completeness of resection[d] — no. (%)		
R0 (no residual tumour)	124 (83.2)	105 (77.8)
R1 (microscopic residual tumour)	16 (10.7)	21 (15.6)
R2 (macroscopic residual tumour)	5 (3.4)	4 (3.0)
Rx (unknown)	4 (2.7)	5 (3.7)
Sampled lymph nodes — median (IQR)	19 (12–25)	18.5 (10–26)
Median length of hospital stay — days (IQR)	10.0 (7.0–14.0)	10.0 (7.0–15.0)
Median length of hospital stay by surgery type — days (IQR)	10.0 (7.0–15.0)	9.0 (6.0–14.0)
Lobectomy		
Pneumonectomy	10.0 (8.0–13.0)	11.0 (9.0–16.0)
Other[‡i]	8.5 (4.0–13.0)	9.0 (7.0–14.0)
Median length of hospital stay by region — days (IQR)		
North America	4.0 (4.0–7.0)	6.0 (4.0–8.0)
Europe	9.5 (8.0–14.0)	13.0 (7.0–18.0)
Asia	11.0 (9.0–16.0)	13.0 (10.0–16.0)

Abbreviation: ITT, Intent-to-treat; IQR, interquartile range; PDC, Platinum doublet chemotherapy

Notes:

[a] Definitive surgery was not reported in 2 patients in the Nivolumab plus PDC group and 7 in the chemotherapy group.

[b] Other reasons were patient refusal in 9 patients in the Nivolumab plus PDC arm and 8 patients in the chemotherapy arm; consent withdrawal in 3 patients in the chemotherapy arm; COVID-19 in 1 patient in the chemotherapy arm; unfit for surgery due to poor lung function in 2 patients in the Nivolumab plus PDC arm and 4 patients in the chemotherapy arm; and unresectability in 2 patients in each arm.

[c] Time from last dose to neoadjuvant surgery >6 weeks.

[d] Denominator based on patients with definitive surgery (N=149 in the Nivolumab plus PDC group, N=135 in the chemotherapy group).

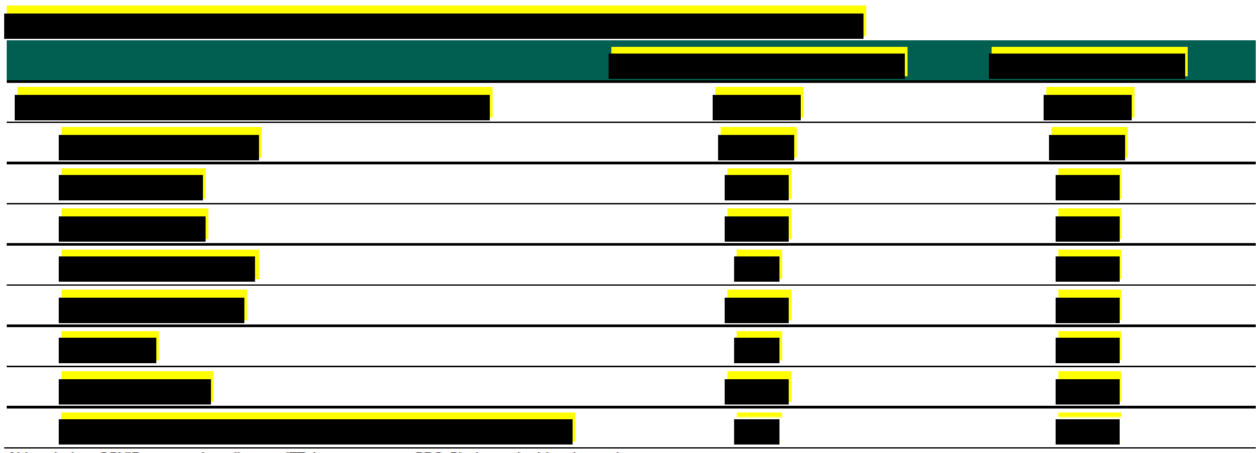
[e] Denominator based on patients with delayed surgery.

[f] Patients with reported duration of surgery: Nivolumab plus PDC, 122; chemotherapy, 121.

[§] Thoracoscopic/robotic.

[h] Patients may have had more than one surgery type.

[I] Includes bilobectomy, sleeve lobectomy, and other.
Reference: (13)

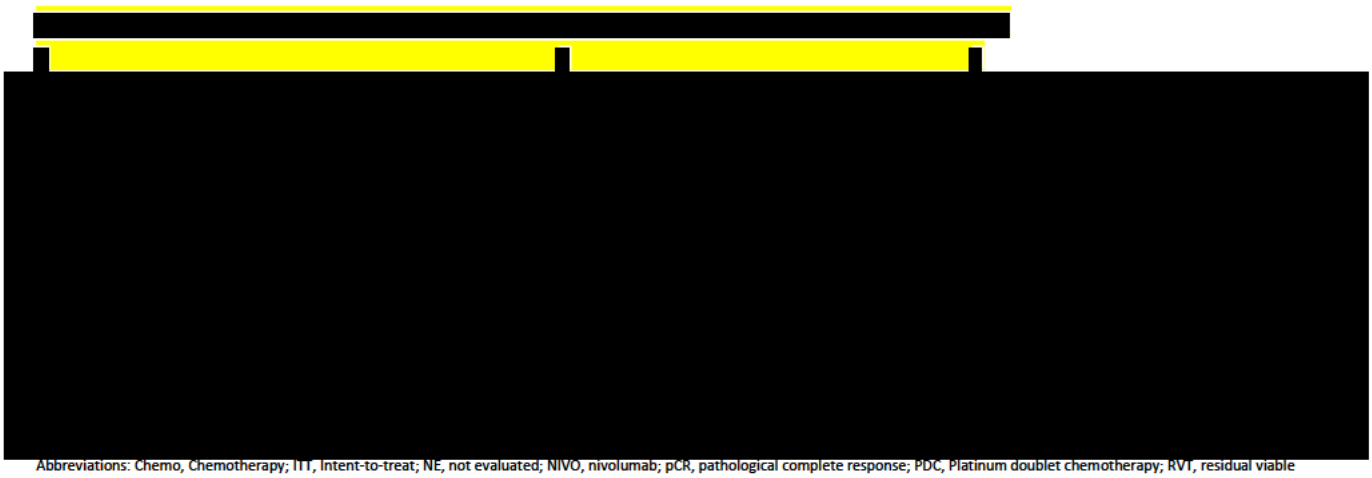


Abbreviation: COVID, coronavirus disease; ITT, Intent-to-treat; PDC, Platinum doublet chemotherapy.
Reference: (36)

At the October 2022 data cut, an interim analysis presented EFS rates by surgery type—minimally invasive surgery vs thoracotomy or conversion. For minimal invasive surgery, median EFS was not reached for nivolumab plus PDC nor PDC alone (HR: 0.61, 95% CI: 0.28–1.29) (Figure 11A). For thoracotomy or conversion surgery, median EFS was not reached for nivolumab plus PDC while PDC alone the median EFS was 42.1 month (HR: 0.61, 95% CI: 0.28–1.29) (Figure 11B) (12).

At the October 2022 data cut, recurrence patterns of patients who underwent surgery are presented in Figure 12. Of patients who underwent surgery, 42 of 149 patients (28%) in the nivolumab plus PDC arm and 56 of 135 patients (42%) in the PDC alone arms had recurrence post-surgery (12).

Abbreviations: Chemo, Chemotherapy; CI, confidence interval; EFS, event free survival; HR, hazard ratio; ITT, Intent-to-treat; mo, months; NIVO, nivolumab; NA, not reached; pCR, pathological complete response; PDC, Platinum doublet chemotherapy.
Note: The analysis presents data on all patient who underwent surgery (the total patients who underwent minimally invasive surgery or thoracotomy: n=149 for nivolumab plus PDC; n=135 for PDC alone).
[a] Among patients with definitive surgery in the nivolumab plus PDC and PDC alone arms, respectively, 30% and 21% had minimally invasive surgery; 70% and 79% had thoracotomy or conversion.
[b–e] 95% CIs for 3-year EFS rates: [b]50–80; [c]33–70; [d]51–70; e40–61.
Reference: (12)



Abbreviations: Chemo, Chemotherapy; ITT, Intent-to-treat; NE, not evaluated; NIVO, nivolumab; pCR, pathological complete response; PDC, Platinum doublet chemotherapy; RVT, residual viable tumour cells.
[a] Some patients with locoregional recurrence may have had distant recurrence events.
[b] Defined as 0% residual viable tumour cells (RVT) in both primary tumour (lung) and sampled LN (*One patient had an MPR, which was defined as ≤ 10% RVT in both primary tumour and sampled LN). [c] In the primary tumour only.
Reference: (12)

7.1.2.1.6.1 Surgery rates in CheckMate 816 compared to previous studies

In CheckMate 816, the proportion of patients that underwent definitive surgery was 83% and 75% in the nivolumab plus PDC and the PDC alone group, respectively. These rates in CheckMate 816 are comparable to definitive surgery rates after neoadjuvant treatment reported in the literature. Recently published results from the AEGEAN study—a study that assessed neoadjuvant treatment with durvalumab plus PDC vs placebo plus PDC—suggested surgery rates of about 80% following the neoadjuvant phase of the trial (37). The results from phase 2 NADIM trial, which also looked at nivolumab plus PDC in the neoadjuvant setting, reported 93% and 69% of definitive surgery rate among patients who received neoadjuvant treatment with nivolumab plus PDC or PDC alone, respectively (34). Felip 2010 looked at outcomes of preoperative (neoadjuvant) chemotherapy, postoperative (adjuvant) chemotherapy, and surgery alone in early-stage NSCLC. Felip 2010 reported 91%, 95.7%, and 95.2%, received planned surgery, respectively (9).

Start of treatment can also be affected by whether neoadjuvant or adjuvant treatment is expected along surgery. While lower surgery rates have been reported in the CheckMate 816 neoadjuvant setting compared to both the adjuvant and neoadjuvant setting in Felip 2010, Felip 2010 reported that 33.8% of the patients who were allocated to receive adjuvant chemotherapy did not start the planned treatment (9). In contrast, in CheckMate 816, 98% of patients randomised started neoadjuvant treatment in both treatment arms.

7.1.2.1.6.2 Pathological response

At the October 2021 data cut, for the ITT population, the addition of nivolumab to PDC was associated with a statistically significant increase in rates of pCR, which was defined as 0% residual viable tumour cells in both primary tumour (lung) and sampled lymph nodes. The pCR rate in the ITT population was 24.0% for nivolumab plus PDC compared to 2.2% for PDC (difference of 21.6%, calculated by stratified Cochran–Mantel–Haenszel method, p<0.0001). The OR for pCR was 13.94 (99% confidence interval [CI], 3.49–55.75, p<0.0001, Figure 13A). In patients who underwent definitive surgery and had an evaluable pathology sample, the pCR rate was 30.5% for nivolumab plus PDC compared to 3.2% for PDC (Figure 13B). When only considering the response in the primary tumour in the ITT population, the pCR rate was 25.7% for nivolumab plus PDC compared to 2.8% for PDC (Figure 13C). Furthermore, pCR improvement with nivolumab plus PDC was observed regardless of radiological down-staging. The pCR rate in patients with radiographic down-staging was 31% with nivolumab plus PDC vs 7% with PDC, and was 22% with nivolumab plus PDC vs 1% with PDC in patients without radiographic down-staging. Moreover, differences in pCR favoured nivolumab plus PDC vs PDC for most subgroups considered, including disease stage (according to TNM version 7) at entry

(nivolumab plus PDC vs PDC: Stage IB, 40 vs 0%; stage IIA, 23 vs 3%; stage IIB, 24 vs 9% and stage IIIA; 23 vs 1%, although it is worth noting the small patient numbers for stage IB, (

Figure [redacted], histology (nivolumab plus PDC vs PDC: Squamous, 25 vs 4% and non-squamous, 23 vs 0%) and PD-L1 status (nivolumab plus PDC vs PDC: PD-L1<1%, 17 vs 3%; PD-L1≥1%, 33 vs 2%; PD-L1 1–49%, 24 vs 0% and PD-L1≥50%, 45 vs 5%; Figure 15) (6).

[redacted]

Abbreviations: BIPR, blinded independent pathological review; CI, confidence interval; ChT, Chemotherapy, ITT, intent-to-treat; NIVO, nivolumab; OR, odds ratio; pCR, pathological complete response; PDC, Platinum doublet chemotherapy; ypT0, no residual viable tumour cells in the primary tumour; ypT0N0, no residual viable tumour cells in primary tumour and lymph node.
Notes:
[a] Per BIPR; pCR: 0% residual viable tumour cells in both primary tumour (lung) and sampled lymph nodes.
[b] ITT principle: patients who did not undergo surgery counted as non-responders for primary analysis.
[c] Calculated by stratified Cochran–Mantel–Haenszel method.
[d] pCR rates 95% CI: NIVO plus PDC, 18.0–31.0; PDC alone, 0.6–5.6.
[e] Patients who underwent definitive surgery with an evaluable pathology sample for BIPR.
Reference: (6)

[redacted]

Abbreviations: BIPR, blinded independent pathological review; BL, baseline; CI, confidence interval; CRF, case report form; ChT, Chemotherapy; ITT, Intent-to-treat; NIVO, nivolumab; pCR, pathological complete response; TNM, classification of malignant tumours.
Notes:
[a] Per BIPR in the ITT population; neither of the 2 patients with stage IV disease (1 in each arm) achieved pCR.
[b] 95% CI: NIVO plus PDC, PDC alone (stage): 12.2–73.8, 0.0–36.9 (IB); 9.9–42.3, 0.1–16.2 (IIA); 9.4–45.1, 1.1–28.0 (IIB); 15.6–31.9, 0.0–4.7 (IIIA).
[c] Baseline stage of disease by CRF, TNM 7th edition used for classification.
Reference: (7)

[redacted]

Abbreviations: BIPIR, blinded independent pathological review; ChT, chemotherapy; ITT, intent to treat; NIVO, nivolumab; pCR, pathologic complete response; PD-L1, programmed cell death protein ligand 1; TMB, Tumour mutational burden.
Reference: (6)

When considering the depth of pathological regression in the primary tumour by disease stage (according to TNM version 7), at the October 2021 data cut, the median residual viable tumour percentage in stage IB/II was 28% in the nivolumab plus PDC group compared to 79% in the PDC alone group, and in stage IIIA it was 8% and 70%, respectively [redacted] (6).

Despite potential differences in the definition of pCR, numerous studies of neoadjuvant PDC ± RT have demonstrated that achieving a pCR is clinically meaningful, as this has been shown to be associated with improved EFS and OS (38). Thus, the statistically significant increases in pCR observed with nivolumab plus PDC vs PDC alone suggest that neoadjuvant nivolumab plus PDC may improve survival outcomes compared with PDC alone.

[redacted]

Abbreviations: ChT, Chemotherapy; NIVO, nivolumab; PDC, Platinum doublet chemotherapy
Note:
[a] Response-evaluable patients
Reference: (7)

pCR in patients with tumour PD-L1 expression ≥1%, stage II – IIIA per TNM version 7

At the initial September 2020 data cut, the pCR rate for patients with PD-L1 expression ≥1%, stage II – IIIA (TNM version 7) was 31.1% (95% CI: 22.22–43.4) vs 2.3% (95% CI: 0.3–8.1%) for nivolumab plus PDC and PDC alone, respectively, showing a difference of 29.8% (95% CI: 19.0–40.7%) (11).

7.1.2.1.7 Safety

7.1.2.1.7.1 Incidence of AEs

Nivolumab plus PDC as neoadjuvant therapy was generally well tolerated, having a similar incidence of treatment-related AEs, surgery-related AEs, AEs leading to discontinuation and SAEs compared with neoadjuvant PDC. At the October 2022 data cut, the safety profile of nivolumab plus PDC was consistent with the primary analysis, with no new safety signals observed (12).

The overall frequencies of any grade all-cause and treatment-related AEs were similar between the nivolumab plus PDC group and the PDC group (all cause: 94% vs 98%; treatment-related: 84% vs 90%, Table 12). The frequencies of grade 3/4 all-cause and treatment-related AEs were also similar between nivolumab plus PDC compared to PDC (all cause: 43% vs 45%; treatment-related, 36% vs 38%). Furthermore, approximately 10% of patients in each group discontinued neoadjuvant therapy due to AEs or treatment-related AEs (Table 12).

All-cause, any grade SAEs were experienced by 17% of patients in the nivolumab plus PDC group compared with 14% of patients in the PDC group (Table 12). No deaths due to study drug toxicity were reported in the nivolumab plus PDC group; however, there were three deaths due to study drug toxicity in the PDC group. These were attributed to pancytopenia, diarrhoea, acute kidney injury (all in 1 patient), enterocolitis, and pneumonia (12).

AEs accounted for 7% (i.e., 2 of 28 patients) of all surgery cancellations in the nivolumab plus PDC group vs 3% (1 of 37 patients) in the PDC alone group (Table 10). Adverse events caused delay in surgery in 19% (6 of 31 patients) and 37.5% (9 of 24 patients) of patients who received nivolumab plus PDC or PDC alone, respectively (Table 10). Surgery-related AEs reported up to 90 days after definitive surgery were observed in 45% (nivolumab plus PDC) and 49% (PDC) of patients with the incidence of grade 3/4 AEs being 11% and 15%, respectively (Table 12) (12). The only grade 3/4 surgery-related complications reported in ≥2% of patients in both groups were anaemia (2% for each group) and pneumonia (2% for nivolumab plus PDC vs 3% for PDC) (Table 13). Grade 5 surgery-related AEs (defined as events that led to death within 24 hours of AE onset) were reported in two patients in the nivolumab plus PDC group and were deemed unrelated to study drug per investigator (one each due to pulmonary embolism and aortic rupture) (12).

Table 12: Summary of AEs in patients treated with nivolumab plus PDC and PDC alone from CheckMate 816, ITT population (October 2022)

Event, n (%)	Nivolumab plus PDC (N=176)		PDC alone (N=176)	
	Any Grade	Grade 3 or 4	Any Grade	Grade 3 or 4
All-cause adverse events[a]				
All[b]	165 (94)	76 (43)	173 (98)	79 (45)
Leading to discontinuation	18 (10)	10 (6)	20 (11)	7 (4)
Serious	30 (17)	19 (11)	24 (14)	17 (10)
Treatment-related adverse events[a]				
All	147 (84)	63 (36)	159 (90)	67 (38)
Leading to discontinuation	18 (10)	10 (6)	17 (10)	6 (3)
Serious	21 (12)	15 (8)	18 (10)	14 (8)
Deaths[c]	0		3 (2)	
Surgery-related adverse events[d,e,f]				
All	67 (45)	17 (11)	66 (49)	20 (15)

Abbreviations: AEs, adverse events; CTCAE, Common Terminology Criteria for Adverse Events; ITT, Intent-to-treat; MedDRA, Medical Dictionary for Regulatory Activities; NIVO, nivolumab; PDC, Platinum-doublet chemotherapy; SAEs, serious adverse events.
Notes: AEs were assessed at baseline, continuously while on treatment, and within 100 days after the last dose of neoadjuvant therapy or 90 days after surgery, or up to 30 days after the last dose of adjuvant therapy (whichever was longest). In order to avoid confounding toxicities of subsequent therapies, AEs were reported within 30 days after the last dose of neoadjuvant treatment, except for surgery-related AEs (up to 90 days after definitive surgery) and for immune-mediated, serious or fatal AEs (up to 100 days) (13). Because these AE assessment windows were passed already at the time of the first database lock for pCR (September 16, 2020), the safety data reported at AACR 2021 are similar to that reported at AACR 2022 for the EFS database lock (October 20, 2021) (39, 40)Notes: AEs were assessed at baseline, continuously while on treatment, and within 100 days after the last dose of neoadjuvant therapy or 90 days after surgery, or up to 30 days after the last dose of adjuvant therapy (whichever was longest). In order to avoid confounding toxicities of subsequent therapies, AEs were reported within 30 days after the last dose of neoadjuvant treatment, except for surgery-related AEs (up to 90 days after definitive surgery) and for immune-mediated, serious or fatal AEs (up to 100 days) (13). Because these AE assessment windows were passed already at the time of the first database lock for pCR (September 16, 2020), the safety data reported at AACR 2021 are similar to that reported at AACR 2022 for the EFS database lock (October 20, 2021) (39, 40), although minor edits were made by the investigators in the case report forms
All patients were off treatment for ≥18 months.
[a] Includes events reported between first neoadjuvant dose and 30 days after last dose of neoadjuvant. Common Terminology Criteria for Adverse Events (CTCAE) Version 4.0; Medical Dictionary for Regulatory Affairs (MedDRA) Version 24.0.
[b] Adverse Events by Worst CTC Grade Reported in ≥ 10% of All Treated Subjects
[c] Denominator based on patients with definitive surgery (N=149 in the Nivolumab plus PDC arm, N=135 in the chemotherapy arm).
[d] Includes events reported up to 90 days after definitive surgery. CTCAE Version 4.0; MedDRA Version 24.0.
[e] Grade 5 surgery-related adverse events (defined as events that led to death within 24 hours of adverse event onset) were reported in 2 patients in the Nivolumab plus PDC arm and were deemed unrelated to study drug per investigator (1 each due to pulmonary embolism and aortic rupture).
[f] Treatment-related deaths in the chemotherapy arm were due to pancytopenia, diarrhoea, acute kidney injury (all in one patient), enterocolitis, and pneumonia.
Reference: (12)

[redacted]

Event, n (%)	Nivolumab plus PDC (N=149)		PDC alone (N=135)	
	Any Grade	Grade 3 or 4	Any Grade	Grade 3 or 4
[redacted]				

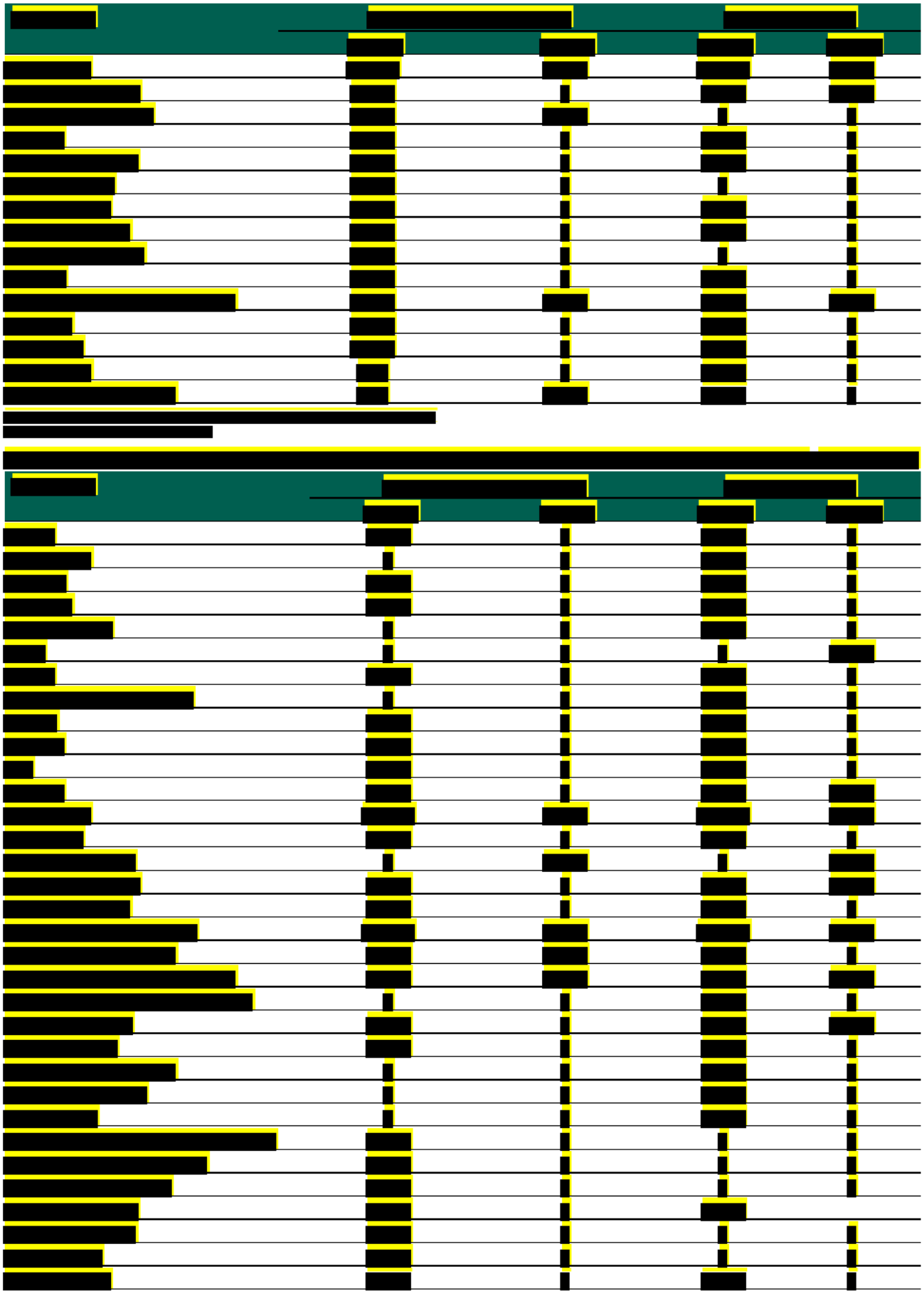
In both the nivolumab plus PDC and PDC alone groups, the majority of AEs were grade 1 and 2. Among patients who were treated with neoadjuvant nivolumab plus PDC and PDC alone, [redacted] and [redacted] of the treated patients, respectively, experienced only grade 1 and 2 AEs. The most frequently (≥15%) reported any-grade treatment-related AEs (TRAEs) were nausea, anaemia, constipation, decreased appetite and neutropenia in both groups, plus decreased neutrophil count in the PDC group only (Table 14). For each, the incidence was similar between groups or numerically higher in the PDC group. Finally, treatment-related AEs (TRAEs) of grade 3 or 4 that occurred in at least two patients are reported in Table 15, while all grade 3 or 4 AEs that occurred in at least one patient are reported in [redacted]

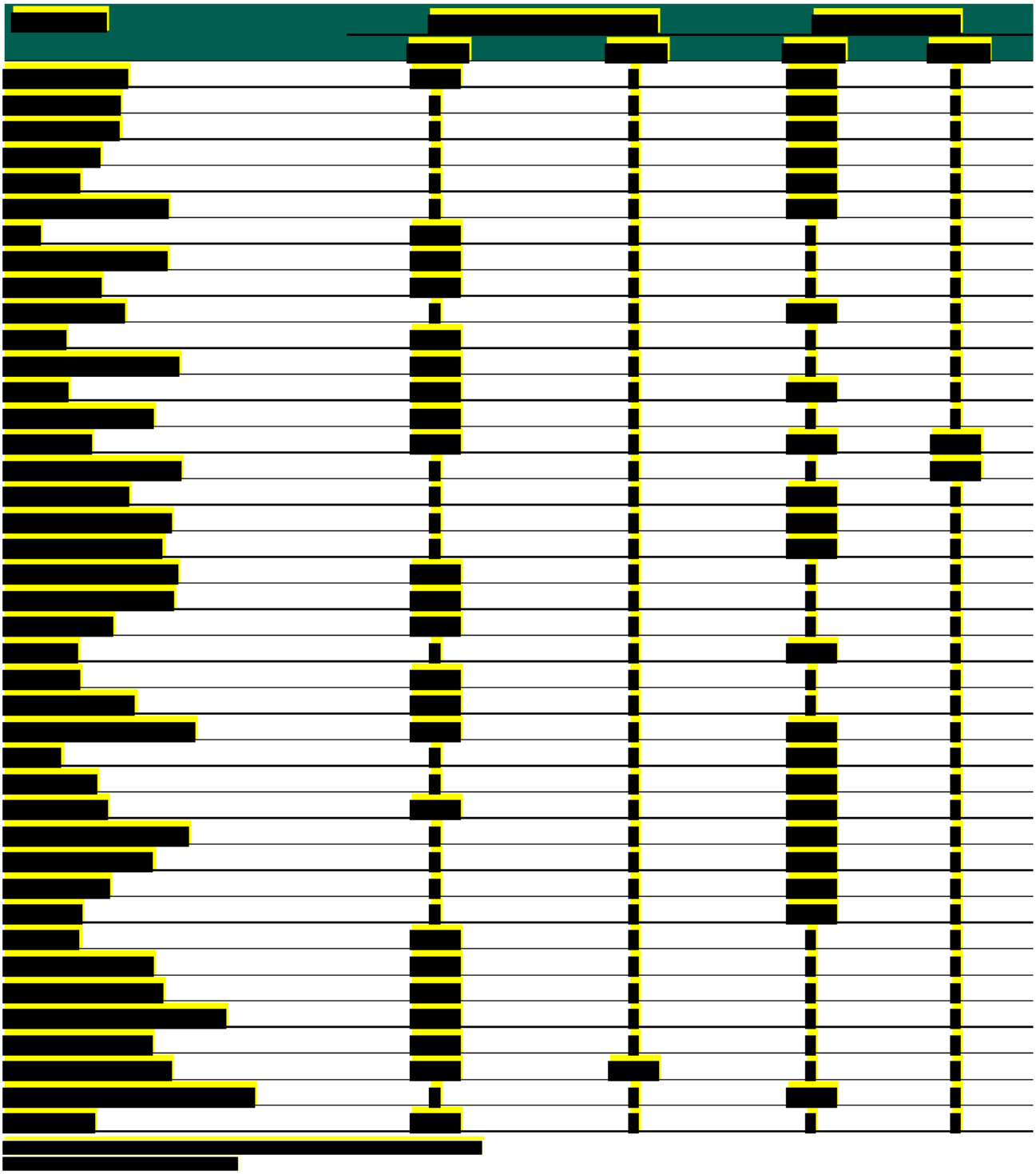
Table 14: TRAEs of any grade in ≥15% of patients in CheckMate 816 (October 2022)

Event, n (%)	Nivolumab plus PDC (N = 176)	PDC alone (N = 176)
All	147 (83.5)	159 (90.3)
Nausea	58 (33.0)	74 (42.0)
Anaemia	41 (23.3)	42 (23.9)
Constipation	37 (21.0)	36 (20.5)
Decreased appetite	30 (17.0)	38 (21.6)
Neutropenia	30 (17.0)	30 (17.0)
Decreased neutrophil count	26 (14.8)	38 (21.6)

Abbreviation: AEs, adverse events; PDC, Platinum doublet chemotherapy
Note:
[a] Included events reported between the first neoadjuvant dose and 30 days after the last neoadjuvant dose as per Common Terminology Criteria for Adverse Events (CTCAE) Version 4.0; Medical Dictionary for Regulatory Activities (MedDRA) Version 25.0.
Reference: (11)

[redacted]





7.1.2.1.7.2 Immune-mediated AEs

AEs considered to be immune-mediated included AEs that were considered as potential immune-mediated events by the investigator and which occurred within 100 days of neoadjuvant therapy, regardless of causality. In addition, to be considered as immune-mediated, AEs were required to have been treated with immune modulating medication, with the exception of endocrine events (adrenal insufficiency, hypophysitis, hypothyroidism/thyroiditis, hyperthyroidism, and diabetes mellitus), which were included in the analysis, regardless of treatment, since these events are often managed without immunosuppression. Immune-mediated AEs observed with neoadjuvant nivolumab plus PDC corresponded to the known safety profile of nivolumab and most were mild or moderate in severity.

At the October 2022 data cut, for the ITT population, the incidence of individual immune-mediated AEs was similar to outcomes in the previous, October 2021 data cut. [redacted]

Event, n (%)	Nivolumab plus PDC (N=176)		PDC alone (N=176)	
	Any Grade	Grade 3 or 4	Any Grade	Grade 3 or 4
[redacted]				

7.1.2.2 Patients reported outcomes (PROs)

In the CheckMate 816 trial, health related quality of life (HRQoL) was assessed using EuroQol 5 Dimension 5 Level (EQ-5D). The HRQoL assessments were performed at baseline (cycle 1 day 1) after randomisation, prior to the first dose, before cycles 2 and 3, at post-neoadjuvant visit 1 (approximately 30 days after the last dose), and at post-neoadjuvant visit 2 (approximately 70 days after the post-neoadjuvant visit 1). As shown in [redacted] the EQ-5D visual analogue scale (VAS) score in all randomised patients was preserved from baseline during the neoadjuvant treatment period in both neoadjuvant nivolumab plus PDC and PDC alone treatment groups.

[redacted]

Abbreviations: Chemo, Chemotherapy; CI, Confidence interval; EQ-5D: EuroQol-5D; ITT, Intent-to-treat; Nivo, Nivolumab; VAS: visual analogue scale
Notes:
*EQ-5D VAS ranges from 0 to 100, with higher scores indicating better functioning.
[1]Referenced from Szende 2014 (42)
[2]Referenced from Pickard 2007 (43)
Reference: (44)

Among patients who received surgery, treatment with nivolumab plus PDC did not impact postoperative PROs in comparison with the PDC alone group. Further, similar postoperative decline in EQ-5D VAS scores were observed (approximately 2 months after surgery) in both treatment arms [redacted] Also, no notable differences were seen in EQ-5D VAS scores between nivolumab plus PDC and PDC alone groups across patient subgroups [redacted] As such, the HRQoL of the ITT population is expected to be generalisable to the HRQoL of the EMA label population.

[redacted]

Abbreviations: Chemo, chemotherapy; CI, Confidence interval; EQ-5D, EuroQol-5D; ITT, Intent-to-treat; Nivo nivolumab; IQR, Interquartile range; VAS, visual analogue scale
Notes:
[a] EQ-5D VAS ranges from 0 to 100, with higher scores indicating better functioning.
[b] Median (IQR) time from last neoadjuvant dose to definitive surgery was 5.3 (4.6–6.0) weeks with nivolumab plus PDC and 5.0 (4.6–5.9) weeks with PDC alone for all patients with definitive surgery.
[1] Referenced from Szende 2014 (42); [2] Referenced from Pickard 2007 (43)
Reference: (44)

[redacted]

Abbreviations: Chemo, chemotherapy; CI, Confidence interval; EQ-5D, EuroQol-5D; ITT, Intent-to-treat; MMRM, Mixed model for repeated measures; Nivo, nivolumab; PD-L1, Programmed death-ligand 1; VAS, visual analogue scale
Notes:
[a] EQ-5D VAS ranges from 0 to 100, with higher scores indicating better functioning.
[b] The MMRM included the change from baseline PRO score as the dependent variable. The baseline PRO score and IRT stratification factors (PD-L1 level [≥ 1% versus < 1%], disease stage [IB/II versus IIIA], and sex [male versus female]) were included as covariates. The mixed model contains neoadjuvant treatment group, study visit (as a categorical variable), the relevant subgroup as fixed effects, the interaction between neoadjuvant treatment group and subgroup, and the interaction between neoadjuvant treatment group and study visit. Study visit is fitted as a repeated effect (repeated by patient).
[c] Difference in change from baseline least squares means (95% CI), including post-neoadjuvant Visit
[d] N-value reflects number of patients in the chemo arm completing the EQ-5D VAS
Reference: (44)

7.1.3 Comparative analyses of efficacy and safety

CheckMate 816 presented an in-trial comparison of neoadjuvant treatment with the nivolumab plus PDC versus neoadjuvant treatment with PDC alone (as proxy for adjuvant treatment with PDC alone. Further information on section 5.2.2). Therefore, no additional comparative analyses are warranted.

As mentioned in section 5.2, atezolizumab as adjuvant treatment was approved by the Danish Medicines Council (DMC) in March 2023 but is not yet reflected in the latest clinical guidelines released in November 2022 (20), and is not considered as standard of care for this group of patients. The relevance of atezolizumab as a comparator to nivolumab plus PDC, as well as a comparison on the respective IMPOWER010 and CheckMate 816 trials, is presented in Appendix O. Overall, the two trials—CheckMate 816 and IMPOWER010—differ in study design, reflecting different study populations and measurements of study outcomes. Particularly, nivolumab plus PDC is available to a broader patient population (resectable PD-L1 expression >1% patients with stage II – IIIA per TNM version 7) than atezolizumab (PD-L1 ≥50% patients with completely resected tumours who have completed at least 1 cycle of adjuvant chemotherapy). Such differences in patient populations and study designs, which violate standard indirect treatment comparison assumptions, make any comparisons between these two studies extremely challenging. As per instruction from the DMC secretariat, BMS has provided a side-by-side comparison of select data-points to enable a naïve comparison, see Appendix O.

8 Health economic analysis

The objective of the analysis is to estimate the cost-effectiveness of nivolumab plus PDC as neoadjuvant treatment for resectable, non-metastatic NSCLC. For this analysis, a cost-effectiveness model (CEM) was developed.

The model was developed in accordance with recommendations from the International Society for Pharmacoeconomics and Outcomes Research (ISPOR) Modelling Good Research Practices report (45). The design was also informed by requirements from key health technology assessment (HTA) bodies, such as the National Institute for Health and Care Excellence (NICE) (46), Canadian Agency for Drugs and Technologies in Health (CADTH) (47), Haute Autorité de Santé (HAS) (48), and Pharmaceutical Benefits Advisory Committee (PBAC) (49). The model has been adapted to the Danish setting with regards to the Danish guidelines (50).

The model Includes deterministic and probabilistic sensitivity analyses, allowing for a robust evaluation of methodological, parametric, and structural uncertainties.

This analysis utilizes a direct comparison of neoadjuvant nivolumab plus PDC versus neoadjuvant PDC alone from CheckMate 816, where neoadjuvant PDC is used as a proxy for the most relevant comparator, adjuvant PDC (see section 5.2.2). Clinical experts have confirmed this approach as reasonable due to the expected outcome of treatment with neoadjuvant PDC and adjuvant PDC to be comparable (see Appendix N).

Patients entering the model are newly diagnosed with histologically confirmed resectable, non-metastatic NSCLC with PD-L1 expression ≥1%. While in clinical practice patients with high risk of recurrence might be restricted to TNM stages II-IIIA (TNM version 7), these patients are expected to be similar to the patient population represented in the model, as the number of patients and baseline characteristics in both groups were very similar (see Table 75 and Table 76 in section 15 Appendix C and no major differences in outcomes have been observed between groups (see section 29 Appendix Q for considerations in EFS and OS outcomes between the patient populations). Therefore, the model outcomes are expected to be valid for the expected population in Danish clinical practice. Specific baseline characteristics, such as age, sex, and disease stage, mirror those of the PD-L1 expression ≥1% subgroup in the CheckMate 816 trial and are presented in Table 74.

8.1 Model

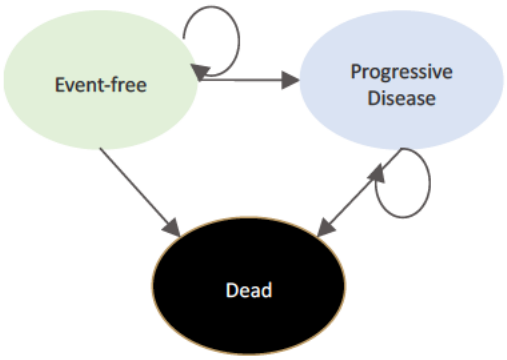
8.1.1 Model structure

A three-state Markov cohort model was developed and implemented in Microsoft Excel®. The schematic for the model is depicted in Figure 20.

As described in Section 8, to inform the choice of model structure a review of recent HTA submissions for neoadjuvant/adjuvant treatments in nonmetastatic solid tumours was conducted in 2021. A Markov model approach was used in 17 out of 21 submissions, where the remaining four submissions used a partitioned survival approach.

Within the context of NSCLC, progression in the disease is not uncommon, therefore it was important to accurately capture this within the model structure. The chosen three-state Markov model structure was considered the most appropriate in terms of simplicity and transparency and in relation to flexibility of enabling use of available data from CheckMate 816 as well as external sources to inform the model, and at the same time enabling the analyst to investigate different assumptions around key parameters.

Figure 20: Overview of the model structure



This model includes three health states: event-free (EF), progressive disease (PD), and death. All patients enter the model in the EF health state. In the EF health state, patients may experience either progression (moving to the PD state) or death (moving to the dead health state). Patients who are in the PD health state remain in the PD state until they die, at which point they transition to the dead health state. Costs were assigned to each health state, and utilities were applied according to patients' disease progression status and adjusted to population-age throughout. The model includes functionality to further modify utilities according to treatment received and any AEs experienced.

In CheckMate 816, all except one patient received neoadjuvant treatment (due to a non-treatment related AE) and in the model the neoadjuvant PDC arm from the trial is used as a proxy for adjuvant PDC.

Health states were selected based on the CheckMate 816 trial endpoints and the current understanding of the disease area. The EF health state was designed to align with the definition of EFS used in CheckMate 816, where EFS was a primary endpoint. EFS begins from the time of randomisation, rather than from the time of surgery. This allows the model to articulate the possibility that some patients who are unresponsive to neoadjuvant therapy could see their disease progress prior to surgical resection. The transition probabilities used by the model are calculated based on results from CheckMate 816.

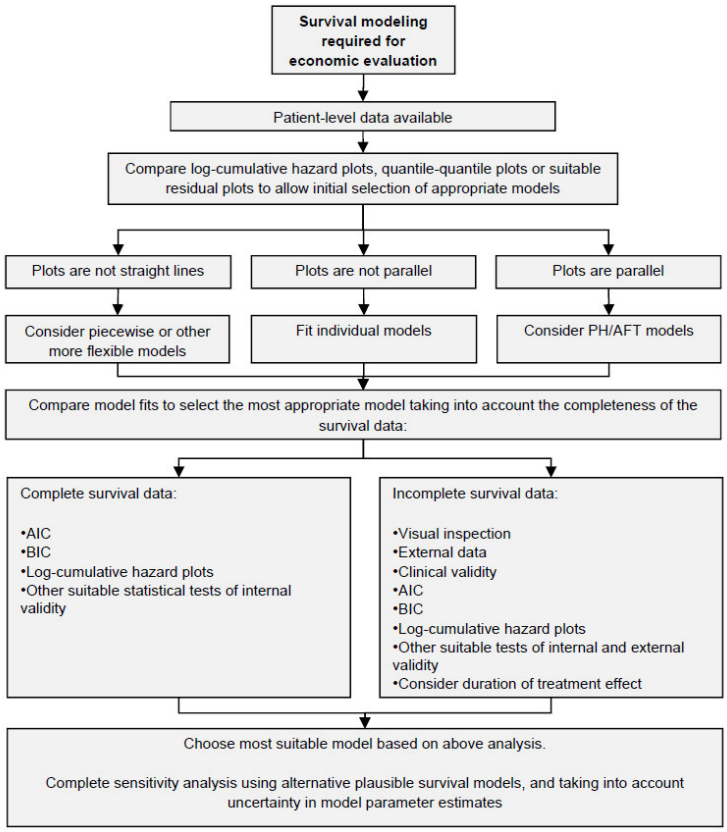
In the EF health state patients receive either nivolumab plus PDC or PDC alone. Once patients experience progression and enter the PD health state, additional treatment is initiated to manage their worsening NSCLC, inclusive of three lines of treatment: treatments for locoregional recurrence (LR) progression, and two lines of treatments for patients with distant metastasis [DM] progression).

8.1.2 Efficacy inputs

8.1.2.1 Approach to parametric fitting and assessment

To maximize flexibility and allow the model to accurately reflect clinical data from CheckMate 816, parametric survival modelling was conducted. This allows for estimation of time-dependent transition probabilities beyond the end of the existing trial data. The survival estimates were further validated using Danish registry data presented in section 8.3.1.4. The approach is summarized in Figure 21.

Figure 21: Survival model selection process algorithm presented by NICE DSU, and referenced by other HTA agencies



Abbreviations: AFT, Accelerated failure time; AIC, Akaike s Information Criteria; BIC, Bayesian Information Criteria; DSU, Decision Support Unit; HTA, Health Technology Assessment; NICE, National Institute for Health and Care Excellence; PH, Proportional hazard
Source: (46)

8.1.2.2 Cycle length

The model adopts a 21-day (i.e., 3-week) cycle length. This aligns with the treatment schedule for nivolumab plus PDC in the CheckMate 816 trial, where treatments are administered once every 3 weeks. The 3-week cycle length also aligns with the dosage schedule for many current and potential treatment options in the adjuvant and post-progression settings (e.g., docetaxel, pemetrexed, cisplatin, carboplatin, paclitaxel, and pembrolizumab).

Most results are adjusted using a half-cycle correction, distributing the costs, LYs and QALYs accrued across the cycle duration. Half-cycle correction is not applied to drug acquisition and administration costs since all patients received pharmacological treatment at the start of each cycle.

8.1.2.3 Perspective

In line with DMC guidelines, a restricted societal perspective is applied (50).

8.1.2.4 Discounting

A discount rate of 3.5% is applied for both costs and health outcomes in the base case analysis (51). Since the time horizon of the model is limited to 35 years, the same discount rate is used for all years in the analysis. A scenario without discounting of costs and QALYs is also included as a scenario analysis.

8.1.2.5 Time horizon

The model takes a lifetime horizon in the base case, although the model is flexible and can consider shorter time horizons (e.g., one year, five years, 15 years, or 20 years). There are two key reasons why a lifetime horizon is employed in the base case. First, nivolumab plus PDC is anticipated to extend patient lifespans. Second, these patients will require continued healthcare visits and other care over time; many will require subsequent treatment if their disease progresses. Thus, a lifetime horizon can fully capture the costs and benefits of nivolumab plus PDC as neoadjuvant treatment for resectable non-metastatic NSCLC.

Lifetime is implemented as the point in time where fewer than 1% of patients are alive in the model engine. It was found that this threshold was crossed at approximately 35.47 years. Rounding to the nearest integer, the lifetime time horizon used in the base case analysis was 35 years.

8.1.2.6 Model outcomes

The model has flexibility to conduct both cost-effectiveness analyses and cost-utility analyses. For the former analysis, the key outcome of interest is the incremental cost per LY gained, and for the latter analysis, the key outcome of interest is the incremental cost per QALY gained.

In addition, the model also presents LYs and QALYs accrued in each health state, as well as costs stratified by category (and health state, where applicable). The list of model outputs is provided in Table 18.

Table 18: Model outputs

Outcome type	Outcome	
Health	LYs	LYs EF
		LYs in PD
	QALYs	QALYs EF
		QALYs in PD
Cost	Comparator acquisition costs	
	Comparator administration costs	
	Surgery costs	
	Cost of adjuvant treatment for strategies including neoadjuvant treatment	
	Treatment cost in PD	
	MRU	While EF
		In PD
	Treatment monitoring	While EF
		In PD
	AE management costs	
	Terminal costs	
Incremental	Incremental cost	
	Incremental LYs	
	Incremental QALYs	
	Incremental cost per LY (ICER)	
	Incremental cost per QALY (ICER)	

Abbreviations: AE, Adverse event; EF, Event free; ICER, Incremental cost-effectiveness ratio; LY, Life year; MRU, Medical resource use; PD, Progressive disease; QALY, Quality-adjusted life year

8.1.2.7 Cure assumption

Long-term evidence suggests patients who are treated for resectable non-metastatic NSCLC may be able to achieve cure, defined as 1) no risk of progression and 2) no excess cancer-related mortality compared to an age- and sex-matched population.

In general, inclusion of cure in the model was based on four key pillars:

- **Empirical evidence,** where a reduction in hazard of progression at five years is seen in the trial data, and a "plateau" beyond five years is seen in the EFS data among patients treated with neoadjuvant PDC alone
- **Precedent**, namely, inclusion of the cure assumption in NICE TA761 (osimertinib in resected NSCLC) and NICE TA823 (atezolizumab in resected NSCLC), and NICE's finding that this inclusion was indeed appropriate. Cure was also included in the DMC assessments of osimertinib and atezolizumab as adjuvant treatments for NSCLC (20, 52)
- **Feedback from clinical experts (global and Nordic),** among whom there was consensus that the cure assumption was reasonable in this indication.
- **Danish clinical guidelines** for potential curative treatment of resectable NSCLC (10). In the guidelines, it is stated that the active follow-up period ends after 5 years as there is a very low risk of recurrence at that time, also with reference to Demicheli 2012.

In terms of empirical data**,** two bodies of evidence were assessed that suggest cure. The first of these was a paper published by Demicheli 2012 (53). In this study, the authors sought to investigate how the hazard of different types of progression changes over time among patients with resected NSCLC. As depicted in [redacted], results of the study suggest that the risk of LR or DM fluctuates over the first five years post-resection, approaching zero at approximately five years.

[redacted]

Long-term EFS outcomes were also assessed across studies evaluating neoadjuvant PDC. Additional detail on the sources cited are provided in Appendix G. In general, the trend across all the included studies showed that the EFS curves flatten out at approximately five years, as shown in [redacted]

The implementation of cure in the model uses three inputs:

- The proportion of patients achieving cure
- The timepoint at which cure is applied
- The period over which cure occurs

The pool of patients that achieve cure consists of those who have not yet experienced progression at the cure timepoint. Once the cure timepoint is reached, cure is applied using a constant rate over a flexible period—with the specific rate calculated as a function of the period and cure proportion—until the cure proportion is reached. While the same cure parameters are applied to both nivolumab plus PDC and PDC alone, the actual cured proportion will differ across treatments because 1) the cure proportion is applied to patients currently in EFS, and 2) EFS differs between treatments. The base case cure parameters describing cure are summarized in Table 19.

Table 19: Base case cure parameters

Parameter	Input
Time at which patients in EFS begin to be considered cured	5 years
Time from beginning to end of cure process	2 years
Percentage of patients cured at completion of cure process	95%

Abbreviation: EFS, Event-free survival

8.1.2.8 Sensitivity analysis

8.1.2.8.1 Deterministic sensitivity analyses

All major model variables in the base case were tested in a one-way deterministic sensitivity analysis (DSA) to identify model results drivers and understand the impact of uncertainty of the specific model parameters. Where possible, CIs or published ranges were used as alternative values. In the absence of CIs or published ranges, lower and upper bounds tested in the one-way sensitivity analysis were calculated as ± 20% of the mean value. Results are reported, including tornado diagrams depicting the DSA outcomes.

8.1.2.8.2 Probabilistic sensitivity analyses

For the probabilistic sensitivity analyses (PSA), uncertainties in parameter values were estimated, including the parametric values of long-term extrapolations, disease management costs, treatment costs, and utilities. For each

parametric function in the model, a Cholesky decomposition of the covariance matrix was used to correlate the function parameters. Distributions used in the PSA are presented in Table 20. Measurement of uncertainties was captured by 95% CI or standard errors (SE) of each parameter. In the absence of CIs or SEs from published ranges, the SE of the parameter was assumed to be 20% of the mean value.

Table 20: Model parameters varied in PSA and distributions

Category	Parameter	Distribution for PSA
Patient characteristics	Starting age	Normal
	Weight	Normal
	BSA	Normal
Clinical inputs	EF to progression— Nivolumab plus PDC, survival parameters	Normal / Cholesky
	EF to progression— PDC, survival parameters	Normal / Cholesky
	Death during EF, survival parameters	Normal / Cholesky
	Death during PD, survival parameters	Normal / Cholesky
Treatment costs	Drug acquisition cost, per cycle	Gamma
	Drug administration cost, per cycle (initial, subsequent)	Gamma
	Adjuvant costs after neoadjuvant care	Gamma
	Surgery cost	Gamma
	Cost for LR treatments	Gamma
	% LR patients experiencing secondary progression to DM	Beta
	Cost for 1L DM treatments	Gamma
	% 1L DM patients who go on to receive 2L DM treatments	Beta
	Cost for 2L DM treatments	Gamma
Disease management	MRU per cycle (EF, PD)	Gamma
	Monitoring per cycle (EF, PD)	Gamma
	Terminal care cost	Gamma
	AE cost	Gamma
	Income loss per cycle (EF, PD)	Gamma
Utility values	Utility values— EF, PD	Beta
	Aggregated AE disutility	Beta

Abbreviations: 1L, First line; 2L, Second line; AE, Adverse event; BSA, Body surface area; DM, Distant metastasis; EF, Event-free; LR, Locoregional recurrence; MRU, medical resource use; PD, Progressive disease; PDC, Platinum-doublet chemotherapy; PSA, Probabilistic sensitivity analysis

8.1.3 Model summary

A summary of the core elements of the economic model is shown in Table 21.

Table 21: Model summary

Aspect	Details	Comment
Analytical method	Three-health state Markov model	Analytical technique that has been applied in previous technology appraisals for anti-cancer treatments
Software used	Microsoft Excel®	Transparent, widely available software
Time horizon	Up to 35 years	Captures lifelong benefits of the cohort
Cycle length	21 days	Aligns with the treatment schedule for nivolumab and PDC in the CheckMate 816 trial; treatments are administered once every three weeks
Discounting options	Costs and health outcomes	Both costs and outcomes were subject to annual discounting in the evaluation (3.5% in line with DMC guidelines)
Treatment arms	• Neoadjuvant nivolumab plus PDC • Neoadjuvant PDC alone	The comparator is based on the comparator in the CheckMate 816 clinical trial, and is a proxy for adjuvant PDC

Aspect	Details	Comment
Half-cycle correction	Yes	Applied to: costs, LYs, and QALYs, accrued across the cycle duration Not applied to: drug acquisition and administration costs since all patients received pharmacological treatment at the start of each cycle
Input		
Clinical efficacy and safety	CheckMate 816 trial	Relevant clinical trial
Costs	Estimates provided by clinical experts	Clinical experts were interviewed to validate inputs informing costs
Nivolumab and PDC dosage	Nivolumab: 360 mg every 3 weeks PDC: BSA	The dosing regimen for each treatment option included in the neoadjuvant and adjuvant setting was based on the dosing used in the CheckMate 816 trial; dosing of some intravenous treatments is dependent on a patient's BSA
Utilities	CheckMate 816 EQ-5D-3L data (utilities for EF and PD), tariff applied from the Danish 5L value set	Health state specific utilities were used for the base case, no treatment specific utilities were explored
Consideration of subsequent therapies	Yes	Subsequent treatment options and proportions were validated by clinical experts
Output		
Costs	Aggregate and breakdown	-
Outcomes	Aggregate and breakdown	-
ICER	Ratios presented alongside the incremental costs and outcomes	-
Incremental cost-effectiveness plane	Yes	-
Cost-effectiveness acceptability curve and frontiers	Yes	-
Automated PSA and DSA	Yes	-

Abbreviations. PDC, Platinum-doublet chemotherapy; LYs, Life years; QALYs; Quality-adjusted life years; BSA, Body surface area; EF, Event free; PD, Progressive disease; UK, United Kingdom.

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

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

The input data used to inform clinical effect, adverse reactions, and health state utility values (HSUV) in the model have been sourced from CheckMate 816. Certain model inputs are influenced by PD-L1 status, and for these inputs, PD-L1 expression ≥ 1% subgroup data collected from CheckMate-816 were used in the model. Inputs that are not expected to vary based on PD-L1 status were informed based on the ITT population. Table 22 summarises whether the model inputs were PD-L1 expression ≥ 1% subgroup specific or based on the ITT population.

Table 22: Summary of PD-L1 expression ≥ 1% subgroup specific inputs

Inputs	Based on PD-L1 expression ≥ 1% subgroup population	Based on ITT population
Patient characteristics	X	
Transition probabilities from EF to PD, EF to death, and PD to death	X	
Relative efficacy for comparators not included in CheckMate 816	X	
Proportion of patients receiving surgery and type of surgery		X
Proportion of patients continue to receive adjuvant care after neoadjuvant treatments	X	
Type of progression (proportion of LR and DM progression)	X	
Treatment mix during LR		X
Treatment mix during DM	X	

Inputs	Based on PD-L1 expression ≥ 1% subgroup population	Based on ITT population
AE incidence		X
Utility		X

Abbreviations: AE, adverse events; DM, distant metastasis; EF, event free; ITT, intention-to-treat; LR, locoregional recurrence; PD, progressive disease; PD-L1, programmed death-ligand 1.

The aim of the cost-effectiveness analysis is to capture the likely outcomes in Danish clinical practice as accurately as possible. Danish clinical experts were not consulted for this HTA application. In the absence of Danish clinical experts, and in line with DMC guidelines, insights from clinical experts from other Nordic countries were considered. Norwegian clinical experts had been consulted as part of the CheckMate 816 indication to the Norwegian Medicines Agency (Statens legemiddelverk, [SLV]). These experts were presented with data from CheckMate 816 and were asked to give input to patient characteristics and other relevant model inputs and assumptions. In addition, relevant information from Danish clinical guidelines, knowledge of Danish clinical practice as well as available Danish registry data have been used to support the model adaptation, assumptions and validation.

An overview of the input data used in the model and how they were obtained is presented in Table 23.

Table 23: Input data used in the model

	Variable	Value at source	Input value used in the model	How the input value was obtained/estimated
Patient inputs	% Female among patients	26.4%	26.4%	CheckMate 816
	Patients' starting age	63.8 years	63.8 years	CheckMate 816
	Patients' weight	68.85 kg	68.85 kg	CheckMate 816
	Patient's BSA	-	1.84 m^2	Derived based on patient characteristics in the CheckMate 816 trial (Table 47) and average general population height (validated by clinical expert)
Clinical inputs	Cure timepoint	-	5 years	Validated by clinical expert
	Gradual onset of cure in population	-	2 years	Validated by clinical expert
	Cure percentage	-	95%	Assumption, tested in scenario analyses
	Transition from EF to PD	Time dependent	Time dependent	Analysis of CheckMate 816 data (time to any progression)
	Transition from EF to death	Time dependent	Time dependent	Analysis of CheckMate 816 data (time to death); pooled (from the two treatment arms in CheckMate 816) mortality estimate for all patients who are EF
	Transition from PD to death	Time dependent	Time dependent	Analyses of Checkmate 816 data (time to death after progression) including both treatment arms (nivolumab + PDC and PDC)
	EF to PD parametric fitting for nivolumab plus PDC and neoadjuvant PDC	N/A	Joint Lognormal	EF to PD estimations of nivolumab plus PDC and PDC alone are based on individual patient level data (IPD) analyses of CheckMate 816.
	EF to Death parametric fitting	N/A	Exponential	Informed by CheckMate 816 Exponential is the recommended base case based on statistical assessment and clinical expert feedback.
	PD to Death parametric fitting	N/A	Log-normal	Informed by CheckMate 816 Log-normal is the recommended base case based on statistical assessment and clinical expert feedback.

	Variable	Value at source	Input value used in the model	How the input value was obtained/estimated
Utility inputs	Utility during EF for all comparators	[redacted]	[redacted]	CheckMate 816 EQ-5D-3L responses were mapped to 5L and utilities were estimated from Danish 5L value set (59, 60).
	Utility during PD for all comparators	[redacted]	[redacted]	CheckMate 816 EQ-5D-3L responses were mapped to 5L and utilities were estimated from Danish 5L value set.
	AE disutility	N/A	Excluded	Assumed to be captured in the health state utilities.
AEs	Probability of grade 3 or 4 AEs	Based on grade 3 and 4 AE in 2 or more individuals in CheckMate 816; See section 7.1.2.1.4		CheckMate 816

Abbreviations: AE, Adverse event; BSA, Body surface area; EF, Event-free; kg, Kilograms; m, Meters; PD, Progressive disease; PDC, Platinum-doublet chemotherapy; UK, United Kingdom

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

8.2.2.1 Patient population

8.2.2.1.1 Danish clinical practice

In Denmark, the relevant patient population corresponds to adults with resectable NSCLC at high risk of recurrence (defined as patients with stage IIB-IIIB N2 disease according to TNM version 8) whose tumours have PD-L1 expression ≥ 1%. This population corresponds to the subgroup of patients included in CheckMate 816 with PD-L1 expression ≥ 1% and histologically confirmed stage II and IIIA NSCLC (based on TNM version 7). Of 4973 patients diagnosed with lung cancer in 2021, we have estimated that roughly 160 would be considered eligible for neoadjuvant treatment with nivolumab plus PDC each year, see Section 5.1.2.

8.2.2.1.2 Clinical documentation submitted (in relation to clinical practice)

Patients enrolled in CheckMate 816 were assigned to receive up to three cycles of neoadjuvant treatment, followed by surgery within six weeks of completing neoadjuvant treatment. After surgery, patients could receive adjuvant PDC and/or radiotherapy at the discretion of the investigator. Key trial inclusion and exclusion criteria are summarized in Table 24.

Table 24: CheckMate 816: Key inclusion/exclusion criteria

Inclusion Criteria	Exclusion Criteria
• **At least 18 years of age** • **Histologically confirmed stage IB (≥4 cm), II, IIIA NSCLC (per the 7th edition IASLC TNM staging criteria) that is considered resectable** • **ECOG performance status of 0–1** • **Pulmonary function capacity capable of tolerating the proposed lung resection, and absence of any pathologies that would increase surgery risk to an unacceptable level**	• Presence of locally advanced unresectable disease (regardless of stage) or metastatic (i.e., stage IV) disease • Known EGFR or ALK mutations • Presence of brain metastases • Active, known, or suspected autoimmune diseases • Presence of any conditions requiring systemic treatment with either corticosteroids or other immunosuppressive medications • Prior treatment with any chemotherapy or other cancer therapy for early-stage NSCLC • Prior therapy with anti-PD-1, anti-PD-L2, or anti-CTLA-4 antibodies • Prior malignancy active within the previous 3 years (except for locally curable cancers)

Abbreviations: ALK, Anaplastic lymphoma kinase; CTLA, Cytotoxic T lymphocyte-associated antigen; ECOG, Eastern Cooperative Group; EGFR, Epidermal growth factor receptor; IASLC, International Association for the Study of Lung Cancer; NSCLC, Non-small cell lung cancer; PD-1, Programmed-death 1; PD-L2, Programmed cell death-ligand 2; TNM, Tumour-node-metastasis

8.2.2.1.3 Model submitted (according to clinical documentation and clinical practice):

Patients entering the model are newly diagnosed with histologically confirmed resectable, non-metastatic NSCLC with PD-L1 expression ≥ 1%. While the population represented in the model considers patients in all disease stages, the label population is restricted to stage II-IIIA (TNM version 7). Despite this small difference, the number of patients and baseline characteristics are similar between both populations (see [redacted] and Table 76 in Appendix C) and no major differences in outcomes have been observed between groups (see sections 7.1.2.1.1 and 7.1.2.1.3 for considerations in EFS and OS, respectively). Therefore, the model outcomes are expected to be valid for the label population.

Specific baseline characteristics, such as age, sex, and disease stage, mirror those of the PD-L1 ≥ 1% subgroup in CheckMate 816 and are presented in [redacted].

8.2.2.2 Intervention

The intervention is nivolumab plus PDC, further described in section 5.3.

8.2.2.3 Comparators

8.2.2.3.1 Danish clinical practice

As mentioned in section 5.2.2, the most relevant comparator for neoadjuvant treatment with nivolumab plus PDC in the Danish treatment setting is adjuvant PDC treatment.

8.2.2.3.2 Clinical documentation submitted (in relation to clinical practice)

In the phase 3, clinical trial, CheckMate 816, neoadjuvant treatment with nivolumab plus PDC was compared with neoadjuvant PDC alone, in patients with resectable, non-metastatic NSCLC (6, 7).

8.2.2.3.3 Model submitted (according to clinical documentation and clinical practice)

Based on current literature, neoadjuvant and adjuvant PDC have been shown to have similar clinical efficacy in patients with resectable NSCLC (8, 9, 61); this has also been supported by clinical experts (18, 19). As such, the direct, in-trial comparison in CheckMate 816 is considered for the health economic model, where neoadjuvant PDC will be used as a proxy for adjuvant PDC (see Appendix N).

8.2.2.4 Relative efficacy outcomes

8.2.2.4.1 Clinical documentation submitted (in relation to clinical practice)

Primary study outcomes in CheckMate 816 were EFS and pCR. Secondary outcomes were MPR, OS, and TTDM. Results from key outcomes are summarised in Table 79.

8.2.2.4.2 Model submitted (according to clinical documentation and clinical practice)

The health economic model utilises the study outcomes from CheckMate 816 as EFS, PD and death. To allow for estimation of time-dependent transition probabilities beyond the end of the existing trial data, parametric survival modelling was conducted to inform the transition probabilities. Table 25 provides a summary of the transition probabilities considered by the model and sources used to inform the base-case analysis.

Table 25: Summary of efficacy inputs

Transition captured		Base-case source
From	To	
EF	PD	Analysis of CheckMate 816 IA2 PD-L1 ≥ 1% subgroup data (time to any progression)
	Death	Analysis of CheckMate 816 IA2 PD-L1 ≥ 1% subgroup data (time to death); pooled mortality estimated for all patients who are EF
PD	Death	Analysis of pooled CheckMate 816 IA2 PD-L1 ≥ 1% subgroup data (time to death after progression) pooled (from the two treatment arms in CheckMate 816) mortality estimate for all patients who have progressed

Abbreviations: EF, Event free; PD, Progressive disease

8.2.2.5 Adverse reaction outcomes

As previously mentioned, AE incidence was not expected to vary based on PD-L1 status and was therefore informed based on the ITT population. Treatment-related AEs of grades 3 and 4 were collected from CheckMate 816 trial data for neoadjuvant nivolumab plus PDC and neoadjuvant PDC alone. Lower-grade AEs (i.e., grade 1 to 2) were not considered, as they have an insignificant impact on cost or health-related quality of life (HRQoL) implications; typically, grade 1 to 2 AEs are manageable by the patient, such as via over-the-counter medication, whereas grade 3 or 4 AEs require inpatient management.

Specific events included were grade 3 or 4 TRAE experienced by at least 2 or more patients in at least one of the treatment arms in the CheckMate 816 trial. The consequences of AE captured by the model were expressed in terms of their management cost and utility. In addition, only AEs associated with initial treatment (i.e., current line) were included, and AEs associated with subsequent lines were excluded.

The percentage of patients experiencing a grade 3 or 4 TRAE by treatment arm are shown in [redacted] in Section 7.1.2.1.4.

8.3 Extrapolation of relative efficacy

8.3.1 Time to event data

8.3.1.1 Time to any progression, PD-L1 expression ≥1% subgroup

8.3.1.1.1 Observed data for time to any progression in the PD-L1 expression ≥1% subgroup

Estimates for time to any progression were based on data collected from the CheckMate 816 trial. The observed time to any progression curves were derived from the EFS curves by censoring death events. At the October 2022 data cut, a total of [redacted] progression events were observed in the nivolumab plus PDC arm [redacted] and [redacted] progression events were observed in the PDC alone arm [redacted] in the PD-L1 expression ≥ 1% subgroup. The median time to progression could not be estimated for neither the nivolumab plus PDC nor PDC alone treatment arms. The data translated to an overall [redacted] for nivolumab plus PDC vs. PDC alone. A summary of the observations, and the constructed Kaplan Meier (KM) curves, are depicted in [redacted] and [redacted]

[redacted]

Diagnostic plots assessing whether accelerated failure time (AFT) or proportional hazards (PH) assumptions hold between the two treatment arms are presented in [redacted] The statistical tests suggested that both AFT and PH assumptions hold, and therefore, the use of jointly fitted distributions with treatment arm as predictor was recommended for estimating time to any progression.

[redacted]

8.3.1.1.2 Extrapolations for time to any progression in the PD-L1 expression ≥1% subgroup

The short-term projections of the standard parametric functions are depicted in [redacted], for the nivolumab plus PDC and PDC alone arms, respectively. Goodness-of-fit statistics are summarised in [redacted] Most of the curves did not fit the KM data particularly well during the within-trial period, with the exception of the Gompertz distribution. Based on AIC and BIC criteria [redacted] the log-normal distribution was deemed a plausible candidate and explored further. The Generalized gamma distribution appeared to have convergence issues and was excluded from the analyses. Since the curves are jointly fitted, the same goodness-of-fit statistics apply to both arms.

[redacted]

The smoothed hazard plots presented in [redacted] suggest an initial increase in the hazard for any progression followed by a decrease, for both arms. The increase in hazards for nivolumab plus PDC towards the tail of the hazard plot is due to censoring, a sudden drop in the nivolumab plus PDC survival curve due to censoring. The expectation with regards to longer term extrapolation of hazards is nevertheless decreased hazards over time both for nivolumab plus PDC and for PDC.

[redacted]

Most of the curves did not fit the KM data particularly well during the within-trial period, with the exception of the Gompertz distribution. Based on AIC and BIC criteria [redacted] the log-normal distribution was deemed a plausible candidate and explored further.

[redacted]

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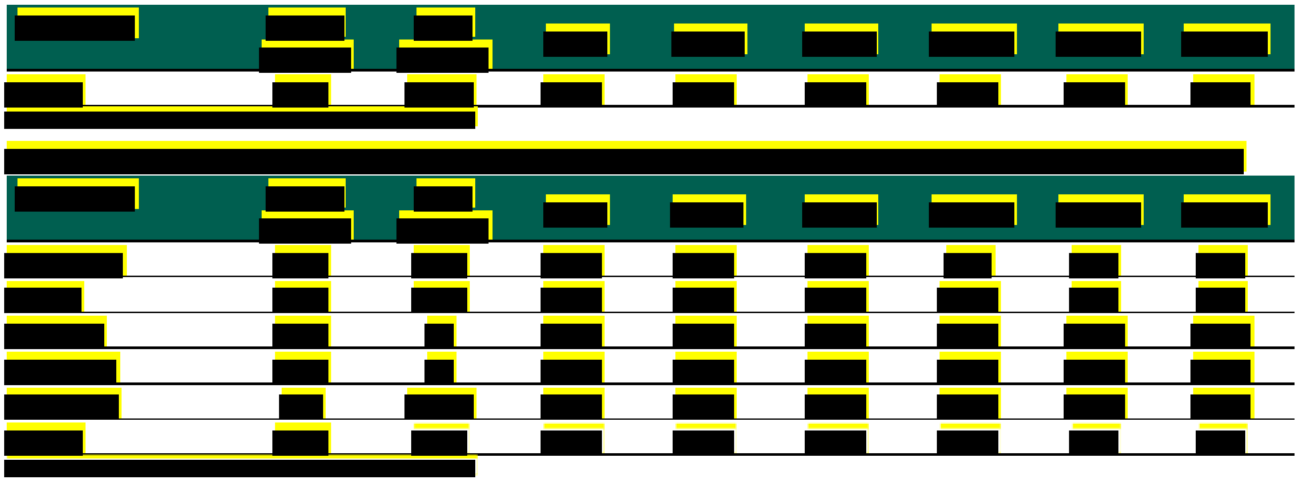
[redacted]

8.3.1.1.3 Long-term extrapolated outcomes and context for time to any progression in the PD-L1 expression ≥1% subgroup

Long-term extrapolations are shown compared to KM data for the nivolumab and PDC arm in [redacted] and [redacted] respectively. [redacted] and [redacted] detail the predicted median and mean months of time to any progression for all the distributions, along with the percentage of those who were EF at one, three, five, 10, 20, and 30 years for the nivolumab plus PDC and PDC alone arms.

[redacted]



Visual inspection of observed vs. predicted time-to-progression curves showed poor fit during the observed follow-up for most distributions, with the exception of Gompertz, which hewed closely to the KM curves. Based on statistical assessment, the jointly fitted log-normal and Gompertz distribution provided the best fit to the observed time to any progression data. However, in the long term, substantial differences were observed in the tails for each extrapolation.

Published evidence on time to progression or EFS in the PD-L1 expression ≥1% population is not available to allow comparison of the estimates against external sources. Therefore, the base case selections for the model currently rely primarily on visual fit during the within-trial period, statistical fitting measures (AIC and BIC), and considerations around the plausibility of long-term hazards given the cure assumption.

Based on visual fit and AIC/BIC, the Gompertz distribution would be considered the prime candidate for the base case projection. However, the Gompertz distribution also produces an unrealistically quick reduction in progression risk and extremely flat tails, and no risk for progression from around 72 months as indicated by the hazard plots, that imply approximately 70% of patients receiving nivolumab plus PDC and approximately 50% of patients receiving PDC would never experience disease progression. Therefore, we argue that the log-normal distribution, which was the next-best fitting distribution during the within trial period by both visual inspection and AIC/BIC, but with a much more conservative tail, should be considered the base case projection.

The time to progression endpoint observed smoothed hazard plots vs joint fits predicted hazard plots for nivolumab plus PDC and PDC alone [redacted] give some guidance to the curve selection. Generally, the exponential, gamma and Weibull distributions don't predict according to the expectation of increasing and subsequently falling hazards over time and can be ruled out. Log-logistic seems to be quite close to log-normal in terms of development of hazards over time but loses in terms of the statistical fit to observed data, hence we are left with the log-normal in our base case.

[redacted]

8.3.1.1.4 Summary: Base-case input selection for time to progression in the PD-L1 expression ≥1% subgroup

To conclude, several steps have been taken to inform the choice of the base-case input selection. The sections above are summarized below:

- The standard parametric distributions (exponential, Weibull, log-normal, log-logistic, Gompertz, generalized gamma, and gamma) were fitted to the time to any progression from the PD-L1 ≥1% subgroup data both jointly and independently to each arm of CheckMate 816
- Jointly fitted parametric extrapolations were recommended based on diagnostic testing
- Visual inspection of the within-trial data suggested most extrapolations did not fit the data well, with the exception of the Gompertz distribution. Assessment of AIC/BIC criteria suggested the log-normal distribution was also a plausible candidate distribution
- Investigations of the observed as well as long term hazards suggested that the log-normal distribution was closer to the expected hazard pattern of an initial increase in the risk for progression followed by a decrease
- Expert feedback from an advisory board suggested the log-normal distribution was plausible for EFS, which is understood to be applicable to time to any progression, given that it represents a subset of EFS outcomes

Therefore, the log-normal distribution is used in the base case to describe time to any progression for EF patients for both the neoadjuvant nivolumab plus PDC and neoadjuvant PDC alone arms of the model.

In the preparations for the dossier, fittings for time to progression were also made based on the CheckMate 816 ITT population, and the PD-L1 expression ≥1% base case selections are in line with what would have been put forward as the suggested base case analysis for the ITT population.

8.3.1.2 Mortality in EF patients in the PD-L1 expression ≥1% subgroup

8.3.1.2.1 Observed data for mortality in EF patients in the PD-L1 expression ≥1% subgroup

Data characterising mortality risks for patients who had not yet experienced a non-fatal event was available from CheckMate 816. In general, the number of pre-progression deaths in the PD-L1 expression ≥1% subgroup was low; [redacted]

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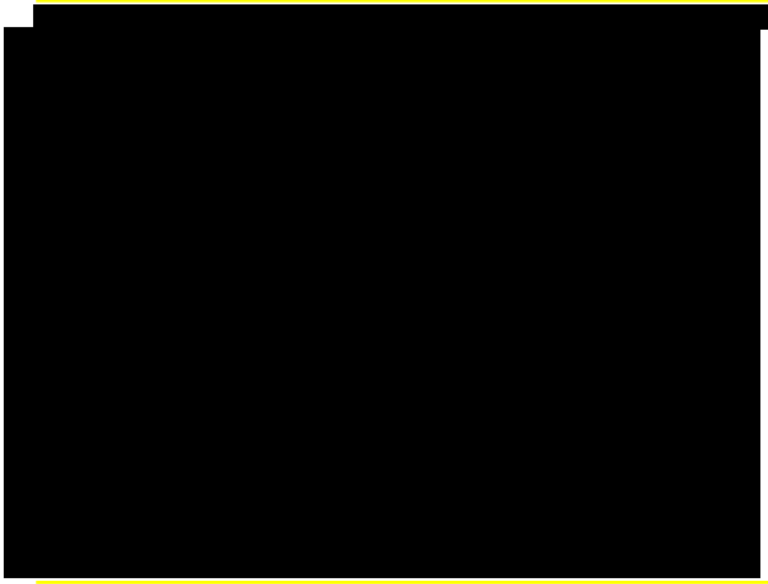
[redacted] Therefore, data from both the treatment arms were pooled for conducting the parametric survival analyses of EF mortality. This is an inherently conservative approach, as it assumes that there is no treatment-specific mortality benefit to neoadjuvant nivolumab plus PDC; rather, any survival benefit gained via neoadjuvant nivolumab plus PDC is mediated through extended EFS. The pooled KM curve is illustrated in [redacted]

[redacted]



[redacted]

[redacted]

8.3.1.2.2 Extrapolations for mortality in EF patients in the PD-L1 expression ≥1% subgroup

Smoothed hazard plots for mortality in EF patients are presented in [redacted]. Provided that only very few death events inform the hazard plots it is difficult to provide meaningful interpretations.

[redacted]

[redacted] The goodness-of-fit statistics (AIC and BIC) of all distributions fitted are presented in Table 30. Based on the goodness-of-fit statistics, [redacted] distributions provided the best fit to the observed data.

[redacted]

[redacted]

[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]

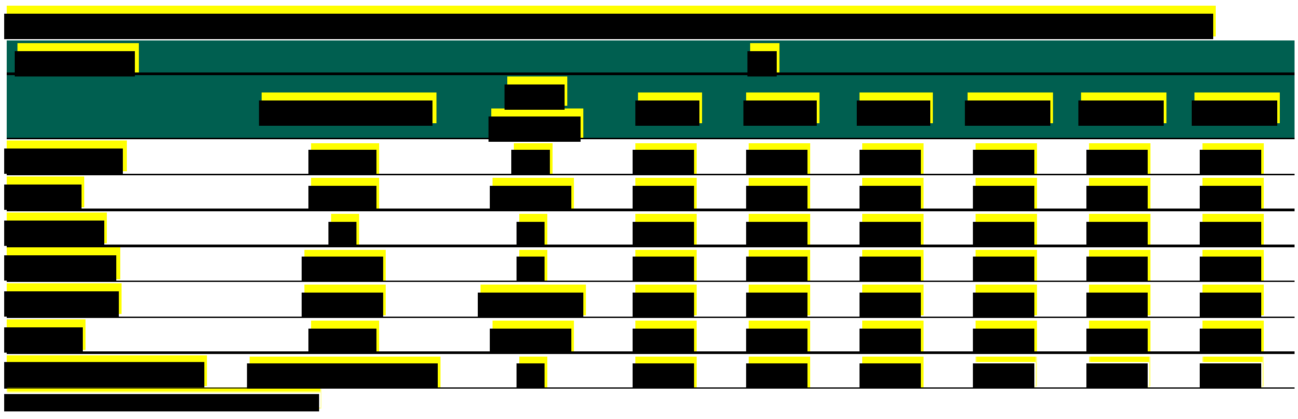
[redacted]

The long-term projections ([redacted] from log-normal, log-logistic, Weibull, and gamma were similar. Long-term projections from Gompertz suggested a plateau after 60 months (5 years) similar to the generalized gamma. The long-term projections from exponential were relatively shorter.

[redacted] details the predicted median and mean alive months from EF for all the distributions, along with the percentage of those who were EF at one, three, five, 10, 20, and 30 years for the pooled population. However, without further adjustment all projections effectively assume a much better overall survival than the general population mortality would entail.

It is clear from [redacted] that all distributions over-estimate long term survival compared to general population mortality, but the exponential distribution to a less extent than alternatives. Figure 36 shows that this still holds true after adjusting the extrapolations to account for general population mortality.

[redacted]



[redacted]

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8.3.1.2.3 Summary: base-case input selection for mortality for EF patients in the PD-L1 expression ≥1% subgroup

To summarise the base-case input selections for EF patients in the PD-L1 expression ≥1% subgroup:

- The standard parametric distributions (exponential, Weibull, log-normal, log-logistic, Gompertz, generalized gamma, and gamma) were fit to the time to death for event-free patients from the PD-L1 ≥ 1% subgroup from CheckMate-816. Pooled data from both treatment arms included in the trial were used, as the observed difference across treatment arms was not statistically significant (i.e., the 95% CI for the estimated HR crossed 1).
- Visual inspection of the within-trial data suggested that most extrapolations fit the data well. Assessment of AIC / BIC criteria suggested that the exponential and generalized gamma distributions could be plausible candidates for the base case extrapolations.
- Out of the parametric distributions explored, the exponential was assessed to be the most reasonable option to estimate survival over time in the EF state. In regard to other options such as log-normal or gamma, exponential can be seen as a conservative choice.
- Very few death events make interpretation and judgment based on statistical criteria and hazard plots less reliable. All distributions overestimate survival in comparison to general population mortality, but the exponential distribution to a less extent than alternatives, even when capping the long-term projection for mortality in EF patients by general population mortality.

The exponential distribution was used in the base case to describe time to death for all EF patients in the model, regardless of treatment strategy.

Because a reliable external source is not available to validate the time to death for EF patients among the PD-L1 expression ≥1% population, this base case selection is subject to uncertainty. Therefore, scenario analyses were conducted to explore different parametric extrapolations (further described in section 8.7.1.1) and the results suggest that OS in the EF state is not a driver of the results in the model, assuming same mortality risk regardless of treatment. This finding is strengthened by the DSA results, which also did not identify OS in EF state as a major driver of model results (see tornado diagram in Figure 47).

8.3.1.3 Mortality in PD patients in the PD-L1 expression ≥1% subgroup

8.3.1.3.1 Observed data for mortality in PD patients in the PD-L1 expression ≥1% subgroup

Similar to EF mortality, the KM curves of mortality for patients in the PD-L1 expression ≥1% subgroup who have experienced PD in CheckMate 816 were overlapping [redacted] Therefore, data from both treatment arms were pooled for conducting the parametric survival analyses of PD mortality, as shown in [redacted]

[redacted]

8.3.1.3.2 Extrapolations for mortality in PD patients in the PD-L1 expression ≥1% subgroup

The goodness-of-fit statistics (AIC and BIC) of all distributions fitted are presented in [redacted] Based on the goodness-of-fit statistics, the log-normal [redacted] distribution provided the best fit to the observed data. However, the difference in the AIC and BIC between all distributions was minimal (<4 points). Therefore, long-term projections and hazards should also be considered for selecting the best clinically plausible distribution.

[redacted]

In concordance with the small observed difference between AIC / BIC, visual inspection of the extrapolations during the within-trial period ([redacted] showed that most of the projections fit the KM curve similarly well. However, the long-

term projections ([redacted]) for the distributions differed substantially. The Gompertz distribution yielded a very flat tail, with approximately 30% of patients predicted to survive indefinitely after five years. The remaining projections were observed to split broadly into two groups: one more optimistic, and the other more pessimistic. The optimistic extrapolations were generalized gamma, log-normal, and log-logistic. The more pessimistic functions were exponential, Weibull, and gamma. These observations did not differ when the extrapolations were adjusted to account for general population mortality[redacted]

The predicted median and mean alive months from PD for all the distributions, along with the percentage of those who were PD at one, three, five, 10, 20, and 30 years for the pooled population are presented in [redacted]

[redacted]

[redacted]

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The observed hazards for death for progressed patients in CheckMate 816 (local or distant metastasis) suggests an initial increase followed by a reduction in the hazards over time [redacted] This pattern is generally in line with expectations of long-term survival after introduction of immunotherapies for progressed NSCLC disease (62, 63).

Thus, considering statistical fit criteria as well as long term hazards and survival, the log-normal distribution seems to be a reasonable alternative, as it falls in between the generalized gamma and log-logistic, projecting approximately 12% alive at 10 years in a population with PD-L1 expression ≥1% [redacted]) with a mix of local and distant recurrences.

8.3.1.3.3 Comparison vs external data for mortality in PD patients in the PD-L1 expression ≥1% subgroup

The extrapolated estimates for mortality in PD patients in the PD-L1 expression ≥1% subgroup were compared against estimates from external data to assess the plausibility of the extrapolations. A source that precisely replicated the PD patients from CheckMate 816 PD-L1 ≥ 1% was not available. Therefore, sources including populations that were similar to the PD patients from CheckMate 816 PD-L1 expression ≥ 1% subgroup were explored, to serve as a benchmark. As the PD state includes two types of progression (LR and DM progressions), separate sources were used to estimate survival for each type of progression. These external data sources were:

- Representative of patients with LR: The placebo arm from PACIFIC PD-L1 ≥ 1% subgroup: a trial of durvalumab in patients with stage III, unresectable NSCLC; PD-L1 ≥ 1% subgroup survival outcomes were reported
- Representative of patients with DM: KEYNOTE-042: a trial of pembrolizumab versus chemotherapy as 1L therapy in patients with NSCLC and PD-L1 expression ≥ 1%. Both the pembrolizumab and chemotherapy curves are used. Each treatment-specific curve is weighted based on proportions reflecting distribution of immunotherapy vs. chemotherapy used to estimate cost in the PD health state (66.3% immunotherapy / 11.8% chemotherapy and 22.0% best supportive care (BSC).

Next, OS curves from the two studies were weighted based on the observed distribution of progression events in the CheckMate 816 PD-L1 ≥ 1% subgroup, pooled across treatment arms. [redacted]

The external data is summarized in [redacted]. The comparison of the best-fitting lognormal curve (selected from section 8.3.1.3.2) with the weighted curve derived from the external data are depicted in [redacted] The close alignment of the lognormal projection and the external data further supports the clinical validity of using lognormal distribution to estimate mortality in PD.

[redacted]

8.3.1.3.4 Summary: base-case input selection for mortality in PD patients in the PD-L1 expression ≥1% subgroup

- The standard parametric distributions (exponential, Weibull, log-normal, log-logistic, Gompertz, generalized gamma, and gamma) were fit to the time to death for patients with progressive disease from the PD-L1 ≥ 1% subgroup from CheckMate-816. Pooled data from both treatment arms included in the trial were used, as the observed difference across treatment arms was both small [redacted] and not considered to be statistically significant (i.e., the 95% CI for the estimated HR crossed 1).
- Visual inspection of the within-trial data suggested that most extrapolations fit the data well. Assessment of AIC / BIC criteria suggested the log-normal distribution would be the best-fitting extrapolation, although the exponential distribution was considered to be second-best.
- The log-normal distribution hazards over time are aligned with expectations in this setting, with an initial increase followed by decreasing hazards
- Comparison with external data further supported the clinical plausibility of the log-normal distribution.

Therefore, the log-normal distribution was used in the base case to describe time to death for all patients with PD in the model with adjustments in addition to adjusting for the general population mortality, regardless of treatment strategy.

8.3.1.4 Validation

8.3.1.4.1 Survival analysis validation using Danish registry data

The survival estimates from the economic model were validated against Danish registry data. The base case settings for extrapolating the results in CheckMate 816 are summarised in Table 35 below.

Table 35: Model settings for external validation

Parameter	Input
Cure timing	5 years (2-year ramp up)
Fitting for EF to any progression	Joint log-normal
Fitting for EF to death	Exponential
Fitting for PD to death	Log-normal

Abbreviations: EF, event free; PD, progressive disease

Since neoadjuvant nivolumab plus PDC is a novel intervention for the target population and its survival outcomes were not investigated in any previous studies, it was not feasible to validate the long-term OS of nivolumab plus PDC against the external data. Therefore, the long-term OS validation was conducted for the neoadjuvant PDC alone arm only.

Data from the Danish cancer registry were identified as the most appropriate source for survival outcomes from patients with stage II to IIIA NSCLC (TNM version 7) receiving neoadjuvant therapy (64). OS data was available for patients who received adjuvant chemotherapy treatment, independent of their disease stage, for year 1, 2 and 5. Survival data by stage was also available from the registry to allow the construction of a weighted OS to reflect patients' stage distribution in CheckMate 816 which were used to inform the validation from year 5 and onwards (figure 8.2.1.5a in Dansk Lunge Cancer Register Årsrapport 2021).

Survival outcomes at year 1 and 2 for patients receiving adjuvant chemotherapy treatment in the registry (table 8.3.1.4 in the registry report), matches modelled neoadjuvant PDC OS closely (Figure 44). Although with limitations, this is supportive of the overall assumption of similar outcomes between neoadjuvant PDC and adjuvant PDC.

At year 5, differences between the modelled OS for PDC, for the all comers and PD-L1 expression ≥1% population from Checkmate 816 become apparent, however the OS is still quite close to the 5-year expected survival outcomes for

patients treated with adjuvant chemotherapy from the registry. This is expected given that the registry data survival is not restricted by PD-L1 expression. It is further expected that the patients with PD-L1 expression ≥1% will have slightly better long-term OS than all comers.

Furthermore, the pathological tumour node metastasis (pTNM) cohort, was sourced from Danish registry data and weighted by the corresponding stage proportions in Checkmate 816 (36% stage IIA-IIB and 64% stage IIIA-IIIB (N2), TNM version 8). From year 5 onwards, this cohort's survival more closely aligned with the modelled survival for PDC alone for the ITT population than for the PD-L1 expression ≥1% subgroup population, which aligned with expectations. Of note the long-term model predictions seems to match quite well the slope of the pTNM weighted cohort curve from years 5-12

compares OS at different time points, also known as a landmark comparison.

There are some limitations comparing populations in CheckMate 816 with the Danish registry data. Firstly, the population in CheckMate 816 are randomized to treatment before surgery compared with the Danish registry data, which consists of resected patients (pTNM) or patients receiving adjuvant chemotherapy irrespective of stage, meaning there can be some discrepancy in the comparability of the populations. Secondly, the Danish registry data spans over a time horizon of 12 years, meaning clinical practice may have changed during this period and, thus, may affect outcomes. The Danish registry data includes patients diagnosed from 2003 – 2021. Survival from year 1 – 5 have improved significantly over the past 10 years, and as such, the data available in the weighted pTNM curve is not representative of what one might expect with today's standards year 1-5 or even from 5 years and onwards. For instance, in Table 8.2.1.6 of the Danish registry report for patients diagnosed in 2003 - 2014 vs patients diagnosed after 2015, there is a remarkable improvement in 1-year survival of 83.6% vs 91.4%, respectively (64).

8.3.1.4.1.1 Validation against OS data from CheckMate 816

To further validate the modelled OS in this analysis, the observed OS was used to compare the relative difference between neoadjuvant nivolumab plus PDC vs neoadjuvant PDC alone with the label population (PD-L1 expression ≥1% stage II-IIIA TNM version 7). A visual comparison of the observed KM data from CheckMate 816 and the modelled (and extrapolated) OS shows that the modelled curves for nivolumab plus PDC and PDC alone are closer to each other than

the observed KM curves, indicating that the estimated benefit is conservative (see [redacted] displays the landmark OS and differences for years 2 and 3.

[redacted]

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

8.4.1 Overview of health state utility values (HSUV)

8.4.1.1 Health state utility values identified from systematic literature search

Health related quality of life data was collected in the CheckMate 816 trial—including EQ-5D-3L utility values—and were used to support this health technology assessment. As such, an SLR is redundant for this application.

8.4.1.2 Health state utility values reported in trial data

EQ-5D-3L utility data were collected in the CheckMate 816 clinical study in line with the clinical study protocol. The utility analysis used the EQ-5D-3L index score (utility index) at all timepoints in the study.

As per protocol, patients completed the EQ-5D-3L on the first day of each 3-week treatment cycle at baseline (day 1 of the first 3-week cycle) and on day 1 of every cycle during the neoadjuvant period (baseline and two on-treatment assessments), then post-neoadjuvant visits one (30 days from last dose and prior to surgery) and two (70 days from post-neoadjuvant Visit 1). EQ-5D-3L was also completed in the adjuvant period (three months after post-neoadjuvant Visit 2, or post-surgery) every 3 weeks for up to four cycles. The timing and number of EQ-5D-3L assessments were the same during the neoadjuvant period (Baseline, Week 4, Week 7, and post-neoadjuvant Visit 1) but after that could vary within patients and between treatment arms depending on whether patients underwent surgery or received adjuvant

treatment. The dates of the EQ-5D-3L assessments were used in assignment of EQ-5D-3L assessments to health states (days were calculated relative to the date of randomisation + 1).

8.4.1.3 EQ-5D analyses

The date of progression or recurrence used matches the primary analysis method in CheckMate 816 (i.e., date of progression was assigned based on BICR).

The dates of the EQ-5D-3L assessments were compared with the date of progression or recurrence; EQ-5D-3L assessments prior to the date of progression / recurrence (i.e., including baseline) were considered to be pre-progression or recurrence (i.e., applicable to event free [EF] patients), while EQ-5D-3L assessments on the same date or afterward were considered to be post-progression or recurrence (i.e., applicable to progressive disease [PD] patients).

The completion rate of EQ-5D-3L data is shown in [redacted] (nivolumab plus PDC arm) and [redacted] (PDC alone arm) below. The completion rate is out of the population of patients who were expected to complete the EQ-5D-3L at that timepoint (i.e., consists of all patients alive and on-study at the assessment timepoint). The available data rate (i.e., using all randomized patients in the study as the denominator) is also provided.

[redacted]

To estimate mean values of EQ-5D-3L for each health state, a mixed-model approach was used to account for repeated EQ-5D-3L measurements per patient within a health state (mixed model for repeated measures [MMRM]). The initial model (intercept only) did not include any health states, to estimate the mean utility overall and by treatment group. For each health-state model, two statistical models were fit: one with and one without treatment. The variable(s) defining health states, treatment, and their interaction, if any, were included in the model as fixed effects. The model without treatment included the health states only. The model with treatment included treatment, health state, and the interaction of treatment and health state in the model. A random intercept was used to account for repeated measurements within each patient. An unstructured covariance structure was used. The baseline EQ-5D-3L was considered a pre-progression value (not included as a covariate), and there was no imputation of missing data.

Additionally, EQ-5D-3L mapping to the five-level version (EQ-5D-5L) was applied for the Danish utility index values. The ordered logistic regression (including adjacent dimensions and a latent factor) approach using the van Hout and Shaw algorithm was used to predict EQ-5D-5L responses from EQ-5D-3L responses for each individual assessment as collected in the study (as per the preferred model in Table 2 of van Hout and Shaw 2021 (59)). Then, the Danish EQ-5D-5L value set was used to obtain the predicted EQ-5D-5L utility score for each individual assessment.

The mean utility estimates, using Danish preference weights, for type of recurrence health state utilities (pre-progression or recurrence) are provided in [redacted] The comparison of models with and without treatment did not show any statistically significant difference in model fit [redacted] indicating no significant difference between treatments. Please see Appendix I Mapping of HRQoL data for model fit statistics.

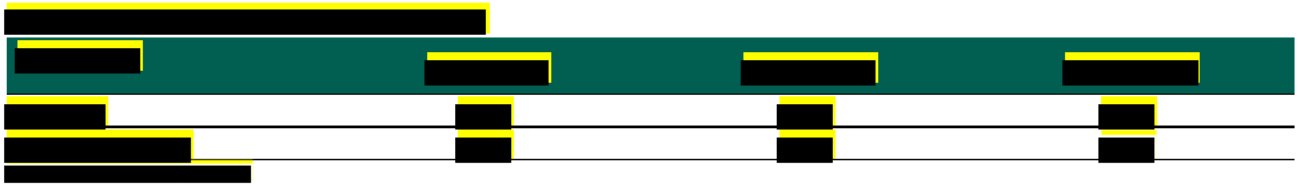
8.4.2 Health state utility values used in the health economic model

As previously mentioned, utility values were not expected to vary based on PD-L1 status and were, therefore, informed based on the ITT population. Utility values were applied to each health state in the model to capture patient quality of life associated with treatment and disease outcomes. Utility values were derived from an analysis of EQ-5D-3L data from CheckMate 816 and mapped to Danish EQ-5D-5L (see Appendix I for more information on the mapping method applied).

For the base case, the same utility is used across both treatment arms in each health state, treatment-specific utility values for the EFS and PD states are tested in scenario analyses.

The HRQoL outcomes are impacted by the occurrence of grade 3 and 4 AEs. It is assumed that any disutilities due to AEs have already been incorporated into the health state trial-derived utilities and incorporating an additional disutility could be considered double-counting. This approach was used in the base case.

Utilities used in the base case are summarized in Table 41. Overall non-treatment specific utilities by health state were used, applicable for all treatment arms equally.



8.4.2.1 Age-adjusted utilities

In line with DMC guidelines, an age-adjustment of the utility values was performed to ensure that a relative level of utility values would decline in a rate consistent with the expected decline in HRQoL observed within the general Danish population (50). The adjustment index provided by the DMC was used for this analysis, in line with their recommendations (50, 65).

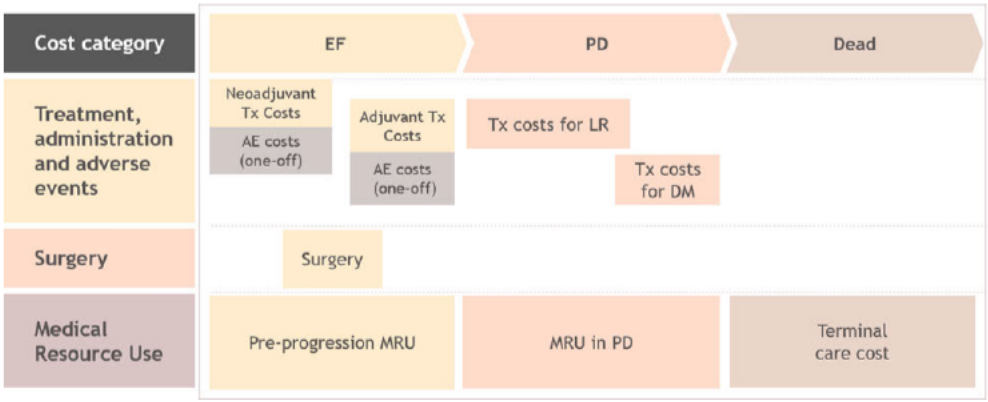
8.5 Resource use and costs

Cost input values and frequencies for the analysis was obtained from the Danish treatment guidelines and validated by clinical experts (18, 19, 66). Where experts provided different frequency estimates, the arithmetic mean from the different estimates was used as input values for the model.

Different sources were used to obtain the unit cost for all resource types, generally the DRG grouper and medicinpriser.dk was used to source costs for 2023.

An overview of cost categories per health state is presented in Figure 46.

Figure 46: Diagram of costs per health state

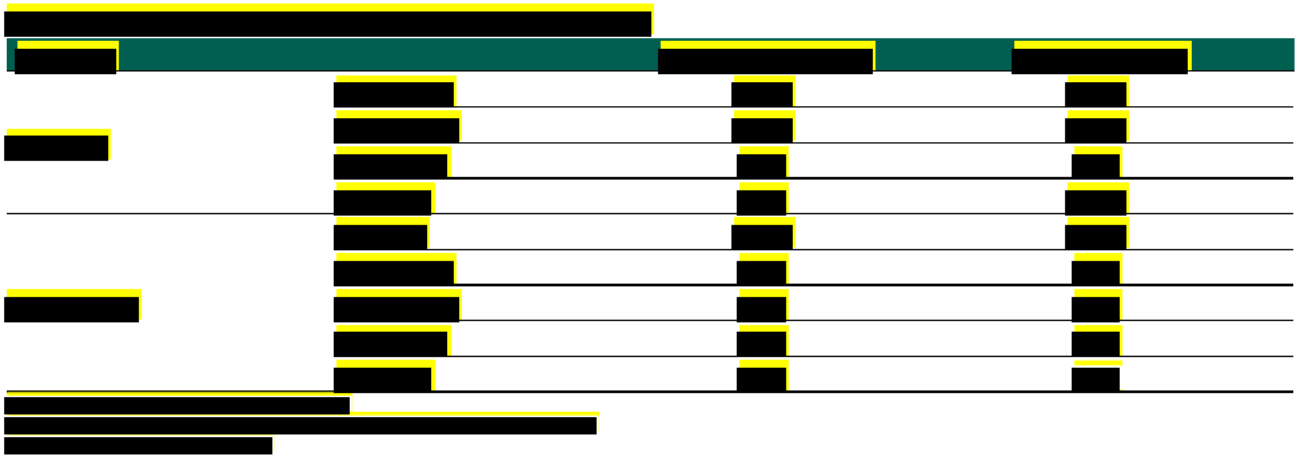


Abbreviations: AE, adverse event; DM, distant metastasis; EF, event-free; LR, locoregional recurrence; MRU, medical resource use; PD, progressive disease; Tx, treatment

8.5.1 Treatment-related costs

8.5.1.1 Neoadjuvant treatment

The cost of neoadjuvant treatment reflects nivolumab and the basket of PDC received in CheckMate 816. The composition of PDC in the nivolumab plus PDC and PDC alone treatment arms is described in [redacted]. For patients in the nivolumab plus PDC arm, all patients received nivolumab in addition to the listed distribution of PDC. Patients incurred costs of neoadjuvant treatment for three full cycles of treatment, at an assumed relative dose intensity (RDI) of 100%. For patients who progressed before completing three cycles of treatment, costs of neoadjuvant treatment were applied until the time of progression.



For patients who continue to receive adjuvant treatment after surgery, costs were adjusted for the proportion of patients receiving adjuvant treatment and the type of treatment received informed by the CheckMate 816 trial. Treatment costs were applied for the mean number of treatment cycles received among patients in the adjuvant setting in the CheckMate 816 trial.

8.5.1.2 Adjuvant treatment

In the CheckMate 816 trial, some of the patients that received neoadjuvant treatment later received adjuvant systemic therapy or radiotherapy. The proportions are shown in Table 43. The distribution of treatment regimens for adjuvant PDC was assumed to be the same as neoadjuvant PDC as described in Table 42. Adjuvant PDC is administered for three cycles.

Table 43 Patients on neoadjuvant treatments who continue with adjuvant treatments

Treatment	[redacted]	Unit cost of radiotherapy
Nivolumab + PDC		DKK 8247
PDC (neoadjuvant)		DKK 8247

[redacted] BMS data on file 2023 and Interaktiv DRG 2023, DRG 27MP10. (DC349) Kræft i lunge UNS + (BWGC23) Stereotaktisk stralebehandling af lungerDisease management costs (67, 68).

The costs for disease management and drug monitoring are considered separately.

Healthcare resource utilization relates to disease management that is beyond the healthcare resources that are required related to each treatment alternative. The healthcare resource use is expected to differ between EF and PD health states, which has been validated by Nordic clinical experts (18, 19). Municipal costs are included to reflect non-specialist treatments, such as home care nurse visits.

Table 44 presents the disease management costs divided by municipal and regional costs for patients in the EF and PD health states.

Table 44: Disease management costs in the event-free and progressed disease health states

Resource name	Resource use in Health state EF, per year	Resource use in Health state PD, per year	Unit cost (DKK)	Reference for unit costs
Municipal costs				
Home Care Nurse visit	0	0.5	467.24	Kommunernes og Regionernes Løndatakontor 2023, Syge- og Sundhedspersonale, basis KL (Sygeplejersker). bruttolön Nov 2022, no newer data available. available from: https://krl.dk/#/sirka Calculated: salary/hours per month according to Medicine council 2022.
Regional costs				
Oncology visit	1.2	1.6	1234.00	Interaktiv DRG 2023, DRG 04MA98. (DC349) Kræft i lunge UNS + (ZZ9030) Aktuel behandling
General practitioner visit	1.2	1.6	929.80	Kommunernes og Regionernes Løndatakontor 2023, Kommunallæger (Overlæger). bruttolön Nov 2022, no newer data available. available from: https://krl.dk/#/sirka Calculated: salary/hours per month according to Medicine council 2022.
Other specialist visit	0	0.6	1234.00	Interaktiv DRG 2023, DRG 04MA98. (DC349) Kræft i lunge UNS + (ZZ9030) Aktuel behandling
CT scan	1.6	5	3488.00	Interaktiv DRG 2023, DRG 36PR07. (DC349) Kræft i lunge UNS + (WMBCSXYXX)CT Thorax på SPECT/CT
MRI	0	0.2	3488.00	Interaktiv DRG 2023, DRG 36PR07. (DC349) Kræft i lunge UNS + (WMAMPXYXX)MR WB på PET/MR

Abbreviation: DKK, Danish Kroner; DRG, Diagnosis Related Groups; EF, Event-free; PD, progressive disease; CT, computerised tomography; MRI, Magnetic resonance imaging

The treatment monitoring costs relate to specific test required for each of the treatment alternatives (i.e., nivolumab plus PDC and PDC alone), based on Nordic clinical expert feedback (18, 19). Treatment monitoring costs were applied when patients were on treatment and receiving monitoring tests, such as full blood count or liver function test. Table 45 presents the frequency of patients receiving monitoring tests during EF and PD states, along with the unit costs of the tests.

Table 45: Treatment monitoring costs

	Treatment monitoring frequency per cycle in EF		Treatment monitoring frequency per cycle in PD		Unit cost of tests (DKK)	Frequency source	Source
	Nivolumab plus PDC	PDC alone	Nivolumab plus PDC	PDC alone			
Full blood count	1	1	1	1	116	Assumption	Rigshospitalets Labportal (2023). Test code for complete blood count tests included (codes): NPU02902 (cost for test assumed as proxy for codes: NPU01960, NPU01961, NPU02593), NPU01473 (cost for test assumed as proxy for codes: B-Hb (Hemoglobin), Erc(B)-MCV, Erc(B)-MCH, Erc(B)-MCHC). https://labportal.rh.dk/Labportal.asp
Metabolic panel	1	1	1	1	116		Assumed same as full blood count
Liver function	1	1	1	1	80		Rigshospitalets Labportal (2023). Test code for NPU19651 (ALAT), NPU19654 (ASAT), NPU27783 (fosfatase), NPU19673 (albumin), NPU01370 (bilirubiner), NPU03278 (protein). Accessed: January 2023. Available from: https://labportal.rh.dk/Labportal.asp
Renal function	1	1	1	1	227		Rigshospitalets Labportal (2023). Test code for renal tests included (codes): NPU01459, NPU01472, NPU03429, NPU03230, NPU01536, NPU23745, NPU02192, NPU04998, NPU19673. https://labportal.rh.dk/Labportal.asp

Abbreviations: ALAT, alanine aminotransferase; ASAT; aspartate transaminase; DKK, Danish Kroner; EF, Event-free; PDC, Platinum-doublet chemotherapy; PD, Progressive disease.

8.5.2 Drug acquisition costs

The dosing regimen for each treatment option included in the neoadjuvant and adjuvant setting was based on the dosing used in the CheckMate 816 trial (Table 46). The dosing of some intravenous treatments is dependent on a patient's body surface area (BSA). A mean BSA of 1.84 m^2 was derived based on patient characteristics in the CheckMate 816 trial (Table 47) and average height of the UK population (validated by clinical expert).

Unit costs and package information for each treatment option is presented in Table 48. For treatments that are BSA dependent, there is a potential for drug wastage if perfect vial sharing is not implemented. For the base case, the model included drug wastage (no vial sharing).

Table 46: Dosing regimen for each treatment

Treatment	Dose dependency	Dose per administration	Administration route	Treatment cycle length (weeks)	Number of administrations per treatment cycle
Nivolumab	Fixed dose	360 mg	IV	3	1
		PDC (neoadjuvant and adjuvant)			
Carboplatin	AUC	900 mg	IV	3	1
Cisplatin	BSA	75 mg/m^2	IV	3	1
Paclitaxel	BSA	175 mg/m^2	IV	3	1
Gemcitabine	BSA	1250 mg/m^2	IV	3	2
Pemetrexed	BSA	500 mg/m^2	IV	3	1
Docetaxel	BSA	75 mg/m^2	IV	3	1
Vinorelbine	BSA	25 mg/m^2	IV	3	2
Radiotherapy	1.5 gy twice daily (45 gy in 3 weeks)			3	30

Abbreviations: AUC, area under the curve; BSA, body surface area; gy = Gray *(unit of ionizing radiation dose)*; IV, intravenous; PDC, platinum-doublet chemotherapy

Table 47: Patient characteristics

Patient Characteristics	Mean (SD)	Source
Starting age (years)	63.8 (8.4)	CheckMate 816
Weight (kg)	68.85 (14.94)	CheckMate 816
BSA (m^2)*	1.84 (0.184)	Gehan et al. (UK) (69) Confirmed by clinical expert to be relevant

Abbreviations: BSA, body surface area; SD, standard deviation
BSA estimated using the Gehan and George formula: 0.01545(height^0.54468)*(weight^0.46336)

Table 48: Unit drug acquisition costs

	Treatment	Cost per pack/vial (DKK)	Dose/vial concentration	Pack size/vial volume	Source
PDC	Carboplatin	203.00	450 mg	1	Medicinpriser.dk https://www.medicinpriser.dk/Default.aspx?id=15&vnr=439635
	Cisplatin	200.00	100 mg	1	Medicinpriser.dk https://www.medicinpriser.dk/Default.aspx?id=15&vnr=548680
	Paclitaxel	201.50	300 mg	1	Medicinpriser.dk https://www.medicinpriser.dk/Default.aspx?id=15&vnr=076395
	Gemcitabine	385.00	10 mg/ml	200.0 ml	Medicinpriser.dk https://www.medicinpriser.dk/Default.aspx?id=15&vnr=109326
	Pemetrexed	110.50	25 mg	4	Medicinpriser.dk https://www.medicinpriser.dk/Default.aspx?id=15&vnr=116888
	Docetaxel	150.00	80 mg	4.0 ml	Medicinpriser.dk https://www.medicinpriser.dk/Default.aspx?id=15&vnr=170823
	Vinorelbine	245.00	10 mg	10	Medicinpriser.dk https://www.medicinpriser.dk/Default.aspx?id=15&vnr=054238
Other drugs	Nivolumab	3508.46	10 mg/ml	4 ml	Medicinpriser.dk https://www.medicinpriser.dk/Default.aspx?id=15&vnr=539385
	Pembrolizumab	22 058.88	100 mg	1.0	Medicinpriser.dk https://www.medicinpriser.dk/Default.aspx?id=15&vnr=585359

Treatment	Cost per pack/vial (DKK)	Dose/vial concentration	Pack size/vial volume	Source
Atezolizumab	20 722.76	840 mg	1	Medicinpriser.dk https://www.medicinpriser.dk/Default.aspx?id=15&vnr=540857
Ipilimumab	24 386.89	5 mg/ml	10 ml	Medicinpriser.dk https://www.medicinpriser.dk/Default.aspx?id=15&vnr=597433

Abbreviations: DKK, Danish Kroner; PDC, platinum-doublet chemotherapy; VAT, Value added tax; mg, milligram; ml, millilitre

8.5.3 Drug administration costs

Drug administration costs were applied per administration for drugs administered intravenously. Unit costs for drug administration were based on the DRG tariff for one hospitalisation day for respiratory tract disorders (DRG code 04MA98) (70) (Table 49).

Table 49: Drug administration costs

Administration type	Cost per administration (DKK)	Source
Simple parenteral chemotherapy at first attendance	1234	Interaktiv DRG 2023, DRG 04MA98. (DC349) Kræft i lunge UNS + (BWAA62) Medicingivning ved intravenøs infusion
More complex parenteral chemotherapy at first attendance	1234	
Complex chemotherapy, including prolonged infusion treatment, at first attendance	1234	
Subsequent elements of a chemotherapy cycle	1234	

Abbreviations: DKK, Danish Kroner

8.5.4 Cost of surgery

The proportion of patients receiving surgery after nivolumab plus PDC and neoadjuvant PDC was informed by the CheckMate 816 trial. In the model, the proportion of patients receiving each surgery type was based on Danish real-world data and is described in Table 50 (71). The cost for surgery is described in Table 51.

Table 50: Rate of surgery and distribution by surgical approach

Treatment	% Receiving surgery	% Receiving thoracotomy*	% Receiving minimally invasive*
Neoadjuvant nivolumab plus PDC	83.2%	21.5%	78.5%
Neoadjuvant PDC	75.4%	21.5%	78.5%

Abbreviations: PDC, Platinum doublet chemotherapy
*As a proportion of patients receiving surgery

Table 51: Unit cost for surgery

Surgery approach	Unit cost (DKK)	Source
Thoracotomy	101 943	Interaktiv DRG 2023, DRG 04MP02. (DC349) Kræft i lunge UNS + (KGDA20) Excision af patologisk væv i lunge
Minimally invasive	45 581	Interaktiv DRG 2023, DRG 04MP05. (DC349) Kræft i lunge UNS + (KGDA21) Torakoskopisk excision af patologisk væv i lunge

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

8.5.5 AEs management costs

Costs of grade 3 or 4 AEs experienced by at least two or more patients in at least one of the treatment groups in the CheckMate 816 trial were considered in the model. AE costs were applied as a one-time cost in the first model cycle when patients are receiving active treatments. The total AE cost for each comparator was estimated as a weighted average of treatment costs for each included AE, with weights being the AE rates observed in the trial (see Section 7.1.2.1.7.1). Table 52 below presents the unit costs for each AE considered in the model.

The AEs costs were calculated in the model "Adverse Events" sheet by multiplying the expected frequency for each AE with its associated unit costs for each treatment arm. For example, febrile neutropenia grade 3 were experienced by [redacted] and [redacted] of the patients in the nivolumab plus PDC and PDC arms respectively, and these frequencies were multiplied with the associated unit cost of DKK 1234. The higher unit cost associated with grade 4 AEs (DKK 2240) reflects an expected increase in resource use based on the severity of the AE. Both grade 3 and 4 AEs are expected to require investigations at a hospital and/or hospitalization.

Table 52: AEs management unit costs

Grade	AE	Unit cost (DKK)	Source
Grade 3	All Grade 3 AEs	1234	Interaktiv DRG 2023, DRG 04MA98. (DC349) Kræft i lunge UNS + (ZZ9030) Aktuel behandling
Grade 4	All Grade 4 AEs except anaphylactic reaction	2240	Interaktiv DRG 2023, DRG 16MA98. (DD709A)Neutropeni og agranulocytose forårsaget af lægemiddel + (BXXB0)Tværfaglig udredning og behandling (Akut)
	Anaphylactic reaction	4342	Interaktiv DRG 2023, DRG 21MA01. (DT886)Anafylaktisk shock ved korrekt administration af lægemiddel + (BXXB0)Tværfaglig udredning og behandling (Akut)

Abbreviations: AE, Adverse events; DKK, Danish Kroner.

8.5.6 Post-progression treatment costs

A one-off post-progression cost was applied to all patients at the time of transition to the PD health state. This one-off cost considers the cost of multiple lines of treatment that patients are expected to receive in PD, specifically:

- Treatment for LR
- 1L treatment for DM
- Second-line (2L) treatment for DM

The costs for each line of treatment are subsequently adjusted to consider the distribution of patients in PD based on initial type of progression (LR or DM), the percentage of patients initially progressing to LR who subsequently progress to DM, and the percentage of patients who receive 1L treatment for DM who go on to receive 2L treatment for DM.

The distributions of initial progression types for nivolumab plus PDC and neoadjuvant PDC were informed by the CheckMate 816 trial PD-L1 expression ≥ 1% subgroup and are presented in [redacted]

Patients initially experiencing LR progression can experience secondary progression to DM. An estimate of the percentage of patients experiencing secondary progression could not be obtained from CheckMate 816 data, because any progression events after the first were not tracked in the study. Therefore, we used an estimate based on evidence from the LuCaBIS study (72). The LuCaBIS study is a retrospective study performed in France, Germany, and the UK, which investigated adjuvant treatment patterns and outcomes for NSCLC patients. In the study, 831 adult patients diagnosed with stage IB–IIIA disease (TNM version 7) were included. The patients were diagnosed between January 2009 and December 2011, inclusive, and the study had a median follow-up of 26 months (72). In LuCaBIS, approximately 16.3% of patients who experienced LR later experienced secondary progression to DM (median follow-up of 26 months). These patients incur both LR and DM costs in the model.

Unit costs for each treatment modality were extracted from Danish price lists. The cost of PDC during PD was based on four cycles of cisplatin + pemetrexed. The unit cost for salvage surgery was assumed to be the same as the thoracotomy

cost used for initial resection. Based on these inputs, the total weighted cost of treatment for patients progressing to LR was estimated to be DKK 51 511.56 per patient (Table 54).

Table 54: Treatment costs during LR

Treatment	% Receiving PDC	% Receiving Radiotherapy	% Receiving Surgery
All treatments	60.0%	60.0%	40.0%
Therapy	**Cost (DKK)**	**%**	**Weighted Cost (DKK)**
4 cycles of Cisplatin + Pemetrexed	9643.60	60.0%	5786.16
Radiotherapy– Intraluminal Brachytherapy	8247.00	60.0%	4948.20
Thoracotomy	101 943.00	40.0%	40 777.20
Total weighted cost during LR			51 511.56

Abbreviations; LR, locoregional recurrence; PDC, platinum-doublet chemotherapy

8.5.6.1 First-line treatment for patients with DM

The cost applied to patients for 1L management of DM is based on the mix of therapies that patients would be expected to receive after experiencing distant metastatic progression. The distribution of 1L DM therapies leverages input from clinical experts and assumptions. The model includes functionality to consider re-treatment restrictions that may be in place for immunotherapies. In the base-case analysis, patients who progress on or within six months of treatment with nivolumab plus PDC in the neoadjuvant setting are not eligible for further treatment with immunotherapies; for those patients, immunotherapy weights are set to zero and redistributed across remaining treatment options. Based on data from CheckMate 816, [redacted] of patients treated with nivolumab plus PDC experienced an event while on treatment or within six months of treatment completion and were therefore assumed not eligible for further treatment with immunotherapy.

To estimate the total treatment costs, the model considers the mean duration of these treatments and the dose frequency in a continuous manner. For example, if a treatment is administered once monthly and has a mean duration of 2.5 months, then the cost of 2.5 doses would be applied. Treatment durations for 1L immunotherapies were based on available information, including time-to-treatment discontinuation (TTD) curve extrapolations, from the relevant published assessments within the 1L setting in Denmark.

Table 55 presents the distribution of treatments received in 1L DM used in the model. The distribution was adjusted for nivolumab plus PDC to reflect the retreatment restrictions noted in the previous paragraph. The treatment durations are presented in Table 56.

Table 55: Distribution of 1L DM therapies

Comparator	Pembrolizumab/ carboplatin/ paclitaxel (squamous)	Pembrolizumab/ pemetrexed/ platinum chemotherapy (non-squamous)	Atezolizumab	PDC	BSC
	1L treatments during DM (before retreatment adjustments)				
Nivolumab + PDC	9.7%	39.8%	28.6%	0.0	22.0%
PDC (neoadjuvant)	9.7%	39.8%	28.6%	0.0%	22.0%
	1L treatments during DM (after retreatment adjustment)				
Nivolumab + PDC	8.2%	33.8%	24.3%	11.8%	22.0%
PDC (neoadjuvant)	9.7%	39.8%	28.6%	0.0%	22.0%

Abbreviations: 1L, first line; DM, distant metastasis; PDC, platinum-doublet chemotherapy; BSC, best supportive care
Source: DMC 2022 (73, 74)

Table 56: Treatment duration and estimated cost per course of treatment for 1L DM therapies

	Pembrolizumab/ carboplatin/ paclitaxel (squamous)	Pembrolizumab/ pemetrexed/ platinum chemotherapy (non-squamous)	Atezolizumab	PDC	BSC
Duration, months	11.4	9.805	11.7	2.3	0

	Pembrolizumab/ carboplatin/ paclitaxel (squamous)	Pembrolizumab/ pemetrexed/ platinum chemotherapy (non-squamous)	Atezolizumab	PDC	BSC
Estimated cost per course of treatment, DKK	736 766	644 079	533 129	2 724	0

Abbreviations: 1L, first line; DKK, Danish Kroner; DM, distant metastasis; PDC, platinum-doublet chemotherapy; BSC, best supportive care
Sources: (75-77)

8.5.6.2 Second-line treatment for patients with DM

Based on interviews with clinical experts the model estimates that 70% of patients receiving 1L treatment for DM would go on to receive 2L treatment for DM. The distribution of treatment modalities was assumed to be PDC or single agent chemotherapy for and was based on assumptions in regard to clinical guidelines and assumed to be the same across treatment arms.

The duration of treatment in 2L DM was derived from an advisory board conducted by BMS for 1L NSCLC (78) and is the same as applied in the Danish submission of nivolumab plus ipilimumab plus 2 cycles of PDC (9LA). Table 57 presents the distribution and duration of treatments in 2L DM.

Table 57: Distribution, treatment duration, and estimated cost per course of treatment for 2L DM therapies

	PDC	Single agent chemotherapy
Distribution of 2L treatments, %	65.0%	35.0%
Duration, months	5.09	5.09
Estimated cost per course of treatment, DKK	4936	2651

Abbreviations: 2L = second line; DKK, Danish Kroner; DM = distant metastasis; PDC = platinum-doublet chemotherapy

8.5.7 Terminal care costs

A one-off cost of terminal care was applied to patients who entered the death state. The cost of terminal care is estimated as 100% hospital treatment. Unit costs for terminal care were estimated from a previous DMC assessment of pembrolizumab (73). The one-time cost of terminal care was estimated to be DKK 41 419. A scenario that explores the results without costs for terminal care is presented in Table 66. The inputs used to compute the terminal care costs employed in the model are shown in Table 58 below. Terminal care costs are considered relevant when costing for care in the neoadjuvant setting, as the aim of treatment is cure, and terminal care would be expected for patient who fail to reach cure.

Table 58: Distribution of patients by type of end-of-life care and costs of terminal Care

Resource	% Patient	Cost (DKK)	Source
Hospital	100%	44 419	DRG Grouper 2023, DRG 04MA07 long term stay. (DC349) Cancer of lung UNS + (BXBA) Specialized palliative care. Rate for long stay palliative care. 30-day duration of palliative care assumed according to a previous DMC assessment.(73)

Abbreviations: DRG, Diagnose related groups; DKK, Danish Kroner
Reference: (73)

8.5.8 Patient costs for time spent on treatment and transportation

Costs for patients' time and transportation were included in the base case in line with Danish HTA guidelines (50). These costs aimed to cover the cost paid by patients in regard to the treatments. The number of visits per model cycle was based upon resource utilization frequencies per year for EF and PD health states (Table 44).

The input values used for indirect costs in the cost-effectiveness analysis are the same as what was accepted by the DMC in a previous assessment for nivolumab plus ipilimumab and 2 cycles of PDC (9LA) (73) and are presented in Table 59.

Table 59: Patient costs included in the model

Cost category	Input	Value	Reference
Caregiver and patient costs for leisure	Hourly wage (DKK)	181 DKK per hour patient time	DMC assessment of nivolumab plus ipilimumab and 2 cycles of PDC (9LA) (73)
	Hours per visit EF	2	Assumption
	Hours per visit PD	2	Assumption
Travel costs	Travel cost per visit (DKK)	140 DKK for transportation	DMC assessment of nivolumab plus ipilimumab and 2 cycles of (9LA) (73)
	Mean number of visits per cycle EF	0.230	Clinical experts
	Mean number of visits per cycle PD	0.546	Clinical experts

Abbreviations: DKK, Danish Kroner; DMC, Danish Medicines Council; EF, event free; PD, progressive disease., PDC, platinum-doublet chemotherapy.

8.6 Base case overview

The settings for the base case are presented in Table 60.

Table 60: Base case settings and inputs

Parameter	Base case value	Justification/Source
Model settings		
Time horizon	Lifetime (35 years)	DMC guidelines
Discount rate	3.5% for both health benefits and costs	DMC guidelines
Perspective	Limited societal perspective	DMC guidelines
Clinical inputs		
Time to PD	Log-normal	Judged to be most plausible fitting on basis of statistical fit, clinician feedback, comparison against external sources
Mortality in EFS	Exponential	Judged to be most plausible fitting on basis of statistical fit, clinician feedback, comparison against external sources
Mortality in PD	Log-normal	Judged to be most plausible fitting on basis of statistical fit, clinician feedback, comparison against external sources
Cure assumption	Yes	Evidence from the literature, clinical expert feedback
Onset of cure	5 years	Estimate based on literature and clinical expert feedback
Time from onset to cure	2 years	Assumption
% patients cured	95%	Assumption, 95% of patients who remain event-free for at least five years achieve functional cure, with no risk of progression and mortality equal to that expected for the general population.
Cost inputs		
Duration of neoadjuvant treatment	Three cycles	In CheckMate 816, most patients received the full course of neoadjuvant treatment; Given the relatively higher cost of nivolumab, assuming that all patients who do not progress or die receive the full three cycles of treatment is a conservative assumption
Duration of adjuvant treatment	Three cycles	Based on treatment duration expected in Danish clinical practice
Unit costs	Based on Danish sources	Aligned with this analysis perspective of Denmark
MRU frequency	Based on clinical expert	Clinical experts interviewed who has clinical experience with the relevant treatments
Utility Inputs		
Baseline utility in EFS (CI)	0.903 (0.892-0.915)	Based on data collected in the CheckMate 816 study (Danish weights)
Baseline utility in PD (CI)	0.827 (0.809-0.845)	Based on data collected in the CheckMate 816 study (Danish weights)

Abbreviations: DMC, Danish Medicines Council; EF, event free; PD, progressive disease; LY, life year; MRU, medical resource use; QALY, quality-adjusted life year.

8.6.1 Base case results

Results from the base case are presented in Table 61. Results showed that the use of nivolumab plus PDC led to gains in both LYs and QALYs compared with PDC alone. Given that mortality is the same for patients in the same health state across treatments, LY and QALY gains for nivolumab plus PDC are driven by the extended EFS predicted for nivolumab plus PDC relative to neoadjuvant PDC. Nivolumab plus PDC was associated with higher drug acquisition costs compared with neoadjuvant PDC alone, but this was offset by beneficial costs in other cost categories, particularly treatment costs in the PD health state; Patients treated with neoadjuvant nivolumab plus PDC experienced progression later, and the overall cost of treatment in PD was lower for nivolumab plus PDC compared to PDC alone because patients treated with nivolumab plus PDC were more likely to experience LR progression instead of DM progression, which resulted in lower treatment costs in PD.

The incremental costs, LYs, and QALYs are presented in Table 64. Nivolumab plus PDC was associated with higher LYs and QALYs than neoadjuvant PDC over the 35-year time horizon, accruing an additional 1.72 LYs and 1.52 QALYs vs. neoadjuvant PDC alone. The use of nivolumab plus PDC resulted incremental costs of -40 996 DKK compared to neoadjuvant PDC.

As treatment with nivolumab plus PDC is associated with both higher QALYs and lower costs, PDC alone is dominated by nivolumab plus PDC.

Table 61: Base case deterministic results

	Nivolumab plus PDC	Neoadjuvant PDC alone
Health outcomes (discounted)		
Total life-years	9.75	8.02
LYs in EF	8.43	6.04
LYs in PD	1.32	1.99
Total QALYs	8.34	6.82
QALYs in EF	7.29	5.24
QALYs in PD	1.05	1.58
Cost outcomes DKK (discounted)		
Drug acquisition	90 800	1835
Drug administration	4229	6534
Surgery	48 005	43 505
Adjuvant care after neoadjuvant	26 566	73 781
Treatment cost in PD	80 665	157 179
Resource use	98 682	94 197
EF	68 901	49 370
PD	29 781	44 827
Treatment monitoring	22 452	32 727
EF	2038	1998
PD	20 414	30 728
AE management	497	621
Terminal cost	28 378	30 891
Total costs	400 275	441 270

Abbreviations: AE, adverse event; DKK, Danish Kroner; EF, event free; LY, life year; PD, progressive disease; PDC, platinum-doublet chemotherapy; QALY, quality-adjusted life year.

Patient and municipal costs are included in treatment monitoring and resource use costs presented in Table 61. These costs are presented separately in Table 62. The cost outcomes reporting that distinguish between regional, municipal and patient costs are shown in Table 63.

Table 62: Patient and municipal costs

	Nivolumab plus PDC	Neoadjuvant PDC alone
Patient costs (included in treatment monitoring)		
EF (DKK)	438	430
PD (DKK)	8046	12 112
Municipal costs (included in resource use)		
EF (DKK)	0	0
PD (DKK)	1968	1410

Abbreviations: DKK, Danish Kroner; EF, event free; PD, progressive disease.

Table 63 Base case deterministic results including patient and municipal costs

	Nivolumab plus PDC	Neoadjuvant PDC alone
Cost outcomes DKK (discounted)		
Drug acquisition	90 800	1835
Drug administration	4229	6534
Surgery	48 005	43 505
Adjuvant care after neoadjuvant	26 566	73 781
Treatment cost in PD	80 665	157 179
Resource use	96 713	92 787
EF	68 901	49 370
PD	27 812	43 417
Treatment monitoring	13 968	20 185
EF	1600	1569
PD	12 368	18 617
AE management	497	621
Terminal cost	28 378	30 891
Patient costs	8484	12 541
Municipality costs	1968	1410
Total costs	400 275	441 270

Abbreviations: DKK, Danish Kroner; EF, event free; PD, progressive disease; PDC, platinum-doublet chemotherapy.

Table 64: Base case – Incremental outcomes

Outcome	Nivolumab plus PDC vs. Neoadjuvant PDC alone
Incremental costs (DKK)	-40 996
Incremental LYs	1.72
Incremental QALYs	1.52
ICERs	
Cost per LY (DKK)	Dominant
Cost per QALY (DKK)	Dominant

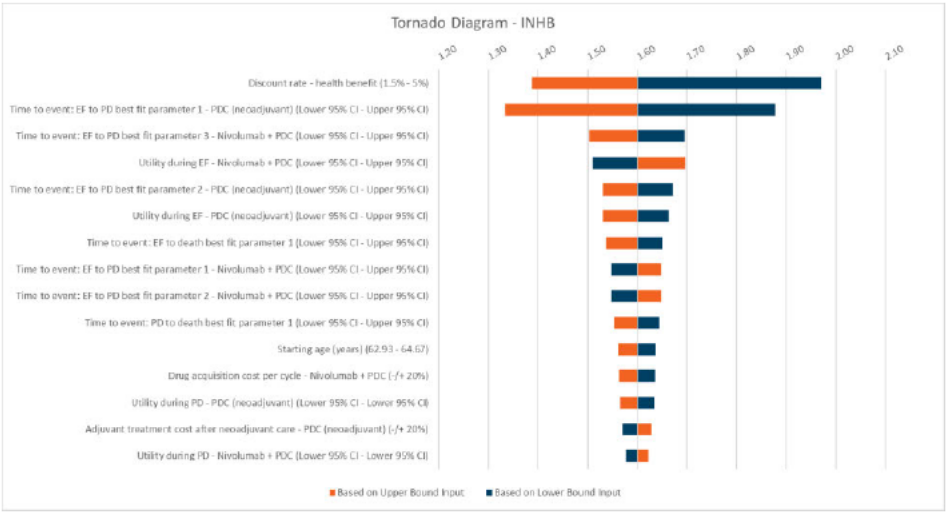
Abbreviations: DKK, Danish Kroner; ICER, incremental cost-effectiveness ratio; LY, life year; PDC, platinum-doublet chemotherapy; QALY, quality-adjusted life year.

8.7 Sensitivity analyses

8.7.1 Deterministic sensitivity analyses

A deterministic sensitivity analysis (DSA) was conducted comparing nivolumab plus PDC to PDC alone in the model. The analyses varied the key model settings, efficacy inputs, costs, and utility values. Results are presented in the form of a tornado diagrams in Figure 47. As the result of the analysis is a dominating scenario where no ICER is available to be varied in the DSA, the incremental net health benefit (INHB) [redacted] was explored instead, demonstrating a positive INHB across scenarios.

Figure 47: Tornado diagram for nivolumab plus PDC vs. PDC alone (neoadjuvant)



Abbreviations: 1L, first line; CI, confidence interval; DM, distant metastasis; EF, event free; ICER, incremental cost-effectiveness ratio; INHB, Incremental net health benefit; PD, progressive disease; PDC, platinum-doublet chemotherapy.

8.7.1.1 Scenario analyses

The list of scenarios tested in the scenario analyses is presented in Table 65.

Table 65: Scenario analyses

Scenario	Base case value	Scenario value	Detailed description
Scenario 1	3.5% costs and health outcomes	0% costs and health outcomes	Discounting: 0% for both costs and QALYs
Scenario 2	Patient age: 63 years	Alternative patient age	Starting age: 63.9 years per CheckMate 816
Scenario 3		Alternative patient age	Starting age: 72 years, per Danish registry report
Scenario 4	Exclude wastage	Include wastage	Vial sharing
Scenario 5	35-year time horizon	15-year time horizon	15-year time horizon
Scenario 6		10-year time horizon	10-year time horizon
Scenario 7	Cure assumption: Event free after 5 years	Cure assumption: Event free after 3 years	Explores a scenario where cure is assumed to occur at three years
Scenario 8		Cure assumption: Event free after 7 years	Explores a scenario where cure is delayed
Scenario 9	Cure assumption: 95% of patients cured	Cure assumption: 90% of patients cured	Explores a scenario where less patients are cured
Scenario 10	Terminal care costs included	Terminal care costs excluded	Explores a scenario where no terminal costs are included
Scenario 11	Fixed dosing for nivolumab plus PDC	Weight based dosing with vial sharing	Aligns with Danish clinical practice
Scenario 12	Utility informed by CheckMate 816	Utility source from Tagrisso DMC assessment	The weighted health state utility is in this scenario informed by the DMC assessment of Tagrisso
Scenario 13	Extrapolation EF to PD Log-normal	Extrapolation EF to PD Exponential	Explores scenarios using different parametric distributions for EF to PD transitions
Scenario 14		Extrapolation EF to PD Weibull	
Scenario 15		Extrapolation EF to PD Gompertz	

Scenario	Base case value	Scenario value	Detailed description
Scenario 16		Extrapolation EF to PD Log-logistic	
Scenario 17		Extrapolation EF to PD Gamma	
Scenario 18		Extrapolation EF to PD Generalized Gamma	

Abbreviations: DMC, Danish Medicines Council; EF, Event free, PD, Progressive disease, OS, Overall survival, QALYs, Quality adjusted life years.
Sources: (52)

Scenario analyses results are presented in Table 66. Overall, all scenarios were below 30 000 DKK per QALY gained, with use of weight-based dosing with vial sharing (scenario 11) having the largest impact.

Table 66: Scenario analyses results

Scenario	Incremental costs vs PDC alone (DKK)	Incremental QALYs vs PDC alone	ICER vs PDC alone (DKK/QALY)
Base case	- 36 939	1.52	Dominant
Scenario 1	- 33 877	2.26	Dominant
Scenario 2	- 36 969	1.51	Dominant
Scenario 3	- 39 396	1.11	Dominant
Scenario 4	- 31 255	1.52	Dominant
Scenario 5	- 36 939	1.52	Dominant
Scenario 6	- 36 939	1.52	Dominant
Scenario 7	- 32 531	1.53	Dominant
Scenario 8	- 38 768	1.49	Dominant
Scenario 9	- 37 273	1.51	Dominant
Scenario 10	- 34 426	1.52	Dominant
Scenario 11	41 396	1.52	27 310
Scenario 12	- 36 939	1.39	Dominant
Scenario 13	- 61 105	2.01	Dominant
Scenario 14	- 52 800	1.86	Dominant
Scenario 15	- 33 263	1.56	Dominant
Scenario 16	- 44 932	1.72	Dominant
Scenario 17	- 56 101	1.92	Dominant
Scenario 18	7066	0.37	18 960

Abbreviations: DKK, Danish Kroner; QALYs, Quality adjusted life years, ICER, incremental cost effectiveness ratio; PDC, Platinum doublet chemotherapy

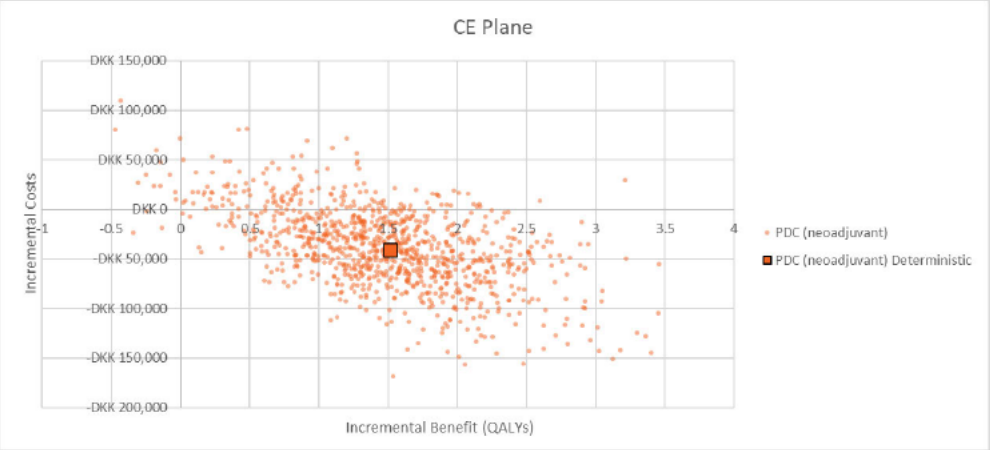
8.7.2 Probabilistic sensitivity analyses

The probabilistic sensitivity analysis (PSA) results are based on 1000 repeated simulations that drew from the distributions of parametric functions, costs, and utility values. The number of replications was considered sufficient, as a plot of the expected values of incremental QALYs and costs by the number of replications demonstrated stability at approximately 300 replications, well below 1000 replications.

The result from the PSA shows a majority of the generated results are in the south-east and north-east quadrant, indicating dominating and cost-effective results.

The incremental cost and QALY results for each iteration are plotted in Figure 48, Figure 49: displays the cost-effectiveness acceptability curve (CEAC). The mean incremental cost, LY, and QALY of nivolumab plus PDC vs. PDC alone in the model over the PSA iterations are summarized in Table 67.

Figure 48: PSA results—Cost-effectiveness plane



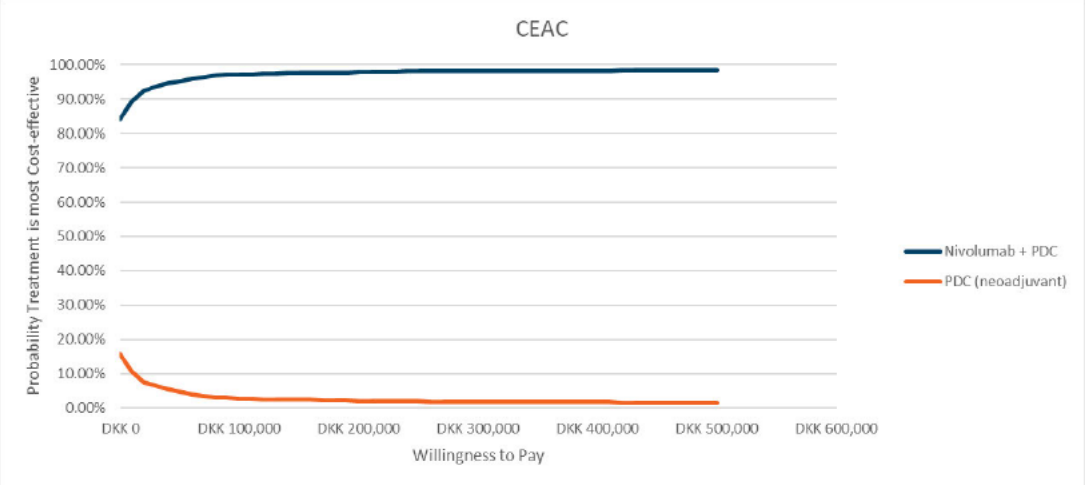
Abbreviations: CE, cost-effectiveness; PDC, platinum-doublet chemotherapy; PSA, probabilistic sensitivity analysis

Table 67: PSA – Mean incremental outcomes

Incremental outcomes	Nivolumab plus PDC vs. PDC alone (neoadjuvant)
Incremental Costs (DKK)	-40 996
Incremental LYs	1.72
Incremental QALYs	1.52
ICER	
Cost per LY (DKK)	Dominant
Cost per QALY (DKK)	Dominant

Abbreviations: DKK, Danish Kroner; ICER, incremental cost-effectiveness ratio; LY, life year; PDC, platinum-doublet chemotherapy; PSA, probabilistic sensitivity analysis; QALY, quality-adjusted life year

Figure 49: PSA results—Cost-effectiveness acceptability curve



Abbreviations: CEAC, cost-effectiveness acceptability curve; PDC, platinum-doublet chemotherapy; PSA, probabilistic sensitivity analysis

9 Budget impact analysis

9.1 Number of patients

A budget impact analysis was performed for the expected additional cost of introducing nivolumab plus PDC. In line with guidelines from DMC, a time horizon of 5 years was used for this analysis and costs are *not* discounted (50). The number of patients eligible for treatment with nivolumab plus chemotherapy in Denmark was estimated to be 160 patients annually, with the number of eligible patients assumed to stay constant each year (for more details see section 5.1.2). If granted reimbursement, it was assumed that 75% of the eligible patients would be treated with nivolumab plus PDC per year. If not granted reimbursement, it was estimated that 0% would be treated with nivolumab plus PDC. See section 5.2.1.2 for more information.

Table 68 describes the number of patients expected to be treated with nivolumab plus PDC and adjuvant or neoadjuvant PDC alone if nivolumab plus PDC receives approved reimbursement. If approval is not granted, the number of patients expected to be treated with adjuvant or neoadjuvant PDC alone is presented in Table 69.

Table 68: Number of patients that are expected to be treated over the next five-year period – if the pharmaceutical is approved for reimbursement

	Year 1	Year 2	Year 3	Year 4	Year 5
Number of patients per year- nivolumab plus PDC	120	120	120	120	120
Number of patients per year – adjuvant or neoadjuvant PDC alone	40	40	40	40	40
Total	160	160	160	160	160

Abbreviations: PDC, platinum-doublet chemotherapy

Table 69: Number of patients expected to be treated during the next five-year period – if the pharmaceutical is NOT approved for reimbursement

	Year 1	Year 2	Year 3	Year 4	Year 5
Number of patients per year- nivolumab plus PDC	0	0	0	0	0
Number of patients per year – adjuvant or neoadjuvant PDC alone	160	160	160	160	160
Total	160	160	160	160	160

Abbreviations: PDC, platinum-doublet chemotherapy

9.2 Budget impact results

The total annual budget impact of the introduction of nivolumab plus PDC in the neoadjuvant setting is estimated to be a cost saving of about 5 000 000 DKK. Detailed budget impact results per year are presented in Table 70, Table 71 and Table 72.

Table 70: Total expenditure per year by cost component – if nivolumab plus PDC is approved for reimbursement (DKK)

	Year 1	Year 2	Year 3	Year 4	Year 5
Drug acquisition costs	10 969 429	10 969 429	10 969 429	10 969 429	10 969 429
Other related costs in the health and care services	22 375 859	28 225 001	32 892 794	36 796 290	38 432 904
Total	33 345 288	39 194 429	43 862 223	47 765 719	49 402 333

Abbreviations: DKK, Danish Kroner; VAT, value added tax; incl., including; PDC, Platinum doublet chemotherapy

Table 71: Total expenditure per year by cost component – if nivolumab plus PDC is not approved for reimbursement (DKK)

	Year 1	Year 2	Year 3	Year 4	Year 5
Drug acquisition costs	293 589	293 589	293 589	293 589	293 589
Other related costs in the health and care services	33 283 499	41 507 021	47 495 534	52 208 756	54 116 066

	Year 1	Year 2	Year 3	Year 4	Year 5
Total	33 577 088	41 800 610	47 789 123	52 502 345	54 409 655

Abbreviations: DKK, Danish Kroner; VAT, value added tax; incl., including PDC, Platinum doublet chemotherapy

Table 72: Expected budget impact with and without approved reimbursement for nivolumab plus PDC (DKK)

	Year 1	Year 2	Year 3	Year 4	Year 5
Total cost if nivolumab plus PDC is approved (DKK)	33 345 288	39 194 429	43 862 223	47 765 719	49 402 333
Total cost if nivolumab plus PDC is not approved (DKK)	33 577 088	41 800 610	47 789 123	52 502 345	54 409 655
Total budget impact (DKK)	-231 800	-2 606 181	-3 926 900	-4 736 626	-5 007 322

Abbreviations: DKK, Danish Kroner; VAT, value added tax; incl., including PDC, Platinum doublet chemotherapy

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10 Discussion on the submitted documentation

In Denmark, lung cancer is the leading cause of death related to cancer. There is a clear need for improved treatment options, particularly among patients who have stage IIIB (TNM version 8) and earlier disease, for whom successful and timely intervention may forestall progression to more advanced and deadly stages of the disease, or even be curative.

The economic model described in this report has several strengths. Based on the current understanding of the natural history and possible outcomes of lung cancer, the model utilizes a simple 3 health state semi-Markov approach to track clinical outcomes. The detailed costing architecture used in PD allows the model to accurately capture PD treatment costs without creating the need to leverage additional clinical inputs. The model is also able to articulate the possibility of cure after successful surgical resection. The selection of modelling approach was supported by review of available HTA submission reports in NSCLC and solid-tumour indications involving neoadjuvant/adjuvant treatment and experience from BMS in Denmark. The model generated life year estimates that would be expected given known data describing the survival of patients with NSCLC, as demonstrated via comparisons between the model-generated OS curve and external sources from Denmark (comparisons with Danish registry data). Model programming was thoroughly validated both by the model developers and a third-party validator.

The economic analysis is not without limitations, although these pertain mostly to the data available to inform the model. Specifically, there is limited follow-up data available from CheckMate 816 with relatively immature OS data. The impact of this uncertainty was demonstrated in the PSA and DSA. Whilst there is some uncertainty in the analysis, the PSA showed a high probability of nivolumab plus PDC being cost effective. The DSA showed variations in the ICER when the high and low 95% CI values for the EF to PD HR are used. Last, with the goal of creating a model that is simple and transparent as feasible, clinical outcomes were not explicitly differentiated by type of progression (i.e., local-recurrence vs distant metastasis), however separate treatment pathways specific to type of progression were considered to compute treatment costs in the PD state.

Results of the economic analysis demonstrated that nivolumab plus PDC delivers a significant survival benefit over PDC alone while saving costs over a lifetime horizon.

Comparisons between neoadjuvant nivolumab plus PDC and PDC alone are informed by direct trial evidence and can thus be relied on with relative certainty. Neoadjuvant PDC alone has in the setting of this analysis been used as a proxy for adjuvant PDC in order to leverage the direct trial comparison. The main reason for this is to be able to submit a robust analysis and the rationale is supported by clinical experts confirming the comparability of neoadjuvant and adjuvant PDC.

11 List of experts

Two Norwegian clinical experts, [redacted] and [redacted], were consulted for this health technology assessment of nivolumab plus PDC for the neoadjuvant treatment of resectable, non-metastatic NSCLC. Please note, Danish clinical experts have not been consulted.

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

The direct, in-trial comparison available through the CheckMate 816 study will be presented to compare neoadjuvant nivolumab plus PDC with neoadjuvant PDC alone, as neoadjuvant PDC is a relevant proxy for the main Danish comparator: adjuvant PDC. As mentioned in Section 5.3.1, adjuvant and neoadjuvant PDC have already been shown to provide similar clinical efficacy in patients with early-stage NSCLC (8, 9), which is acknowledged in the Danish treatment guideline (2). Because the neoadjuvant PDC treatment arm in CheckMate 816 is a known equivalent to the main comparator, adjuvant PDC, the SLR is redundant for this application and is not expected to provide more relevant information than the direct trial, CheckMate 816.

14 Appendix B Main characteristics of included studies

Table 73: Main study characteristics of CheckMate 816

Trial name: CheckMate 816	NCT number: NCT02998528
Objective	The purpose of this neoadjuvant study is to compare Nivolumab plus PDC and chemotherapy alone in terms of safety and effectiveness in treating resectable NSCLC
Publications – title, author, journal, year	Forde et al. N Engl J Med 2022; 386:1973-1985 DOI: 10.1056/NEJMoa2202170
Study type and design	Open-label phase 3 trial where subjects randomised (1:1) to either Nivolumab plus PDC or PDC alone as neoadjuvant treatment; Both groups received treatment in 3-week cycles for three cycles
Sample size (n)	358 patients randomised 1:1 to receive Nivolumab plus PDC or PDC alone
Main inclusion and exclusion criteria	**Key inclusion criteria:** • Newly diagnosed, histologically confirmed, resectable, stage IB (≥4cm)–IIIA NSCLC (according to AJCC seventh edition) • Lung function capacity capable of tolerating the proposed lung surgery • Eastern Cooperative Oncology Group (ECOG) Performance Status 0-1 • Tissue from the primary lung tumour to be available for PD-L1 immunohistochemical testing **Key exclusion criteria:** • Known EGFR mutations or ALK translocations • Brain metastases – all patients with stage II or higher disease and those with suspicion of brain metastases were to be assessed by magnetic resonance imaging (MRI) or computed tomography (CT) of the brain within 28 days prior to randomisation • Known or suspected active autoimmune disease Prior PDC or any other cancer therapy for early-stage NSCLC, or treatment with any checkpoint inhibitor or drug that targets T-cell co-stimulations pathways
Intervention	Nivolumab at a flat dose of 360 mg for 30-minute IV infusion plus PDC (Different regimens of chemotherapy depending on type of NSCLC) – see section 5.3
Comparator	PDC alone
Follow-up time	Minimum follow-up of 24 months
Is the study used in the health economic model?	Included in the health economic model since CheckMate 816 is the market authorization trial of nivolumab plus PDC for the treatment of resectable, stage II (≥4cm)–IIIA NSCLC (TNM version 7)
Primary, secondary, and exploratory endpoints	Primary
	EFS: The length of time from randomisation to any of the following events: any progression of disease precluding surgery, progression, or recurrence of disease (based on BICR assessment per RECIST 1.1) after surgery, or death due to any cause. Patients who did not undergo surgery for reason other than progression were considered to have an event at RECIST 1.1 progression (based on BICR) or death.
	pCR: The number of randomised patients with absence of residual viable tumour cells in both lung and lymph nodes as evaluated by BIPR, divided by the number of randomised patients for each treatment group. Tumour and lymph node collection was mandatory on the day of definitive surgery, and samples had to be processed for histopathologic analysis <72 hours following the procedure. Sampling of ≥5 lymph node stations, including ≥3 mediastinal, was recommended for evaluation. Gross examination of the entire specimen was performed. Central pathology for percentage of residual viable tumour was assessed on haematoxylin and eosin–stained slides from a complete cross-section of tumour bed and all lymph nodes submitted for histology.

Trial name: CheckMate 816		NCT number: NCT02998528
	Secondary	
	MPR	The number of randomised patients with ≤10% residual viable tumour cells in both lung and lymph nodes as evaluated by BIPR, divided by the number of randomised patients for each treatment group. Viable tumours in situ carcinoma not to be included in MPR calculation.
	OS	The time between the date of randomisation and the date of death. OS to be censored on the last date a patient was known to be alive.
	TTDM	The time between the date of randomisation and the first date of distant metastasis or the date of death in the absence of distant metastasis. Distant metastasis to be defined as any new lesion that is outside of the thorax using BICR according to RECIST 1.1. Patients who have not developed distant metastasis or died at the time of analysis are to be censored on the date of their last evaluable tumour assessment.
	Key exploratory endpoints	
	cRR	Clinical response rate (cRR) is defined as proportion of all randomised participants whose overall radiological response prior to definitive surgery is either a complete response or partial response per RECIST 1.1 criteria by BICR.
	pCR, MPR, cRR, EFS, TTDM and OS by PD-L1 status	pCR, MPR, cRR, EFS, TTDM and OS by PD-L1 status
	Feasibility of surgery	Proportion of delayed or cancelled surgery, duration of surgery, length of hospital stay, surgical approach including completeness of surgery, incidence of AE/SAE associated with surgery, including pneumonitis, acute respiratory distress syndrome, re admission to the Intensive Care Unit, atrial fibrillation, or other supraventricular tachycardia to 90 days post-surgery
	Safety and tolerability	The safety and tolerability of nivolumab plus platinum doublet chemotherapy compared to platinum doublet chemotherapy in resectable NSCLC
	Overall health status and health utility	Change in EQ-5D-3L scores
	EFS2	Event Free survival on next line of therapy
Method of analysis	Efficacy analyses included all the patients concurrently assigned to receive nivolumab plus chemotherapy or chemotherapy alone. Pathological complete response was compared between treatment groups with the use of a stratified Cochran–Mantel–Haenszel test. Patients who did not undergo surgery or who had no tissue sample that could be evaluated were counted as not having had a response for the primary analysis. Event-free and overall survival were compared between treatment groups with a stratified log-rank test. Confidence intervals for end points that were not part of the hypothesis testing were not adjusted for multiplicity and should be interpreted descriptively.	
Subgroup analyses	Relevant subgroup analysis included PD-L1 status and TNM stage at baseline	
Other relevant information	**Reported primary endpoints:** EFS, pCR (see Table 4 for definitions) **Other reported endpoints:** MPR, OS, TTDM (see Table 4 for definitions)	

Reference: (13, 79)

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

Table 74: Patient baseline characteristics in CheckMate 816, ITT population

	Nivolumab plus PDC (n=179)	PDC alone (n=179)
Median age, years (range)	64 (41–82)	65 (34–84)
<65 – n (%)	93 (52.0)	83 (46.4)
≥65 – n (%)	86 (48.0)	96 (53.6)
Female, n (%)	51 (28.5)	52 (29.1)
ECOG PS n (%)		
0	124 (69.3)	117 (65.4)
1	55 (30.7)	62 (34.6)
Region, n (%)		
North America	41 (22.9)	50 (27.9)
Europe	41 (22.9)	25 (14.0)
Asia	85 (47.5)	92 (51.4)
Rest of world[a]	12 (6.7)	12 (6.7)
Stage[b], %		
IB–II (A&B)	65 (36.3)	62 (34.6)
IIIA	113 (63.1)	115 (64.2)
Histology, %		
Squamous cell carcinoma	87 (48.6)	95 (53.1)
Non-Squamous	92 (51.4)	84 (46.9)
Smoking status[c], %		
Current/former	160 (89.4)	158 (88.3)
Never	19 (10.6)	20 (11.2)
Tumour PD-L1 expression, %[d]		
Not evaluable	12 (6.7)	13 (7.3)
<1%	78 (43.6)	77 (43.0)
≥1%	89 (49.7)	89 (49.7)
1–49%	51 (28.5)	47 (26.3)
≥50%	38 (21.2)	42 (23.5)
TMB[d], %		
Not evaluable / not reported[e]	91 (50.8)	89 (49.7)
<12.3 mut/Mb	49 (27.4)	53 (29.6)
≥12.3 mut/Mb	39 (21.8)	37 (20.7)

Abbreviations: PDC, chemotherapy; CRF, case report form; ECOG, Eastern Cooperative Oncology Group; NIVO, nivolumab; ITT, intent to treat; PD-L1, programmed cell death protein ligand 1; PS, performance status; TMB, tumour mutational burden; TNM, tumour-node-metastasis cancer staging system.

Notes:

[a] This category includes Argentina and Turkey only.

[b] Disease stage by CRF, with T^{NM} 7^{th} edition used for classification; one patient in each of the NIVO + PDC and PDC arms had stage IV disease.

[c] Smoking status unknown: one patient in PDC arm.

[d] Percentages are based on the primary analysis population

[e] TMB was not analysed for patients in China, and these patients are included in the "not reported" category.

Reference: (13)

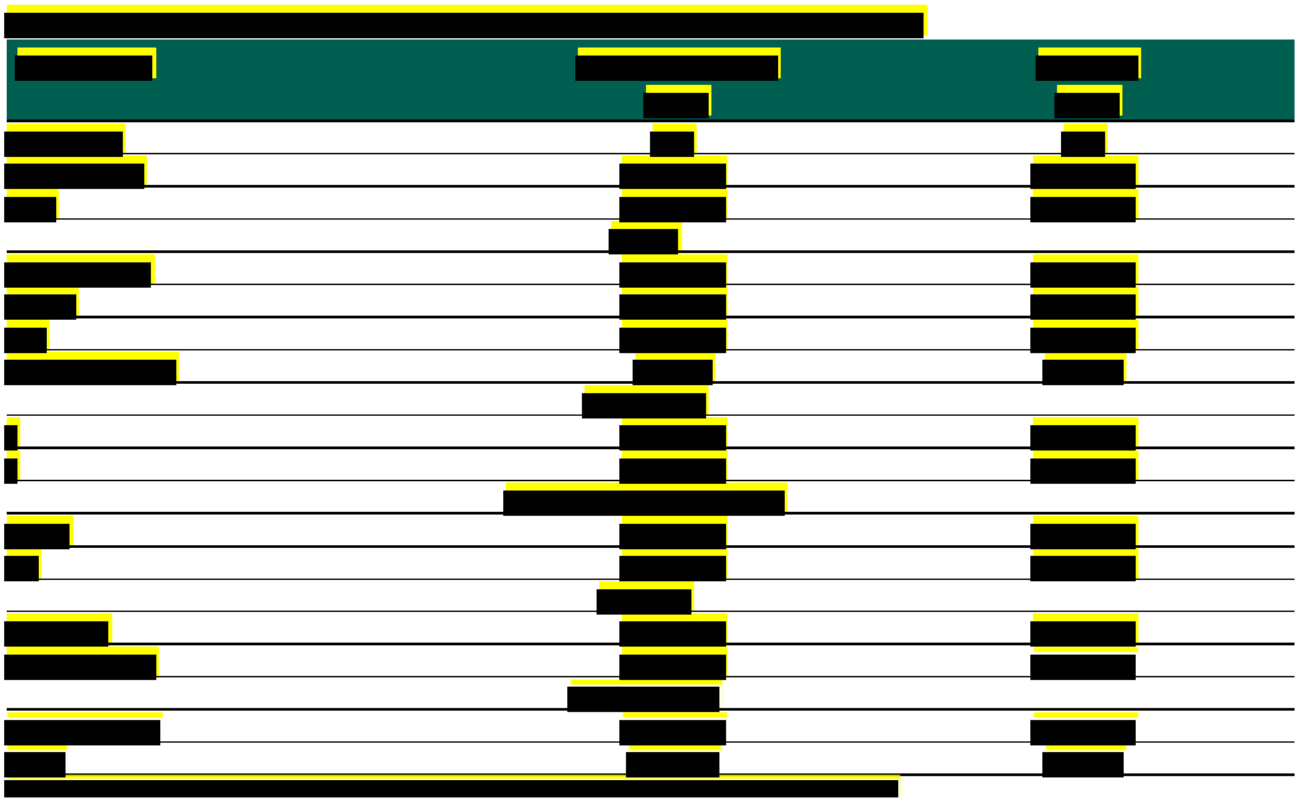

Table 76: Patient baseline characteristics in CheckMate 816, PD-L1 expression ≥1% subgroup, stage II – IIIA (TNM version 7)

	Nivolumab plus PDC (n=81)	PDC alone (n=86)
Age, years		
N	81	86
mean	64.1	63.6
median	64.0	65.5
min, max	47 , 82	41 , 84
Q1, Q3	58.0 , 70.0	59.0 , 70.0
SD	7.3	8.7
Age categorization, n (%)		
< 65 years	44 (54.3)	40 (46.5)
≥ 65	37 (45.7)	46 (53.5)
≥ 65 And < 75 years	32 (39.5)	42 (48.8)
≥ 75 and < 85 years	5 (6.2)	4 (4.7)
≥ 85 years	0	0
Sex, n (%)		
Male	62 (76.5)	62 (72.1)
Female	19 (23.5)	24 (27.9)
Race, n (%)		
White	35 (43.2)	36 (41.9)
Black or African American	1 (1.2)	1 (1.2)
Asian	45 (55.6)	49 (57.0)
Asian Indian	1 (1.2)	0
Chinese	25 (30.9)	28 (32.6)
Japanese	16 (19.8)	20 (23.3)
Asian other	3 (3.7)	1 (1.2)
Other	0	0
Geographic region, n (%)		
North America	14 (17.3)	21 (24.4)
Europe	18 (22.2)	11 (12.8)
Asia	45 (55.6)	49 (57.0)
Rest of the world	4 (4.9)	5 (5.8)

	Nivolumab plus PDC (n=81)	PDC alone (n=86)
Disease stage at study entry, CRF (%)		
Stage 1A	0	0
Stage 1B	0	0
Stage IIA	13 (16.0)	19 (22.1)
Stage IIB	12 (14.8)	11 (12.8)
Stage IIIA	56 (69.1)	56 (65.1)
Stage IIIB	0	0
Stage IV	0	0
Cell type at study entry, n (%)		
Squamous cell carcinoma	42 (51.9)	47 (54.7)
Non-Squamous	39 (48.1)	39 (45.3)
Adenocarcinoma	37 (45.7)	39 (45.3)
Large cell carcinoma	0	0
Other	2 (2.5)	0
Tobacco use, n (%)		
Never	9 (11.1)	8 (9.3)
Current/former	72 (88.9)	77 (89.5)
Unknown	0	1 (1.2)
Baseline ECOG PS, n (%)		
0	59 (72.8)	62 (72.1)
1	22 (27.2)	24 (27.9)
>1	0	0
Baseline weight, kg		
N	81	86
Mean	69.98	67.23
Median	68.50	65.45
Min, max	40.4, 126.3	44.6, 114.6
SD	15.04	13.30
Time from current diagnosis to randomisation, months		
N	81	86
Mean	1.33	1.23
Median	0.99	11.2
Min, max	9.1	3.4
SD	1.13	0.69
Time from current diagnosis to randomisation, n (%)		
< 1 month	42 (51.9)	41 (47.7)
1 – < 2 months	26 (32.1)	34 (39.5)
2 – < 3 months	11 (13.6)	9 (10.5)
3 – < 4 months	1 (1.2)	2 (2.3)
4 – < 5 months	0	0
≥ 5 months	1 (1.2)	0
Tumour PD-L1 expression, n (%)		
<1%	0	0
≥1%	81 (100.0)	86 (100.0)
1–49%	46 (56.8)	46 (53.5)
≥50%	35 (43.2)	40 (46.5)
Not evaluable	0	0
Tumour tissues TMB[d], n (%)		
<12.3 mut/Mb	18 (22.2)	24 (27.9)
≥12.3 mut/Mb	25 (30.9)	22 (25.6)
Not evaluable	4 (4.9)	4 (4.7)
Not reported	34 (42.0)	36 (41.9)

Abbreviations: PDC, chemotherapy; CRF, case report form; ECOG, Eastern Cooperative Oncology Group; PD-L1, programmed cell death protein ligand 1; PS, performance status; TMB, tumour mutational burden; TNM, tumour-node-metastasis cancer staging system.
Notes:
Subpopulation based on baseline PD-L1 expression level recorded on clinical database and disease stage at study entry per CRF
Reference: (11)

Table 77: Chemotherapy given in the nivolumab plus PDC and PDC alone groups of CheckMate 816

Group	Chemotherapy details
Nivolumab plus PDC group	
Non-squamous NSCLC	Nivolumab at a flat dose of 360 mg as 30-minute IV infusion, followed by pemetrexed at a dose of 500 mg/m^2 IV over 10 minutes or per institutional standard and cisplatin at a dose of 75 mg/m^2 IV over 120 minutes or per institutional standard on Day 1 of a 3-week treatment cycle, for up to three cycles.
Squamous NSCLC	Nivolumab at a flat dose of 360 mg as 30-minute IV infusion, followed by gemcitabine at a dose of 1000 mg/m^2 or 1250 mg/m^2 (per local prescribing information) for a 30-minute IV infusion or per institutional standard and cisplatin at a dose of 75 mg/m^2 as a 120-minute IV infusion or per institutional standard, on Day 1 of a 3-week treatment cycle for up to three cycles. Gemcitabine was also to be administered at a dose of 1000 mg/m^2 or 1250 mg/m^2 as a 30-minute IV infusion or per institutional standard on days 1 and 8 of each 3-week treatment cycle.
Any histology	Nivolumab at a flat dose of 360 mg as 30-minute IV infusion, followed by paclitaxel 175 or 200 mg/m^2 IV over 180 minutes or per institutional standard and carboplatin AUC 5 or 6 IV over 30 minutes or per institutional standard on Day 1 of a 3-week treatment cycle, for up to three cycles.
PDC alone group	
Regimen 1	Vinorelbine 25 mg/m^2 or 30 mg/m^2 IV push over 10 minutes (per local prescribing information) or per institutional standard on Days 1 and 8, and cisplatin 75 mg/m^2 IV over 120 minutes or per institutional standard, immediately following vinorelbine, on Day 1 of a 3-week treatment cycle, for up to three cycles.
Regimen 2	Docetaxel 60 mg/m^2 or 75 mg/m^2 IV (per local prescribing information) over 60 minutes or per institutional standard on Day 1, and cisplatin 75 mg/m^2 IV over 120 minutes or per institutional standard, immediately following docetaxel, on Day 1 of a 3-week treatment cycle, for up to three cycles.
Regimen 3 (squamous histology)	Gemcitabine 1000 mg/m^2 or 1250 mg/m^2 IV over 30 minutes (per local prescribing information) or per institutional standard on Days 1 and 8 and cisplatin 75 mg/m^2 IV over 120 minutes or per institutional standard, immediately following gemcitabine, on Day 1 of a 3-week treatment cycle, for up to three cycles.
Regimen 4 (non-squamous histology only)	Pemetrexed 500 mg/m^2 IV over 10 minutes or per institutional standard on Day 1, and cisplatin 75 mg/m^2 IV over 120 minutes or per institutional standard, immediately following pemetrexed, on Day 1 of a 3-week treatment cycle, for up to three cycles.
Regimen 5	Paclitaxel 175 or 200 mg/m^2 IV over 180 minutes or per institutional standard on Day 1, and carboplatin AUC 5 or 6 IV over 30 minutes or per institutional standard, immediately following paclitaxel, on Day 1 of a 3-week treatment cycle, for up to three cycles.

Abbreviations: AUC, area under the curve; IV, intravenous
Reference: (13, 79)

15.1 Comparability of patients across studies

As the direct, in-trial comparison available through the CheckMate 816 is considered, this section is not applicable.

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

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

16 Appendix D Efficacy and safety results per study

16.1 Definition, validity, and clinical relevance of included outcome measures

Prolonging OS is the ultimate goal of therapy but requires a long duration of follow-up for patients receiving treatment for non-metastatic disease and is influenced by subsequent therapies given following disease relapse. A variety of other endpoints have therefore been used in clinical trials involving patients with resectable NSCLC (see Table 78).

The efficacy of adjuvant chemotherapy regimens in non-metastatic NSCLC has been demonstrated in RCTs using OS, disease-free survival (DFS) and recurrence-free/relapse-free survival (RFS) as primary endpoints. Although RFS is often used interchangeably with DFS, DFS can include the occurrence of a second primary cancer as an event, while RFS only includes occurrence of relapse of the original cancer (80). Event-free survival (EFS) is a more appropriate endpoint for studies of neoadjuvant therapy. Indeed, EFS is similar to DFS but also considers disease progression that happens before surgery (i.e., that precludes surgery being given) as an event.

The duration of follow-up and number of patients required to demonstrate statistically significant differences in survival endpoints means these endpoints require a long duration of follow up to demonstrate statistically significant differences. This effectively delays patient access to new therapies. Two surrogate markers for survival—major pathologic response (MPR) and pCR—are alternative endpoints used to assess the efficacy of neoadjuvant therapies. MPR and pCR are measured in the resected primary tumour (and also in sampled lymph nodes if a stringent definition is used) and are an indication of how effectively the therapy has killed the tumour cells in the resected tissues. An MPR indicates that less than 10% of tumour cells are viable, whereas a pCR indicates that no viable tumour cells are detectable. Pathological outcomes can be assessed immediately following surgery. Of note, there is no clear consensus on the definition of some of these endpoints and the methods are not standardized as diagnostic measurements (81). Some commonly used endpoint definitions are presented in Table 78. The definitions used in CheckMate 816 are presented in Table 73 (Appendix B).

Table 78: Definitions of endpoints used in clinical trials in resectable NSCLC

Term	Definition
Overall survival	Time from randomisation until death from any cause (82)
Disease-free survival	Time from randomisation until disease recurrence (including occurrence of a secondary primary cancer) or death from any cause (82)
Recurrence/relapse-free survival	Time from randomisation until disease recurrence or death from any cause (80)
Event-free survival	Time from randomisation to any of the following events: progression of disease before surgery (i.e., that precludes surgery being given), local or distant recurrence, or death due to any cause (82)
Major pathologic response	≤10% residual viable tumour cells in the primary tumour and sampled lymph nodes (81)
Pathologic complete response or complete pathologic response	Absence of any viable tumour cells after complete evaluation of resected lung specimen, including all sampled regional lymph nodes (according to IASLC) (83)

Abbreviations: FDA, Food and Drug Administration; IASLC, International Association for the Study of Lung Cancer; NSCLC, non-small cell lung cancer

The clinical significance of MPR and pCR through their correlation with long-term outcomes, such as EFS and OS, have been demonstrated in various studies of neoadjuvant chemotherapy. For example, a study of neoadjuvant chemotherapy observed a 5-year OS of 80% in patients with a pCR compared with 56% in the non-pCR group [redacted]) (84).

The relationship between pathologic response (pCR and MPR) and survival (OS and EFS) has been investigated further in a recent systematic literature review, which identified 32 studies reporting an association between pathologic response and OS or EFS in patients with non-metastatic NSCLC who received neoadjuvant PDC or CRT (38). Twenty studies (involving 6474 patients) reported on the relationship between pCR and OS. The HR for OS according to pCR status ranged from 0.13–0.78 and the meta-analysis yielded an HR of 0.49 (95% CI: 0.42–0.57), indicating that achievement of pCR (vs no pCR) was associated with a 51% reduction in the risk of death. Similarly, 13 studies (N=1278) examined the relationship between MPR and OS. The HR for OS ranged from 0.13–1.14 and was 0.38 (95% CI: 0.29–0.51) according to the meta-analysis. Achievement of a pCR and MPR also showed statistically significant relationships to EFS, being associated with a 51% (HR: 0.49 [95% CI: 0.41–0.60]) and 47% (HR: 0.53 [95% CI: 0.43–0.67]) reduction, respectively, in the risk of disease progression or death.

16.2 Results per study

The results from the CheckMate 816 trial are presented in Table 79.

Table 79: Results of CheckMate 816 (NCT02998528)

Outcome	Study arm	N	Result (CI)	Estimated absolute difference in effect			Estimated relative difference in effect			Description of methods used for estimation	References
				Difference	95% CI	P value	Difference	95% CI	P value		
EFS for the ITT population	Nivolumab plus PDC	179	Median: NR months (95% CI: 31.57–NR)				HR: 0.68	0.49–0.93		EFS distribution was compared between treatment arms via a 2-sided, log rank test stratified by the randomisation stratification factor (i.e., PD-L1, disease stage [IB/II vs IIIA, TNM version 7] and gender).The HR between treatment arms and the corresponding CI were estimated in a stratified Cox proportional hazards model using the randomised arm as a single covariate. The EFS curves for each randomised arm were estimated using the Kaplan-Meier (KM) product-limit method using a log-log transformation. In addition, EFS rates at 1, 2, 3, and 4 years were estimated using KM estimates on the EFS curve for each randomised arm provided a minimum follow-up is longer than the time point to generate the rate. Associated 2-sided 95% CIs were calculated using the Greenwood formula (using log-log transformation)	(13, 85)
	PDC alone	179	Median: 21.06 months (95% CI: 14.75–42.09)								
EFS for subgroup of patients with stage II-IIIA (TNM version 7) and PD-L1 Expression ≥ 1%	Nivolumab plus PDC	81	NR (44.42 – NR)				HR: 0.49	0.29, 0.83			
	PDC alone	86	26.71 (13.40 –NR)								
EFS for subgroup of patients with PD-L1 Expression ≥ 1%	Nivolumab plus PDC	89	Median: NR (95% CI: 44.42–NR)				HR: 0.46	0.28, 0.77			
	PDC alone	89	Median: 26.71 (95% CI: 13.40–NR)								
OS for the ITT patient population	Nivolumab plus PDC	179	Median: NR (95% CI: NR–NR)				HR: 0.62	0.42–0.90[a]	0.0124	OS curves, OS medians with 95% CIs, and OS rates at 1, 2, 3, and 4 years with 95% CIs were estimated using KM methodology. HR between treatment	
	PDC alone	179	Median: NR (95% CI: 46.8–NR)								

Outcome	Study arm	N	Result (CI)	Estimated absolute difference in effect			Estimated relative difference in effect			Description of methods used for estimation	References
				Difference	95% CI	P value	Difference	95% CI	P value		
OS for subgroup of patients with stage II-IIIA (TNM version 7) and PD-L1 Expression ≥ 1%-	Nivolumab plus PDC	81	Median: NR (NR, NR)				HR: 0.43	0.22, 0.83		arms and corresponding 2-sided 95% CI were estimated using a Cox proportional hazards model with treatment group as a single covariate, stratified by randomisation stratification factors.	
	PDC alone	86	Median: NR (NR, NR)								
TTDM for the ITT patient population	Nivolumab plus PDC	179	NR (95% CI: 48.59–NR)				HR: 0.55	0.39–0.78		TTDM curves, medians with 95% CIs, and rates at 1, 2, 3, and 4 years with 95% CIs were estimated using KM methodology. HR and corresponding 2-sided 95% CI were estimated treatment arms using Cox proportional hazards model with treatment group as a single covariate, stratified by randomisation stratification factors.	
	PDC alone	179	34.27 months (95% CI: 23.56–NR)								
TTDM for subgroup of patients with stage II-IIIA (TNM version 7) and PD-L1 Expression ≥ 1%	Nivolumab plus PDC	81	Not reached (44.42, NR)				HR: 0.40	0.22, 0.72			
	PDC alone	86	Not reached (18.83, NR)								

[redacted]

Abbreviations: CI, confidence interval; CMH, Cochran Mantel-Haenszel; EFS, event-free survival; HR, hazard ratio; KM, Kaplan-Meier; MPR, major pathological response; NR, not reached; OR, odds ratio; OS, overall survival; pCR, pathological complete response; PDC, Chemotherapy; TTDM, time to death or distant metastases.
Reference: (11)

17 Appendix E Safety data for intervention and comparator

For CheckMate 816 safety data, please see Section 7.1.2.1.4.

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18 Appendix F Comparative analysis of efficacy and safety

As the direct, in-trial comparison found in CheckMate 816 was used, no additional comparative analysis was presented. Please see Appendix D for the comparison data between neoadjuvant treatment with nivolumab plus PDC and the relevant comparator, neoadjuvant treatment with PDC alone (used as a proxy for adjuvant PDC).

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19 Appendix G Extrapolation

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20 Appendix H Literature search for HRQoL data

As mentioned in section 8.4.2, the utility values applied in the model were derived from an analysis of EQ-5D-3L data from CheckMate 816. The direct, in-trial comparison available through the CheckMate 816 study will be presented to compare neoadjuvant nivolumab plus PDC with neoadjuvant PDC alone, as neoadjuvant PDC is a relevant proxy for the main Danish comparator: adjuvant PDC. As mentioned in section 5.3.1, adjuvant and neoadjuvant PDC have already been shown to provide similar clinical efficacy in patients with early-stage NSCLC (8, 9), which is acknowledged in the Danish treatment guideline (2). Because the neoadjuvant PDC treatment arm in CheckMate 816 is a known equivalent to the main comparator, adjuvant PDC, the SLR is redundant for this application and is not expected to provide more relevant information than the direct trial, CheckMate 816.

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21 Appendix I Mapping of HRQoL data

Mapping of EQ-5D-3L to the five-level version (EQ-5D-5L) was applied for the Danish utility index values. The ordered logistic regression (including adjacent dimensions and a latent factor) approach using the van Hout and Shaw algorithm was used to predict EQ-5D-5L responses from EQ-5D-3L responses for each individual assessment as collected in the study (as per the preferred model in Table 2 of van Hout and Shaw 2021(59)). Then, the Danish EQ-5D-5L value set was used to obtain the predicted EQ-5D-5L utility score for each individual assessment (relating to the preferred model in Table 2 of Jensen 2021 (60)).

The predicted EQ-5D-5L index value obtained for each individual assessment was used to estimate the mean utility values within the population-based health states of interest (using the methodology described below).

21.1 Health-state models

21.1.1 Progression-based Health-state model

The date of progression or recurrence used matches the primary analysis method in the clinical study (i.e., date of progression was assigned based on the BICR using the variables PROGDT and PROGTYPE).

The dates of the EQ-5D-3L assessments were compared to date of progression or recurrence; EQ-5D-3L assessments prior to the date of progression/recurrence (i.e., including baseline) were considered to be pre-progression or recurrence, while EQ-5D-3L assessments on the same date or afterwards were considered to be post-progression or recurrence.

This relates to Model 2

21.1.2 Type of Recurrence Health-state model

For patients with progression or recurrence, EQ-5D-3L assessments were grouped by the date of the EQ-5D-3L assessment relative to date of progression/recurrence and by the type of recurrence (locoregional or distant metastases) and classified as pre-progression, locoregional recurrence, or distant metastases. Patients with progression type recorded as “not reported” were classified as locoregional recurrence and those with “both locoregional and distant metastases” were classified as distant metastases.

This relates to Model 3

21.1.3 Estimating Utility Value for Health State

To estimate the mean values of EQ-5D-3L for each health state, a mixed model approach was used to account for repeated EQ-5D-3L measurements per patient within a health state (MMRM). An initial model was used to estimate the overall mean utility index values with and without treatment; the outcome was the EQ-5D-3L at each assessment (including baseline). Two further models were fit for each health state analysis, one for progression-based and one for type of recurrence (pre-progression, locoregional, and distant metastases). These models were run twice, one with and one without treatment. The model without treatment included a variable (Overall) to obtain the overall mean utility index and a categorical variable for the health states. The model including treatment included the relevant health states, treatment, and the interaction of treatment and health state as fixed effects. The interaction term was used to obtain estimates of the mean utility index for each health state for each treatment. A random intercept was used to account for repeated measurements within each patient. An unstructured covariance structure was used. There was no imputation of missing data and no additional baseline covariates were included in any of the models. Model

assumptions including the normality and homoscedasticity of the residuals were assessed using plots. The MMRM model allows for valid estimates if the data are missing at random. Details of the models are presented below:

Model 1 (overall estimates, no health states):

- EQ5D = Overall
- EQ5D = Overall + Treatment

Model 2 (pre- and post-progression):

- EQ5D = Overall + Prepostprog
- EQ5D = Overall + Prepostprog + Treatment + Prepostprog*Treatment

Model 3 (pre-progression, locoregional recurrence, and distant metastases):

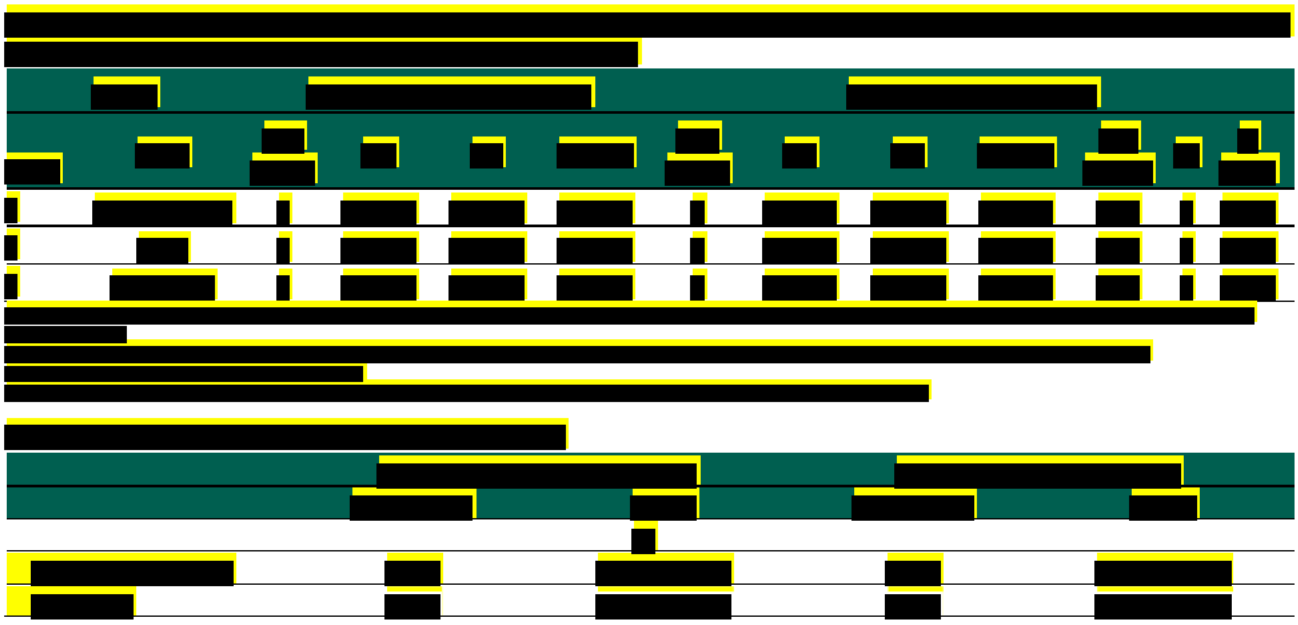
- EQ5D = Overall + RecurrenceType
- EQ5D = Overall + RecurrenceType + Treatment + RecurrenceType*Treatment

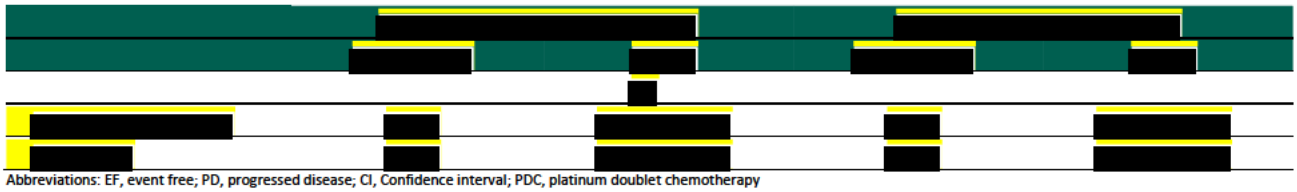
Akaike information criterion (AIC) and Bayesian information criterion (BIC) based on maximum likelihood approach were used to examine the goodness of fit of the model, where lower AIC and BIC values indicate better fit. The -2*log-likelihood (-2*logL) statistics are presented, from which chi-square statistics can be derived to evaluate the statistical significance of nested models with and without treatment.

The number of patients, the number of EQ-5D-3L assessments, least squares (LS) means, standard errors, and 95% confidence intervals (CIs) for the EQ-5D-3L utility index values are presented. Overall (across both treatments) estimates are provided even if there was a statistically significant difference between treatments.

21.1.4 Model fit statistics

The model fit statistics are presented in [redacted] below. The results show that the model without treatment generates lower AIC and BIC estimates. Therefore, the base case includes the treatment agnostic utility values. This is a conservative approach as accounting for treatment effect would yield an even better outcome for nivolumab plus PDC (please see [redacted] below).





Abbreviations: EF, event free; PD, progressed disease; CI, Confidence interval; PDC, platinum doublet chemotherapy
Source: Checkmate 816 utility analysis report (BMS data on file)

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22 Appendix J Probabilistic sensitivity analyses

For the PSA, uncertainties in parameter values were estimated, including the parametric values of long-term extrapolations, disease management costs, treatment costs, and utilities. For each parametric function in the model, a Cholesky decomposition of the covariance matrix was used to correlate the function parameters. Distributions used in the PSA are presented in Table 83. Measurement of uncertainties was captured by 95% CI or standard errors (SE) of each parameter. In the absence of CIs or SEs from published ranges, the SE of the parameter was assumed to be 20% of the mean value.

Upon processing all iterations, the model generates a scatterplot illustrating the distribution of incremental costs and QALYs emerging from the PSA, as well as a cost-effectiveness acceptability curve (CEAC) depicting the likelihood nivolumab + PDC is cost-effective relative to a comparator given maximum willingness to pay for a QALY.

Table 83: Model parameters varied in PSA and distributions

Category	Parameter	Distribution for PSA
Patient characteristics	Starting age	Normal
	Weight	Normal
	BSA	Normal
Clinical inputs	EF to progress–on - Nivolumab plus PDC, survival parameters	Normal / Cholesky
	EF to progress–on - PDC, survival parameters	Normal / Cholesky
	Death during event free, survival parameters	Normal / Cholesky
	Death during PD, survival parameters	Normal / Cholesky
Treatment costs	Drug acquisition cost, per cycle	Gamma
	Drug administration cost, per cycle (initial, subsequent)	Gamma
	Adjuvant costs after neoadjuvant care	Gamma
	Surgery cost	Gamma
	Cost for LR treatments	Gamma
	% LR patients experiencing secondary progression to DM	Beta
	Cost for 1L DM treatments	Gamma
	% 1L DM patients who go on to receive 2L DM treatments	Beta
	Cost for 2L DM treatments	Gamma
Disease management	MRU per cycle (EF, PD)	Gamma
	Monitoring per cycle (EF, PD)	Gamma
	Terminal care cost	Gamma
	AE cost	Gamma
	Income loss per cycle (EF, PD)	Gamma
Utility values	Utility val–es - EF, PD	Beta
	Aggregated AE disutility	Beta

Abbreviations: 1L, first line; 2L, second line; AE, adverse events; BSA, body mass; DM, distant metastasis; EF, event free; LR, locoregional recurrence; PD, progressed disease; PDC, platinum doublet chemotherapy; PSA, probabilistic sensitivity analysis

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23 Appendix K Survival and disease progression in different AJCC TNM staging system for NSCLC (version 7 vs 8)

The AJCC clinical staging system for NSCLC classifies patients at diagnosis into stages of disease (stage from IA-IV/ IA1-IVB) that predict survival outcomes. Clinical staging is crucial to predict prognosis of the disease and choosing the best management option in lung cancer patients. Guidelines are constantly being reviewed as more data becomes available to provide the most accurate prognostic markers, hence aiding in the clinical detection and staging of lung cancer. In 2017, the latest version of AJCC TNM staging, version 8, was published and has become effective internationally from 2018. This version re-categorizes the tumour size and other non-quantitative tumour descriptors (T), and further subclassifies extra-thoracic metastases (M). Version 8 includes the additional stage, IIIC. Furthermore, stage IA is subdivided in the version 8 to include three stages — IA1, IA2 and IA3. The clinical nodal (N) classifier is unchanged as the earlier version correlates well with prognosis.

Table 84 outlines the changes implemented in the TNM stage groupings from version 7 (shown in italics) to version 8 (Bolded).

Table 84: Overall stage based on T, N, and M descriptors

8th T/M	N0	N1	N2	N3
T1a	**IA1** *(IA)*	**IIB** (IIA)	IIIA	IIIB
T1b	**IA2** *(IA)*	**IIB** (IIA)	IIIA	IIIB
T1c	**IA3** *(IA)*	**IIB** (IIA)	IIIA	IIIB
T2a	IB	**IIB** (IIA)	IIIA	IIIB
T2b	**IIA** *(IB)*	**IIB** (IIA)	IIIA	IIIB
T3	**IIB** (IIA)	**IIIA** *(IIB)*	**IIIB** (IIIA)	**IIIC** (IIIB)
T3	IIB	IIIA	**IIIB** (IIIA)	**IIIC** (IIIB)
T4	**IIIA** *(IIB)*	IIIA	**IIIB** (IIIA)	**IIIC** (IIIB)
T4	**IIIA** *(IIB)*	IIIA	**IIIB** (IIIA)	**IIIC** (IIIB)
T2a	**IB** (IIB)	**IIB** (IIIA)	IIIA	IIIB
T2b	**IIA** (IIB)	**IIB** (IIIA)	IIIA	IIIB
T4	IIIA	IIIA	IIIB	**IIIC** (IIIB)
M1a	**IVA** *(IV)*	**IVA** *(IV)*	**IVA** *(IV)*	**IVA** *(IV)*
M1b	**IVA** *(IV)*	**IVA** *(IV)*	**IVA** *(IV)*	**IVA** *(IV)*
M1c	**IVB** *(IV)*	**IVB** *(IV)*	**IVB** *(IV)*	**IVB** *(IV)*

Note: The groupings based on version 8 of TNM staging are in bold, and the stages based on version 8 are in italics.
Reference: The table is adapted from (86)

In the Checkmate 816 trial, the patient inclusion criteria are based on the TNM version 7 criteria and requires patients to have stage IB (with tumour size ≥4 cm) to IIIA disease. This largely corresponds to stages IIA to IIIB N2 in version 8.

Survival for patients with lung cancer is generally poor. In Europe, investigating data from 2000 to 2007 showed that 5-year relative survival in men is ranging from 5–15%, and the corresponding data for women is only 9–20% (87). In the EU5, 5-year relative survival rate ranged from 8–14% in men and 10–18% in women (87).

Survival decreases dramatically with stage of disease. This is illustrated by data for patients with lung cancer in the UK diagnosed between 2013–2017, for which 5-year net survival decreased from 57% for patients diagnosed with stage I disease to 34% for stage II, 13% for stage III and only 3% for stage IV (TNM version 7) (87).

The differences in OS according to stage of disease, as defined using AJCC TNM system, illustrate the wide variation in OS that is determined by the extent of disease at diagnosis. The range in 5-year OS according to the AJCC version 7 and proposed stages in version 8 of staging definitions is shown in [redacted] For patients eligible for nivolumab plus PDC

neoadjuvant therapy, 5-year OS ranged from 36–66% according to the TNM version 7 (i.e., stages IB to IIIA) and from 26–60% according to version 8 (i.e., stages IIA to IIIB N2) (88).

The staging system is based on clinical and pathological assessment of the extent of spread of the tumour. A number of other adverse prognostic factors have also been identified. These include the presence of pulmonary symptoms, non-squamous histology and vascular invasion (89). The decrease in OS with increasing stage of disease reflects an increase in the risk of disease progression. This has been demonstrated in the LuCaBIS study—a retrospective study performed in France, Germany, and the UK which included 831 patients diagnosed with stage IB–IIIA disease (TNM version 7) between January 2009 and December 2011, inclusively (72). Over a median follow-up of 26 months, 33% of patients developed recurrence and 24% progressed to metastatic disease. Median disease-free survival, a measure of the risk of relapse, decreased with increasing disease stage from not being reached for patients with stage IB disease and being 42.3 months for stage IIA disease to 28.5 months for stage IIIA disease.

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24 Appendix L Ongoing studies with supportive evidence

Table 85: Overview of ongoing studies with supportive neoadjuvant therapy with nivolumab plus PDC

Study	Patient's Population	Intervention	Comparator	Endpoints	Start date / Expected End date	Size and design
Neoadjuvant Nivolumab, or Nivolumab in Combination With Ipilimumab, in Resectable NSCLC (NCT02259621)	High-risk resectable NSCLC	Nivolumab Carboplatin Paclitaxel	Nivolumab	Safety as measured by number of participants with Grade 3 and 4 lab abnormalities/ number of Grade 3 and 4 AEs	September 2014 / January 2023	n=45 Non-randomised
Phase II trial Nivolumab, Cisplatin, and Pemetrexed Disodium or Gemcitabine Hydrochloride in Treating Patients With Stage I-IIIA Non-small Cell Lung Cancer That Can Be Removed by Surgery (NCT03366766)	Stage I-IIIA non-small cell lung cancer that can be removed by surgery.	Nivolumab, Cisplatin, Pemetrexed Disodium	Nivolumab, Gemcitabine Hydrochloride	Major pathologic response (mpCR) defined as < 10% viable tumour	December 2017 / July 2022	n= 14 Non-randomised
PERI-adjuvant evidence (nivolumab plus PDC Q3W for 3 cycles) – relevant to pCR rates, but not EFS and OS (due to the option of nivolumab after surgery)						
Neo-Adjuvant Immunotherapy With Nivolumab for Non-Small Cell Lung Cancer Patients (NCT03081689) "NADIM Trial"	Resectable stage IIIA N2-NSCLC adult patients	Nivolumab Carboplatin Paclitaxel	-	PFS	April 2017 / June 2023	n=46 Non-randomised
A Randomized Phase II Study of Neo-adjuvant Chemo/Immunotherapy Versus Chemotherapy Alone for the Treatment of Locally Advanced and Potentially Resectable Non-small Cell Lung Cancer (NSCLC) Patients NADIM-II (NCT03838159)	Resectable clinical stage IIIA (AJ^{CC} 7th edition) NSCLC, ECOG PS 0-1, and no known EGFR/ALK alterations	Neoadjuvant nivolumab + paclitaxel + carboplatin	Paclitaxel + carboplatin	pCR	May 2019 / November 2028	N=87 Randomised

Abbreviations: AE, Adverse event; mpCR, Major pathologic response; NSCLC, Non-small cell lung cancer; PFS, Progression free survival
Reference: (32-34, 90)

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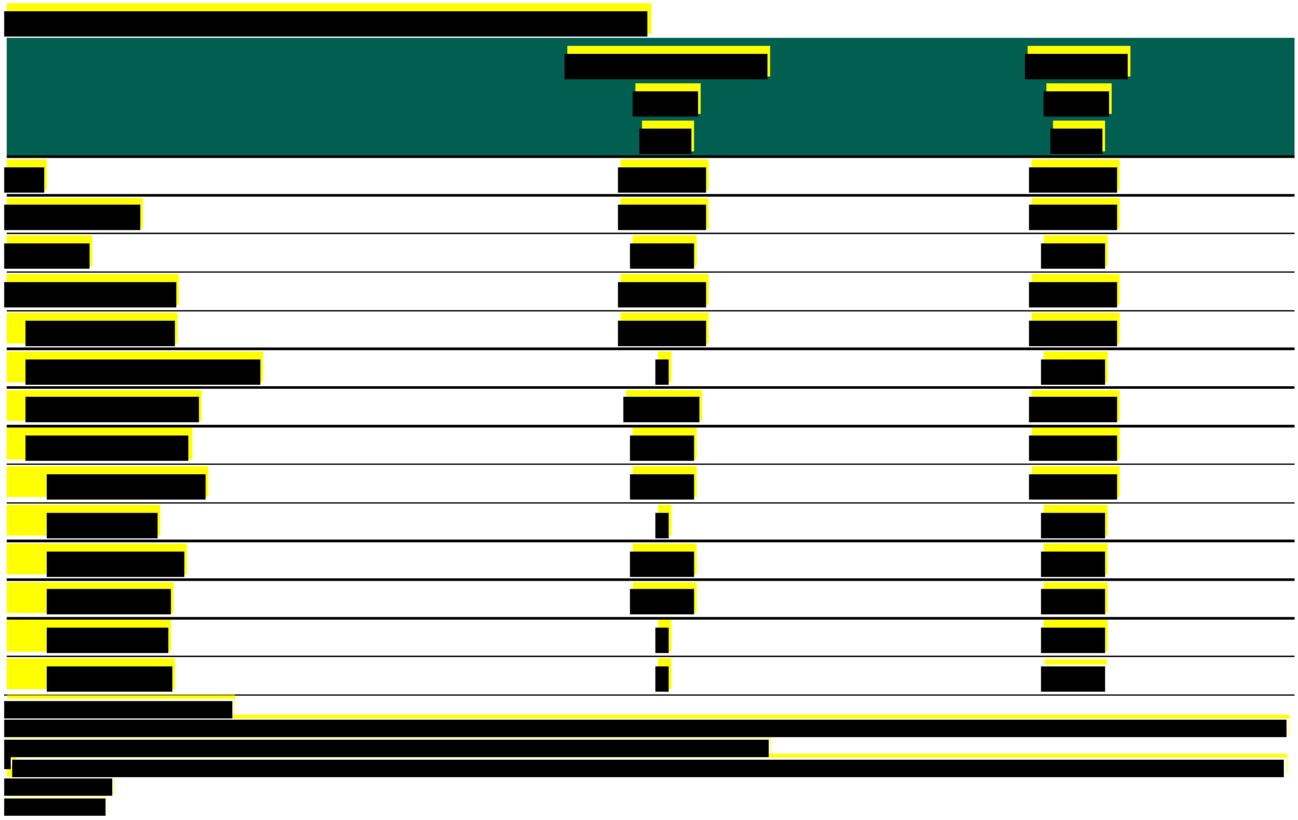
25 Appendix M Subsequent therapies in CheckMate 816



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26 Appendix N Efficacy of neoadjuvant chemotherapy vs. adjuvant chemotherapy

The European Society for Medical Oncology (ESMO) Clinical Practice Guidelines for early and locally advanced NSCLC state that available evidence that compares neoadjuvant PDC with adjuvant PDC shows no major differences; adjuvant PDC treatment may be supported as the timing of choice (16). The 2014 meta-analysis reported by the NSCLC Meta-analysis Collaborative Group, which pooled patient level data from 15 RCTs, estimated a recurrence free survival (RFS) HR of 0.85 (95% CI: 0.76, 0.94) and an OS HR of 0.87 (95% CI: 0.78, 0.96) for the comparison of neoadjuvant PDC vs. surgery (58). The 2008 meta-analysis by the Lung Adjuvant Cisplatin Evaluation (LACE) Collaborative Group, which pooled evidence from five RCTs conducted among completely resected patients, estimated a disease-free survival (DFS) HR of 0.84 (95% CI: 0.78, 0.91) and an OS HR of 0.89 (95% CI: 0.82, 0.96) for the comparison of adjuvant vs. surgery (91). Lastly, a 2009 meta-analysis by Lim et al. reported on an indirect comparison between adjuvant PDC and neoadjuvant PDC; the estimated DFS HR was 0.96 (95% CI: 0.77 to 1.20) for adjuvant PDC vs. neoadjuvant PDC (8). Of note, the study does have some limitations, as the study included RCTs that evaluated 1st and 2nd generation chemotherapy regimens (which are associated with higher toxicity than 3rd generation chemotherapy regimens), and has been criticized for having included a study that was confounded by use of radiotherapy on only one arm (58). The European Society for Medical Oncology (ESMO) Clinical Practice Guidelines for early and locally advanced NSCLC state that available evidence that compares neoadjuvant PDC with adjuvant PDC shows no major differences; adjuvant PDC treatment may be supported as the timing of choice (16). The 2014 meta-analysis reported by the NSCLC Meta-analysis Collaborative Group, which pooled patient level data from 15 RCTs, estimated a recurrence free survival (RFS) HR of 0.85 (95% CI: 0.76, 0.94) and an OS HR of 0.87 (95% CI: 0.78, 0.96) for the comparison of neoadjuvant PDC vs. surgery (58). The 2008 meta-analysis by the Lung Adjuvant Cisplatin Evaluation (LACE) Collaborative Group, which pooled evidence from five RCTs conducted among completely resected patients, estimated a disease-free survival (DFS) HR of 0.84 (95% CI: 0.78, 0.91) and an OS HR of 0.89 (95% CI: 0.82, 0.96) for the comparison of adjuvant vs. surgery (91). Lastly, a 2009 meta-analysis by Lim et al. reported on an indirect comparison between adjuvant PDC and neoadjuvant PDC; the estimated DFS HR was 0.96 (95% CI: 0.77 to 1.20) for adjuvant PDC vs. neoadjuvant PDC (8). Of note, the study does have some limitations, as the study included RCTs that evaluated 1st and 2nd generation chemotherapy regimens (which are associated with higher toxicity than 3rd generation chemotherapy regimens), and has been criticized for having included a study that was confounded by use of radiotherapy on only one arm (58).

Additionally, Felip (2010) conducted an RCT that can contribute evidence for the comparison of adjuvant PDC with neoadjuvant PDC. Within this RCT, when compared with surgery alone, the DFS HR for neoadjuvant PDC was 0.92 (95% CI: 0.81, 1.04), and for adjuvant PDC was 0.96 (95% CI: 0.75, 1.22) (9). This shows both treatments to be comparable to surgery alone. However, as Felip (2010) aimed to compare adjuvant PDC and neoadjuvant PDC vs surgery, the study was not powered to detect a statistically significant difference on the adjuvant PDC vs. neoadjuvant PDC comparison (9). [redacted] shows the DFS outcomes for the individual comparisons of neoadjuvant PDC vs. surgery (A) and adjuvant PDC vs. surgery (B). [redacted] presents OS, further showing no statistically significant differences across the three treatment arms.

In conclusion, current literature suggests that there are no statistically significant differences in EFS/DFS and OS between treatment with adjuvant PDC and neoadjuvant PDC. In order to minimise uncertainties and facilitating the assessment of the current indication, only the direct data from the CheckMate 816 trial was used to inform the submitted CEM (e.g., the model compares neoadjuvant nivolumab plus PDC with neoadjuvant PDC alone, assuming equivalence between neoadjuvant PDC and adjuvant PDC).

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27 Appendix O Nivolumab plus PDC comparison to atezolizumab for treatment of NSCLC

Bristol Myers Squibb was asked by the DMC per mail to explain the differences between CheckMate 816 and IMpower 010 in relation to indirect comparisons. This appendix is based on this request. In March 2023, the DMC recommended atezolizumab following complete resection and adjuvant chemotherapy as an additional post-adjuvant treatment of patients with NSCLC. However, this treatment is not included in the clinical guidelines released in November 2022 (20), and is not currently considered standard of care. As such, adjuvant PDC, as stated by the clinical guidelines, has been considered the most relevant comparator for neoadjuvant nivolumab plus PDC.

Due to notable differences between the market authorisation studies investigating atezolizumab and nivolumab plus PDC and their resulting EU labels, atezolizumab is not a suitable comparator in this submission.

The pivotal studies are CheckMate 816 and IMpower 010 for nivolumab plus PDC and atezolizumab, respectively. Firstly, the two studies were conducted at different time points in a patient's NSCLC pathway. CheckMate 816 enrolled resectable patients (before surgery) to receive 3 cycles of nivolumab in combination with PDC or PDC alone. Patients enrolled in IMpower 010 had to have been completely resected (after surgery, no residual tumour in the body) and had to have completed at least 1 cycle of adjuvant platinum chemotherapy, although the majority of patients in IMpower 010 completed all 4 cycles. Patients in IMpower 010 then received up to 1 year of atezolizumab monotherapy or best supportive care.

In addition to these significant differences in trial designs, the EMA labels for these treatments also differ in relation to the PD-L1 expression targets. CheckMate 816 was approved in a PD-L1 expression >1% population, while IMpower 010 was only approved in a PD-L1 expression >50% population.

One additional difference between the studies relates to the disease stage distribution at diagnosis, with 63 – 64% of patients in CheckMate 816 trail having stage IIIA disease (TNM version 7) compared with 40 – 42% of patients in IMpower 010 (TNM version 7). It is also worth noting that enrolment in IMpower 010 was based on pathological stage while enrolment in CheckMate 816 was based on clinical stage, further complicating comparisons between the two studies.

Finally, key primary outcome between the two studies also differ, with EFS being the co-primary endpoint in CheckMate 816 versus DFS in IMpower 010. In CheckMate 816, EFS is defined as the length of time from randomisation to any of the following events: any progression of disease precluding surgery, progression, or recurrence of disease after surgery, or death due to any cause. Patients who did not undergo surgery for reason other than progression were considered to have an event at RECIST 1.1 progression (based on BICR) or death. In IMpower 010, DFS is defined as the time from randomisation to the date of first recurrence of NSCLC, occurrence of new primary NSCLC, or death from any cause, whichever occurs first.

Given all the differences mentioned above, both in terms of study designs and approved populations, a robust indirect treatment comparison leveraging established methods is not feasible for adjuvant atezolizumab vs neoadjuvant nivolumab plus PDC. For transparency, key outcomes in both studies are summarised in Table 89. When reviewing, the aforementioned differences in study design should be considered, meaning that data cannot be compared directly in a like-for-like fashion.

Note no superiority or inferiority claim can be made based on data shown in Table 89. No detailed subgroup analysis for EFS or OS from CheckMate 816 are available at the time of the submission, however, BMS remains committed to sharing data that is relevant for decision-making, as appropriate, going forward.

Table 87: Comparison between CheckMate 816 and IMPOWER010

	CheckMate 816	IMPOWER010
Licenced population	Neoadjuvant treatment of resectable NSCLC at high risk of recurrence in adult patients whose tumours have PD-L1 expression ≥ 1 and no sensitising EGFR mutation or ALK translocation. The selection criteria for patients with high risk of recurrence is reflective of a patient population with stage II-IIIA (TNM version 7): any patient with a tumour size ≥ 5 cm; any patient with N1 or N2 disease (regardless of primary tumour size); patients with multiple tumour nodules in either the same lobe or different ipsilateral lobes; patients with tumours that are invasive of thoracic structures (directly invade visceral pleura, parietal pleura, chest wall, diaphragm, phrenic nerve, mediastinal pleura, parietal pericardium, mediastinum, heart, great vessels, trachea, recurrent laryngeal nerve, oesophagus, vertebral body, carina) ; or tumours that involve the main bronchus; or tumours that are associated with atelectasis or obstructive pneumonitis that extends to the hilar region or involves the entire lung	Adjuvant treatment following complete resection and platinum-based chemotherapy for adult patients with NSCLC with a high risk of recurrence whose tumours have PD-L1 expression on ≥ 50% of tumour cells (TC) and who do not have EGFR mutant or ALK-positive NSCLC
ITT population	All resectable patients with NSCLC at high risk of recurrence whose tumours have no known sensitising EGFR mutation or ALK translocation	All randomly assigned patients with completely resected stage IB–IIIA NSCLC and after adjuvant cisplatin-based chemotherapy.
Intervention	Neoadjuvant nivolumab plus PDC for 3 months N=179	Adjuvant atezolizumab (1200 mg every 21 days; for 16 cycles or 1 year) N=507
Comparator	PDC (neoadjuvant) N=179	BSC (observation and regular scans for disease Recurrence) N=498
Key inclusion and exclusion criteria	Key inclusion criteria: • Newly diagnosed, histologically confirmed, resectable, stage IB (≥4cm)–IIIA NSCLC (according to AJCC 7th edition) • Lung function capacity capable of tolerating the proposed lung surgery • ECOG Performance Status 0-1 • Tissue from the primary lung tumour to be available for PD-L1 immunohistochemical testing Key exclusion criteria: • Known EGFR mutations or ALK translocations • Brain metastases – all patients with stage II or higher disease and those with suspicion of brain metastases were to be assessed by MRI or CT of the brain within 28 days prior to randomisation • Known or suspected active autoimmune disease • Prior PDC or any other cancer therapy for early-stage NSCLC, or treatment with any checkpoint inhibitor or drug that targets T-cell co-stimulations pathways	Key inclusion criteria: • ECOG Performance Status 0-1 • Histological or cytological diagnosis of Stage IB (tumours greater than or equal to (≥ 4cm)-IIIA NSCLC (According to AJCC 7th version) • Complete resection of NSCLC 4-12 weeks prior to enrolment and must be adequately recovered from surgery • Eligible to receive a cisplatin-based chemotherapy regimen • Adequate hematologic and end-organ function • If mediastinoscopy was not performed preoperatively, it is required that, at a minimum, mediastinal lymph node systematic sampling will have occurred. Key exclusion criteria: • Treatment with prior systemic chemotherapy: Chemotherapy for early stage of malignancy with curative intent • Prior treatment with any CD137 agonists or immune checkpoint inhibitors (anti-PD-L1) • Known tumour PD-L1 expression status as determined by an IHC assay from other clinical studies

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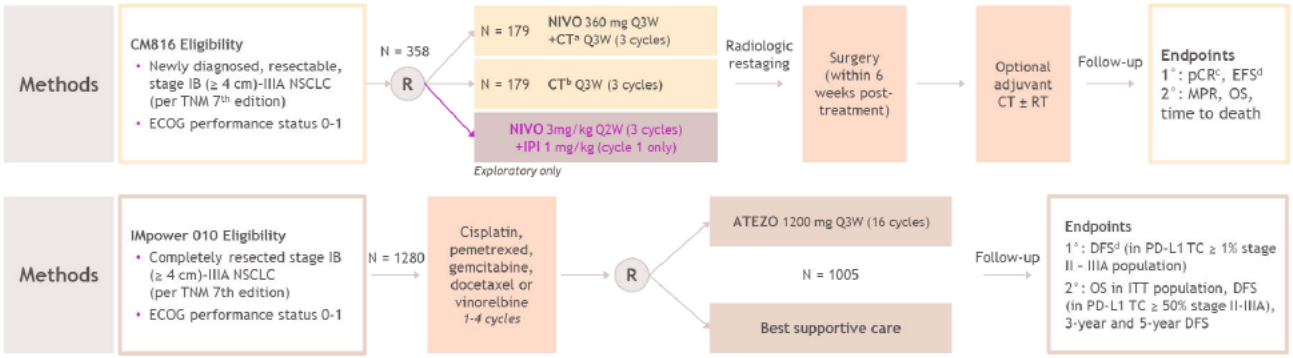
	CheckMate 816	IMPOWER010
Median follow-up	41.4 months	46 months
Primary endpoint	• EFS, pCR	• DFS
Key secondary endpoints	• MPR, TTDM, OS	• OS, DFS, AE, anti-therapeutic antibodies, C_{max} of atezolizumab, C_{min} of atezolizumab
Predefined subgroups	Age, sex, race, region, baseline ECOG performance status, tobacco use, types of platinum therapy, disease stage (Stage IB-II or IIIA), histology (squamous cell carcinoma or non-squamous), PD-L1 expression (PD-L1 <1%, ≥1%, ≥1-49%, or ≥50%)	Age, sex, race, baseline ECOG performance status, type of surgery, EGFR mutation status, ALK rearrangement status, disease stage (Stage IB, IIA, IIB, IIIA), Histology (squamous cell carcinoma or non-squamous), PD-L1 status by SP142 (TC0/1 and IC0/1, TC0/1 and IC2/3, TC2/3 and any IC)

Abbreviations: AE, Adverse event; Cmax, Maximum plasma concentration; Cmin, Minimum serum concentration; DFS, Disease free survival; EFS, Event free survival; MPR, Major pathological response; OS, Overall survival; pCR; Pathologic complete response; PD-L1, Programmed death ligand-1; TC, tumour cells; TTDM, Time to distant metastasis
References: (92, 93)

Figure 54: Comparison of study design between CheckMate 816 and IMPOWER010



Abbreviations: CT, chemotherapy; DFS, disease-free survival; EFS, event-free survival; ITT, intent-to-treat; MPR, major pathologic response; NIVO, nivolumab; OS, overall survival; pCR, pathologic complete response; Q3W, once every 3 weeks; R, randomised; RT, radiotherapy; TC, tumour cells.
[a]NSQ: pemetrexed + cisplatin or paclitaxel + carboplatin; SQ: gemcitabine + cisplatin or paclitaxel + carboplatin.
[b]Vinorelbine + cisplatin, docetaxel + cisplatin, gemcitabine + cisplatin (SQ only), pemetrexed + cisplatin (NSQ only), or paclitaxel + carboplatin.
[c]pCR is defined as 0% residual viable tumour cells in both primary tumour (lung) and sampled lymph nodes LN.
[d]EFS is defined as the length of time from randomisation to (a) any progression of disease precluding surgery, (b) progression or recurrence of disease after surgery, or (c) death due to any cause. DFS is defined as the time from randomisation until disease recurrence or death from any cause. DFS is considered a reasonable endpoint to evaluate new therapy in the adjuvant setting of NSCLC.

Table 88: Comparison of baseline characteristics of patients recruited to CheckMate 816 and IMPOWER010

	CheckMate 816		IMPOWER010a	
	Neoadjuvant nivolumab plus PDC (N=179)	PDC (N=179)	Adjuvant atezolizumab (N=507)	BSC (N=498)
Median age, years (range)	64 (41–82)	65 (34–84)	62 (57–67)	62 (56–68)
<65 – n (%)	93 (52)	83 (46.4)	323 (64)	300 (60)
≥65 – n (%)	86 (48)	96 (53.6)	184 (36)	198 (40)
Female, n (%)	51 (28)	52 (29.1)	170 (34)	164 (33)
ECOG PS n (%)				
0	124 (69)	117 (65.4)	273 (54)	283 (57)
1	55 (31)	62 (34.6)	232 (46)	214 (43)
Stage, %				
IB–II (A&B)	65 (36)	62 (34.6)	302 (60)	290 (58)
IIIA	113 (63)	115 (64.2)	205 (40)	208 (42)
Histology, %				
Squamous cell carcinoma	87 (49)	95 (53.1)	179 (35)	167 (34%)
Non-Squamous	92 (51)	84 (46.9)	328 (65)	331 (67%)
Smoking status, %				
Current/former	160 (89)	158 (88.3)	393 (77)	390 (78)
Never	19 (11)	20 (11.2)	114 (23)	108 (22)
Tumour PD-L1 expression, %				
Not evaluable				
<1%	12 (7)	13 (7.3)		
≥1%	78 (44)	77 (43.0)	210 (41)	234 (47)

	CheckMate 816		IMPOWER010a	
	Neoadjuvant nivolumab plus PDC (N=179)	PDC (N=179)	Adjuvant atezolizumab (N=507)	BSC (N=498)
1–49%	89 (50)	89 (49.7)	283 (56)	252 (51)
≥50%	51 (28)	47 (26.3)	177 (35)	149 (30)
	38 (21)	42 (23.5)	106 (21)	103 (21)

Abbreviations: BSC, Best supportive care; ECOG, Eastern Cooperative Oncology Group NA, Not available; PDC, , Platinum doublet chemotherapy; PD-L1, Programmed death ligand-1.
Notes:
[a] The baseline characteristics of Intention to treat group are reported based on (94, 95)

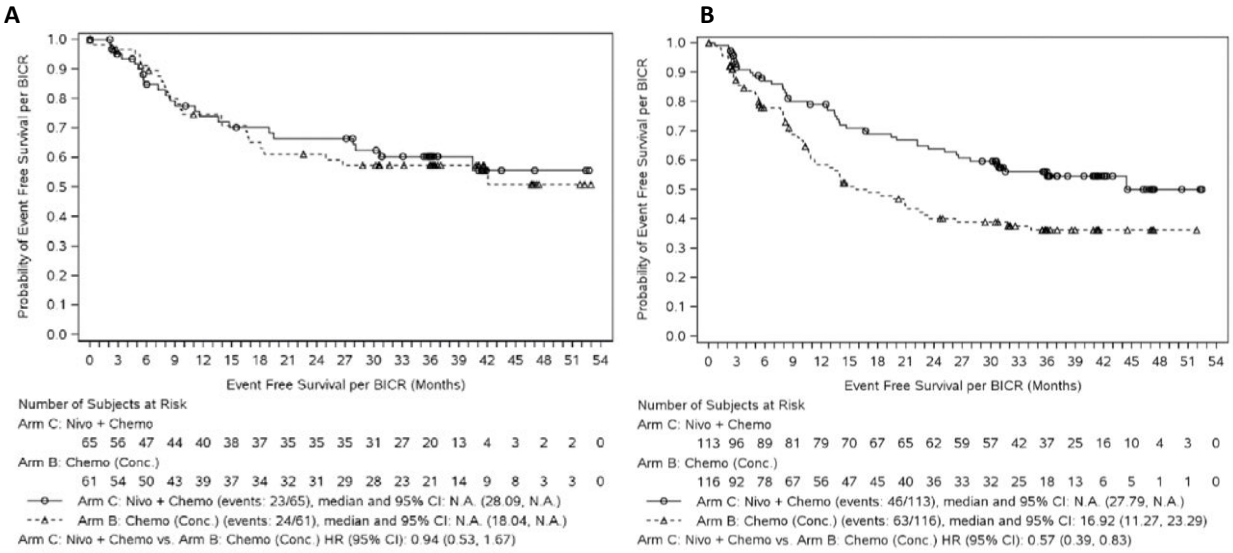
Table 89: Comparison of relative efficacy of neoadjuvant nivolumab plus PDC versus adjuvant atezolizumab treatments in NSCLC patients

	CheckMate 816 (N = 358)			IMPOWER010 (N= 1005)		
	Neoadjuvant nivolumab plus PDC	Neoadjuvant PDC	HR[h] (95% CI)	Adjuvant atezolizumab	BSC	HR (95% CI)
ITT	N=179	N=179		N=507	N=498	
OS rate at 36 months[a]	78%	64%	0.62 (0.42-0.90)[i]	-	-	0.995 (0.78, 1.28)
EFS or DFS at 36 months[b,c]	57%	43%	0.68 (0.49–0.93)	57.9%	52.6%	0.81 (0.67, 0.99)
PD-L1 ≥ 1%[d,e,f]	N=89	N=89		N=248	N=228	
OS rate at 36 months[f]	-	-	-	82.1%	78.9%	0.71 (0.49, 1.03)
EFS or DFS at 36 months	-	-	0.46	60%	48.2%	0.66 (0.50, 0.88)
PD-L1 ≥ 1% stage II – IIIA (TNM version 7)[d]	N=81	N=86		-	-	-
OS rate at 36 months[f]	NR (95% CI: NR–NR)	NR (95% CI: NR–NR)	HR: 0.43 (95% CI: 0.22–0.83)	-	-	-
EFS or DFS at 36 months	NR (95% CI: 44.42–NR)	26.71 (95% CI: 13.40–NR)	HR: 0.49 (95% CI: 0.29–0.83)			
PD-L1 ≥ 50%[g,e]	N=38	N=42		N=106	N=103	
OS rate at 36 months	-	-	-	89.1%	77.5%	0.43 (0.24, 0.78)
EFS or DFS at 36 months	-	-	0.29	-	-	0.42 (0.23, 0.78)
Safety summary ITT	N=176	N=176		N=495	N=495	
All-grade AE%	94	98		92.5	70.9	
TRAE	84	90		67.9	0	
Grade 3-4 AE%	43	45		22.0	11.5	
TRAE Grade 3-4	36	38		10.7	0	
SAE%	17	14		17.8	8.5	
TRSAE	12	10		7.5	0	
AE leading to any treatment withdrawal	10	11		18.2	0	

Abbreviations: AE, Adverse events; BSC, Best supportive care; CI, Confidence interval; DFS, Disease free survival; EFS, Event free survival; HR, Hazard ratio; ITT, Intention-to-treat; NA, Not available; OS, Overall survival; PDC, , Platinum doublet chemotherapy; PD-L1, Programmed death ligand-1; SAE, Serious adverse event; TRAE, Treatment related adverse event; TRSAE, Treatment related serious adverse event
Notes:
[a] Data from IMPOWER010 trial is related to all randomised stage IB-IIIA with median follow-up of 45 months. However, data from CM816 trial is relevant to ITT population (stage IB-IIIA) with median follow-up of 41.4 months
[b] Data from IMPOWER010 is related to median follow-up of 32 months
[c] Confidence intervals for hazard ratio were presented as 99.34% CI and 95% CI for nivolumab plus PDC and atezolizumab treatment groups, respectively.
[d] Data from CM816 trial is related to median follow-up of 41.4 months.
[e] Data from IMPOWER010 is relevant to patients with stage II-IIIA with median follow-up of 46 months
[f] Data from IMPOWER010 trial is related to all randomised stage IB-IIIA with median follow-up of 46 months. For CheckMate 816 trial, OS data by PD-L1 expression subgroup was not available at the time of submission of the current dossier.
[g] Data from IMPOWER010 trial is related patients without EGFR/ALK mutation
[h] Hazard ratio was reported for the time longer than 36 months
i Sourced from (11).
Reference: (12, 96).

28 Appendix P Efficacy of nivolumab plus PDC per CheckMate 816 – supplemental figures

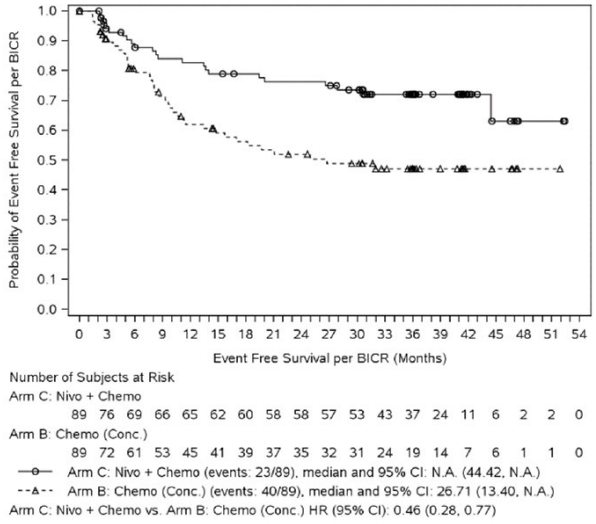
Figure 55: EFS in patients with baseline disease stage IB–II (A), EFS in patients with baseline disease stage IIIA (B) in CheckMate 816 (October 2022)



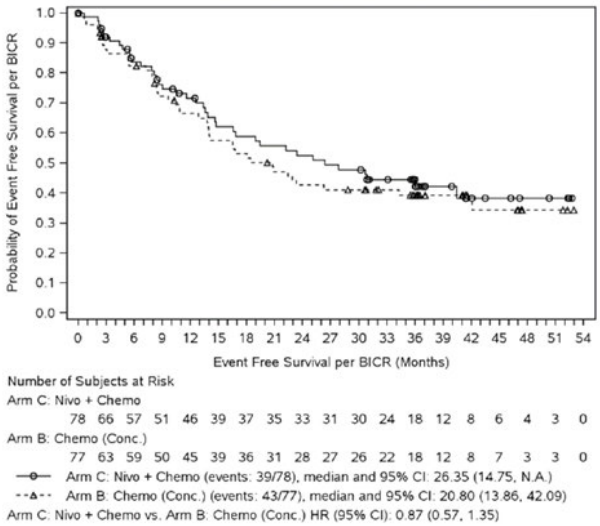
Abbreviations: BICR, Blinded independent central review; CI, Confidence interval; Chemo, Chemotherapy; EFS, event-free survival; HR hazard ratio; Nivo, Nivolumab; N.A, Not reached.
Note: NSCLC stages according to TNM version 7.
Reference: (11)

Figure 56: EFS by tumour PD-L1 expression in CheckMate 816 (October 2022)

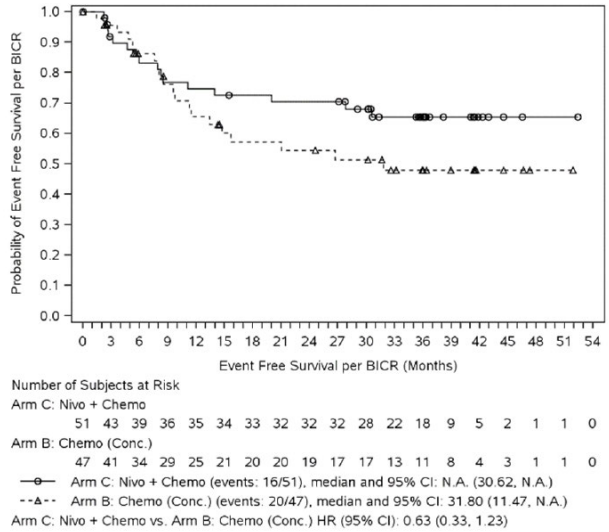
A: PD-L1 expression ≥1%



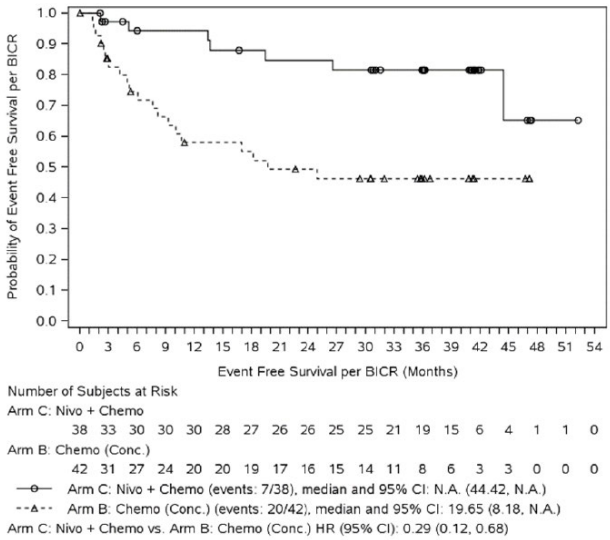
B: PD-L1 expression <1%



C: PD-L1 expression 1–49%

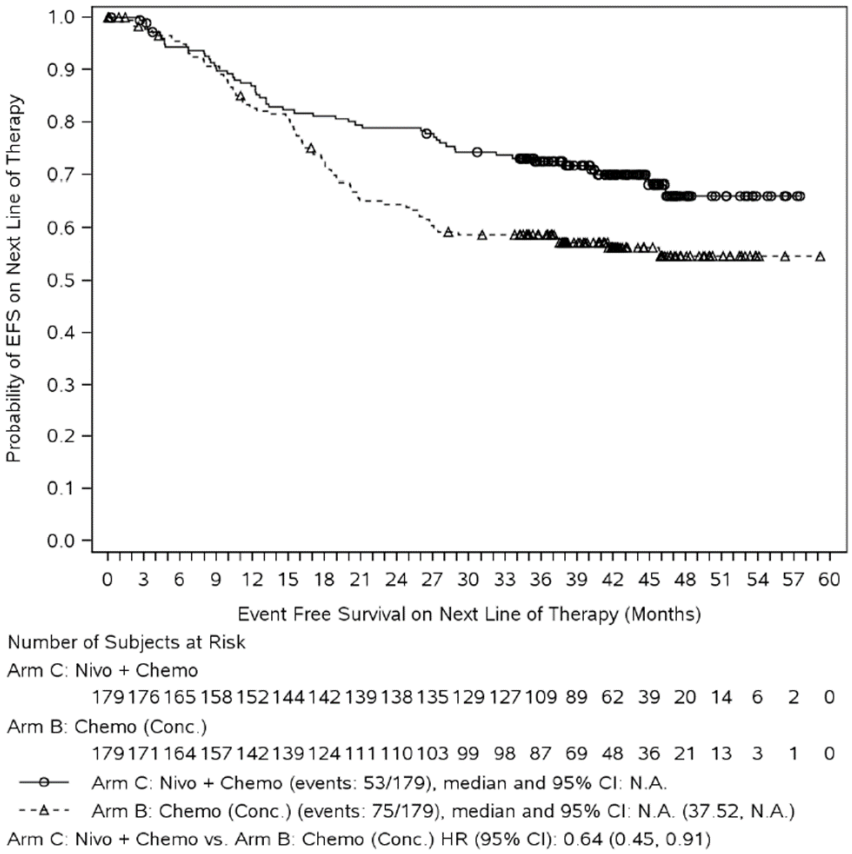


D: PD-L1 expression ≥50%



Abbreviations: BICR, Blinded independent central review; CI, confidence interval; EFS, event-free survival; HR, hazard ratio; Mo, months; NA, not available; PD-L1, programmed death ligand 1
Reference: (11)

Figure 57: EFS2[a] in CheckMate 816, ITT population (October 2022)



Abbreviations: CI, confidence interval; HR, hazard ratio; Mo, months; NR, not reached
Note:
[a] Time from randomisation to objectively documented progression, per investigator assessment, after the next line of therapy or to death from any cause, whichever occurs first; patients without documented progression on the next line who started a second next line of subsequent therapy were considered to have had an event at the start of second next line of therapy
Reference: (11)

29 Appendix Q Considerations in EFS and OS outcomes between the tumour PD-L1 expression ≥1% for all stages vs stage II – IIIA (TNM version 7) patient populations

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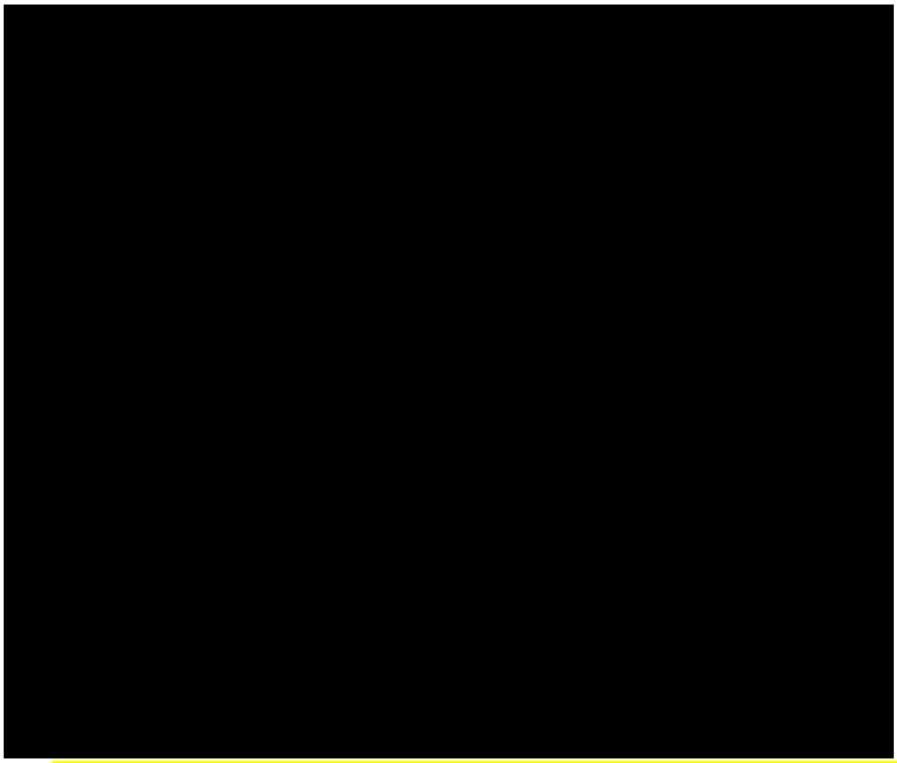

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