Medicinrådet

Bilag til Medicinrådets anbefaling vedr. durvalumab til behandling af ikke-småcellet lungekræft i stadie III efter behandling med kurativt intenderet platinbaseret kemoradioterapi

Patienter med PD-L1-ekspression ≥ 1 % og < 25 %

Vers. 2.0

Bilagsoversigt

1. Ansøgers notat til Rådet vedr. durvalumab
2. Forhandlingsnotat fra Amgros vedr. durvalumab
3. Ansøgers endelige ansøgning vedr. durvalumab

Medicinrådet
Dampfærgevej 21-23, 3. sal
2100 København Ø

21.05.2025

Notat til Medicinrådet udkast til vurdering af durvalumab monoterapi til behandling af voksne med ikke-småcellet lungekræft(NSCLC) i stadie III efter behandling med kurativt intenderet platinbaseret kemoradioterapi for patienter med PD-L1-ekspression ≥ 1 % og < 25 %.

AstraZeneca takker for muligheden for at kommentere på det fremsendt udkast til en vurderingsrapport.
Det er vigtigt at understrege, at den godkendte EMA indikation for durvalumab monoterapi i stadie III NSCLC omfatter patienter med PD-L1 udtryk >1%. Den fulde indikation er efterfølgende blev anbefalet/reimbursed verden over. Danmark afveg dog ved kun at godkende patientpopulationen med PD-L1 udtryk >25% som standardbehandling baseret på en post-hoc analyse.

Medicinrådets fremsendte udkast til vurderingsrapport fokuserer udelukkende på subgruppe-data for PD-L1 ≥ 1% og <25%, hvor PACIFIC-studiet ikke er designet til at demonstrere statistisk signifikans.
Kliniske data for populationen med PD-L1 udtryk >1% blev inkluderet i AstraZenecas genansøgning for at understrege, at data for indikationer viser statistisk signifikans for både OS og PFS. Ydermere, i den oprindelige vurdering fra 2019 understregede det gældende fagudvalg også dette ved at fremhæve data om PD-L1 udtryk >1%[1]:

> 17.1.2 Konklusion for samlet patientpopulation
>
> Fagudvalget vurderer, at durvalumab til patienter med NSCLC i stadie III og PD-L1-ekspression ≥ 1 % giver en **vigtig klinisk merværdi.** Evidensens kvalitet er ikke vurderet, da det ikke var et præspecificeret klinisk spørgsmål.

Vurderingsrapporten nævner i afsnit 2.1, at der er en potentiel risiko for, at effekten i kontrolarmen i PACIFIC bliver undervurderet. Genansøgningen inkluderer real-world data[2] som dokumenterer at effekten af durvalumab i denne population er som observeret i dansk klinisk praksis. Andre real-world evidence studier (RWE) konkluderer, at behandlingseffekten i PACIFIC er sammenlignelig i det der observeres i det kliniske miljø.[3,4,5,6] RWE-studierne inkluderer kohorter, f.eks. fra Canada, Tyskland og Norge.

AstraZeneca ser frem til Medicinrådet beslutning den 30. maj og at durvalumab efter et langt forløb kan anvedes til alle patienter omfattet af indikation.

Med venlig hilsen,
Sara Vinther

Market Access Manager
AstraZeneca A/S

References:

1: https://filer.medicinraadet.dk/media/djpoxwg3/baggrund-for-medicinraadets-anbefaling-vedr-durvalumab-til-ikke-smaacellet-lungekraeft-stadie-iii-vers-1-0_adlegacy.pdf

2: Pøhl M. Real world treatment of Locally advanced NSCLC with patient characteristic, treatment patterns, and overall survival among patients treated in the capital Region of Denmark 2016-2023. 2025.

3: Wang Y ZT, Huang Y, Li W, Zhao J, Yang Y, Li C, Wang L, Bi N. Real-World Safety and Efficacy of Consolidation Durvalumab After Chemoradiation Therapy for Stage III Non-small Cell Lung Cancer: A Systematic Review and Meta-analysis. Int J Radiat Oncol Biol Phys 2022;112(5):1154-64.

4: N. Girard HJMS, A. Sibille, F. McDonald, F. Mornex, M.C.C. Garassino, A.R. Filippi, S. Peters, J.K. Field, D.C. Christoph, R. Fietkau, V.D. Haakensen, J. Bar, C. Chouaid, V. Bray, S. Kao, W. Sawyer, A. Allen, M. Licour, P. Garrido. 1171MO PACIFIC-R real-world study: Treatment duration and interim analysis of progression-free survival in unresectable stage III NSCLC patients treated with durvalumab after chemoradiotherapy. Annals of Oncology. 2021;32:s939-s40.

5: Michael Offin NS, Andreas Rimner, Stephanie Lobaugh, Annemarie F. Shepherd, Charles B. Simone, Daphna Y. Gelblum, Abraham J. Wu, Nancy Lee, Mark G. Kris, Charles M. Rudin, Zhigang Zhang, Matthew D. Hellmann, Jamie E. Chaft, Daniel R. Gomez Clinical outcomes, local–regional control and the role for metastasis-directed therapies in stage III non-small cell lung cancers treated with chemoradiation and durvalumab. Radiotherapy and Oncology. 2020;149:205-11.

6: Martin Faehling CS, Petros Christopoulos, Petra Hoffknecht, Jürgen Alt, Marlitt Horn, Stephan Eisenmann, Anke Schlenska-Lange, Philipp Schütt, Felix Steger, Wolfgang M. Brückl, Daniel C. Christoph. Durvalumab after definitive chemoradiotherapy in locally advanced unresectable non-small cell lung cancer (NSCLC): Real-world data on survival and safety from the German expanded-access program (EAP). Lung Cancer. 2020;150:114-22.

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20.05.2025

DBS/KLE

Forhandlingsnotat

Dato for behandling i Medicinrådet	Juni 2025 (skriftlig godkendelse - revurdering)
Leverandør	AstraZeneca
Lægemiddel	Imfinzi (durvalumab)
Ansøgt indikation	Imfinzi som monoterapi til behandling af lokalt fremskreden, inoperabel ikke-småcellet lungecancer (NSCLC) hos voksne med PD-L1-tumorekspression ≥ 1 %, og hvis sygdom ikke er progredieret efter platinbaseret kemo-strålebehandling
Nyt lægemiddel / indikationsudvidelse	indikationsudvidelse

Prisinformation

Amgros har følgende aftalepris på Imfinzi (durvalumab):

Tabel 1: Aftalepris

Lægemiddel	Styrke	AIP (DKK)	Forhandlet SAIP (DKK)	Rabatprocent ift. AIP
Imfinzi	50 mg/ml, 2,4 ml	4.179,60	[redacted]	[redacted]
Imfinzi	50 mg/ml, 10 ml	17.307,33	[redacted]	[redacted]

[redacted]

Aftaleforhold

[redacted]

Konkurrencesituationen

Imfinzi er på nuværende tidspunkt den eneste immunterapi til denne indikation.

Tabel 1: Sammenligning af lægemiddeludgifter pr. patient

Lægemiddel	Styrke og pakningsstr.	Dosering	Pris pr. pakning (SAIP, DKK)	Lægemiddeludgift pr. år (SAIP, DKK)
Imfinzi	50 mg/ml, 10 ml	1.500 mg hver 4. uge	[redacted]	[redacted]

Status fra andre lande

Tabel 2: Status fra andre lande

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

Opsummering:

[redacted]

Reapplication for Imfinzi (durvalumab) as monotherapy for the treatment of locally advanced, unresectable non-small cell lung cancer (NSCLC) in adults whose tumours express PD-L1 ≥ 1% and <25% following platinum based chemoradiation therapy.

Submitted by AstraZeneca

February 6th 2025

Updated April 16th 2025

Color scheme for text highlighting	
Color of highlighted text	**Definition of highlighted text**
	Confidential information

Contact information

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Foreword

In 2019 DMC approved the use as standard therapy of Durvalumab as monotherapy for the treatment of locally advanced, unresectable non-small cell lung cancer (NSCLC) in adults whose tumours express PD-L1 ≥ 25% following platinum based chemoradiation therapy. The approval was restricted to this population leaving the subgroup of patients with tumors expressing PD-L1 between 1 and 24% without an approval as standard treatment with durvalumab followed by platinum based chemoradiation therapy. Originally the restricted access to only include PD-L1 ≥ 25%, was based on maturity and uncertainty in long term effects. Most other European countries have recommended Durvalumab in the full population, and an unmet medical need remains in Danish patients with the lower PD-L1 expressed tumours. Since the application in 2019, Danish Medicine Council (DMC), have changed methods from value-based assessment to QALY based assessments, which is why a new application needs to be submitted. In late November 2024, DMC agreed that a reapplication could be sent in. DMC have also added a fast-track process for PD-(L)1 inhibitors, which this application fits in, as Durvalumab has a cost similar to other marketed PD-(L)1 inhibitors. Thus, the health economic section is not filled in but durvalumab has been deemed cost-effective by all countries with similar HTA systems (1-3). From the application sent in back in 2019, new data cuts have been published and the confidential net-price makes durvalumab eligible for the fast-track process. Thus, the assessment of the subgroup is based on three elements: new methods in DMC, new data cuts and a new net-price.

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Tables and Figures

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Abbreviation

Abbreviation	Definition
ADA	antidrug antibody
ADCC	antibody-dependent cell-mediated cytotoxicity
AE	adverse event
AESI	adverse event of special interest
BICR	blinded independent central review
BSC	best supportive care
CI	confidence interval

Abbreviation	Definition
CNS	central nervous system
CR	complete response
CRT	chemoradiation therapy
cCRT	concurrent chemoradiation therapy
CT	computed tomography
DoR	duration of response
EGFR	epidermal growth factor receptor
EQ-5D	five-dimension EuroQoL questionnaire
FACT-L	Functional Assessment of Cancer Therapy-Lung
Gy	Gray
HR	hazard ratio
HRQoL	health-related quality of life
imAE	immune-mediated adverse event
irAE	immune-related adverse event
IO	immuno-oncology
ITT	intention-to-treat
IV	Intravenous
KM	Kaplan Meier
LY	life years
mAb	monoclonal antibody
N/A	not available
NS	not significant
NSCLC	non-small cell lung cancer
ORR	overall response rate
OS	overall survival
PD	progressive disease
PD-1	programmed cell death protein 1
PD-L1	programmed cell death-ligand 1
PET	positron emission tomography
PF	progression-free
PFS	progression-free survival
PR	partial response
PROs	patient-reported outcomes
PS	performance score
Q2W	once every two weeks
QLQ-C30	30-item core quality of life questionnaire
QLQ-LC13	13-item lung cancer-specific questionnaire module
QoL	quality of life
RCTs	randomized controlled trials
RECIST	Response Evaluation Criteria In Solid Tumors
SAE	serious adverse event
SCC	squamous cell carcinoma

Abbreviation	Definition
SCLC	small cell lung cancer
SD	standard deviation
SoC	standard of care
TCR	T-cell receptor
TNM	tumor, lymph nodes, metastasized
TRT	thoracic radiotherapy
TTD	time to discontinuation
TTDM	time to death or distant metastasis
VEGF	vascular endothelial growth factor

1. Regulatory information on the medicine

Overview of the medicine	
Proprietary name	Imfinzi
Generic name	Durvalumab
Therapeutic indication as defined by EMA	Imfinzi (durvalumab) as monotherapy is indicated for the treatment of locally advanced, unresectable non-small cell lung cancer (NSCLC) in adults whose tumours express PD-L1 on ≥ 1% of tumour cells and whose disease has not progressed following platinum based chemoradiation therapy.
Marketing authorization holder in Denmark	AstraZeneca AB SE-151 85 Södertälje. Sweden
ATC code	L01FF03
Combination therapy and/or co-medication	No
(Expected) Date of EC approval	Approved 24th September 2018
Has the medicine received a conditional marketing authorization?	No
Accelerated assessment in the European Medicines Agency (EMA)	No
Orphan drug designation (include date)	No
Other therapeutic indications approved by EMA	**Non-Small Cell Lung Cancer (NSCLC)**: • Durvalumab as monotherapy is indicated for the treatment of locally advanced, unresectable non-small cell lung cancer (NSCLC) in adults whose tumours express PD-L1 on ≥ 1% of tumour cells and whose disease has not progressed following platinum-based chemoradiation therapy. • Durvalumab in combination with tremelimumab and platinum-based chemotherapy is indicated for the first-line treatment of adults with metastatic NSCLC with no sensitising EGFR mutations or ALK positive mutations. **Small Cell Lung Cancer (SCLC)** • Durvalumab in combination with etoposide and either carboplatin or cisplatin is indicated for the first-line

Overview of the medicine	
	treatment of adults with extensive-stage small cell lung cancer (ES-SCLC). **Biliary Tract Cancer (BTC)** • Durvalumab in combination with gemcitabine and cisplatin is indicated for the first-line treatment of adults with unresectable or metastatic biliary tract cancer (BTC). **Hepatocellular Carcinoma (HCC)** • Durvalumab as monotherapy is indicated for the first line treatment of adults with advanced or unresectable hepatocellular carcinoma (HCC). • Durvalumab in combination with tremelimumab is indicated for the first line treatment of adults with advanced or unresectable hepatocellular carcinoma (HCC). **Endometrial cancer** • Durvalumab in combination with carboplatin and paclitaxel (chemotherapy medicines) for initial treatment of the disease. For maintenance treatment, it is used on its own when the cancer is mismatch repair deficient (dMMR) and in combination with olaparib when the cancer is mismatch repair proficient (pMMR).
Other indications that have been evaluated by the DMC (yes/no)	Recommendations on: **Non-Small Cell Lung Cancer (NSCLC)** Durvalumab as monotherapy is indicated for the treatment of locally advanced, unresectable non-small cell lung cancer (NSCLC) in adults whose tumours express PD-L1 on ≥ 1% of tumour cells and whose disease has not progressed following platinum-based chemoradiation therapy (Only approved for PD-L1 above 25%). **Biliary Tract Cancer (BTC)** Durvalumab in combination with gemcitabine and cisplatin is indicated for the first-line treatment of adults with unresectable or metastatic biliary tract cancer (BTC). **Small Cell Lung Cancer (SCLC)** Durvalumab in combination with etoposide and either carboplatin or cisplatin is indicated for the first-line treatment of adults with extensive-stage small cell lung cancer (ES-SCLC). **Hepatocellular Carcinoma (HCC)** Durvalumab in combination with tremelimumab is indicated for the first line treatment of adults with advanced or unresectable hepatocellular carcinoma (HCC).

Overview of the medicine	
	Currently in process: **Endometrial cancer** Durvalumab in combination with carboplatin and paclitaxel (chemotherapy medicines) for initial treatment of the disease. For maintenance treatment, it is used on its own when the cancer is mismatch repair deficient (dMMR). **Non Small Cell Lung Cancer** Durvalumab in combination with platinum-based chemotherapy as neoadjuvant treatment, followed by durvalumab as monotherapy as adjuvant treatment, is indicated for the treatment of adults with resectable NSCLC at high risk of recurrence and no known EGFR mutations or ALK rearrangements (expected indication)
Joint Nordic assessment (JNHB)	Are the current treatment practices similar across the Nordic countries (DK, FI, IS, NO, SE)? [yes/no]: • Yes, but Denmark is the only country that has introduced a PD-L1 cut of 25% and only approved the product in PD-L1 above 25% Is the product suitable for a joint Nordic assessment? [yes/no]: • No. The indication/subgroup is already approved in all other Nordic countries
Dispensing group	BEGR
Packaging – types, sizes/number of units and concentrations	2.4 mL of concentrate in vial containing 120 mg durvalumab. Pack size of 1 vial. 10 mL of concentrate in a vial containing 500 mg durvalumab. Pack size of 1 vial.

2. Summary table

Summary	
Indication relevant for the assessment	Imfinzi (durvalumab) as monotherapy for the treatment of locally advanced, unresectable non-small cell lung cancer (NSCLC) in adults whose tumors express PD-L1 ≥ 1% and < 25% and whose disease has not progressed following platinum based chemoradiation therapy
Dosage regiment and administration	10 mg/kg every 2 weeks or 1 500 mg every 4 week until disease progression, unacceptable toxicity, or a maximum of 12 months

Summary	
Choice of comparator	Placebo
Prognosis with current treatment (comparator)	For patients with stage IB–IIIA NSCLC, adjuvant chemotherapy improves overall survival (OS) by ~5% and disease free survival (DFS) by ~6% after five years.(4-6) The five-year NSCLC recurrence rates vary by disease stage, with recurrence seen in approximately 45% of patients with stage IB, which increases to approximately 62% and 76% in patients with stage II and stage III respectively. (6)
Type of evidence for the clinical evaluation	H2H vs Danish standard treatment
Most important efficacy endpoints (Difference/gain compared to comparator)	**ITT (5-year survival DCO January 11, 2021)**: • mOS: 47.5m vs 29.1m for placebo + BSC (HR: 0.72; 95% CI: 0.59-0.89 • PFS: mPFS 16.9m for IMFINZI vs. 5.6m for placebo + BSC; (HR: 0.55; 95% CI: 0.45-0.68) **Post hoc data (5-year survival, DCO 11th January 2021):** **PD-L1 >1%:** OS: Events HR: Events 103/212(48.6%) vs 56/91(61.5%). HR=0.61; 95% CI: 0.44-0.85) • PFS: Events HR: Events 111/212(52.4%) vs 68/91(75.8%). HR=0.47; 95% CI: 0.35-0.64) **PD-L1 1-24%:** • OS: Events 52/97(53.6%) vs 29/47(61.7%) or HR:0.73(0.46-1.14) • PFS: Events 50/97 vs. 36/47(76.6%) or HR=0.51 (0.33-0.78) The *post hoc* analysis was exploratory in nature, based on incomplete and poorly matched data, and therefore, was not powered to detect statistical significance nor treatment guidance.
Most important serious adverse events for the intervention and comparator	• Durvalumab was well-tolerated: 15.4% of patients had to discontinue treatment due to any AE (compared to 9.8% on placebo + BSC) and 11.8% of patients experienced Grade 3-4 AEs (compared to 4.3% on placebo + BSC) • The most common adverse reactions (≥20%) for IMFINZI were cough/productive cough, upper respiratory tract infections, and rash, which can be managed according to standard treatment guidelines.

Summary	
	• 10.7% of patients treated with IMFINZI experienced pneumonitis (vs. 6.8% for placebo + BSC), but Grade 3-4 pneumonitis events were rare for patients treated with both IMFINZI (1.7%) and placebo+BSC (2.6%)
Impact on health-related quality of life	The improvement rate in EORTC QLQ-C30 was 29.4% for the durvalumab group vs. 25.7% in the placebo arm or improvement versus baseline of 19.6 points vs. 17.5 points or an absolute difference of 2.1 points.
Type of economic analysis that is submitted	NA
Data sources used to model the clinical effects	NA
Data sources used to model the health-related quality of life	NA
Life years gained	NA
QALYs gained	NA
Incremental costs	NA
ICER (DKK/QALY)	NA
Uncertainty associated with the ICER estimate	NA
Number of eligible patients in Denmark	**Incidence**: In the initial 2019 application DMC estimated that 340 stage III patients were candidates within the indication. AstraZeneca believe this number is too high for multiple reasons. Some patients will not continue treatment following CRT and more patient than estimated would progress to stage IV. Also, the DMC estimate was based on 2016 numbers with a total of 851 patients in stage IIIa or IIIb. In 2023 that total was 734. [redacted] This is much lower numbers compared to the forecast made by DMC in 2019 based on 2016 numbers. Based on PACIFIC trial data the split between PD-L1 1-24% and above 25% was 47.5%/52.5%. **Prevalence:** It is estimated that around 734 NSCLC patients are stage III and 75-80 % of these are unresectable.

Summary	
	In total the expected number of patients that will receive durvalumab within the subgroup of patients with PD-L1 1-24% is around 80 annually.
Budget impact (in year 5)	NA

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

3.1 The medical condition

Lung cancer is defined as the uncontrolled growth of abnormal cells in the lungs and is the most commonly diagnosed cancer and the leading cause of cancer mortality worldwide. (7) The two predominant forms of lung cancer are NSCLC that accounts for 85% of patients and small-cell-lung cancer (SCLC), accounting for 15% of patients. (8) NSCLC comprises a group of cancers, which exhibit similar behavior and response to treatment. They can be categorized according to the tissue of origin: adenocarcinoma, squamous cell carcinoma and large cell lung cancer; several variants and clinical sub-types exist within each category. (9) Adenocarcinomas are the most common type of NSCLC, accounting for approximately 40% of lung cancers (10, 11) Recurrent driver mutations commonly found in NSCLC have a key role in the development of disease and are targets for therapeutic agents. The most recent Danish Lung Cancer Registry report shows that 5256 patients were diagnosed with lung cancer in Denmark in 2023. (12)

Lung cancer symptoms

Early-stage NSCLC is often asymptomatic, and patients are therefore at risk of delayed diagnosis, which impacts cure rates and survival. Patients may live for several years before showing symptoms, increasing the risk of distant metastases and more advanced disease at diagnosis. In addition to the largely asymptomatic nature of early disease, the initial symptoms are often non-specific, such as a cough (13). As a consequence, approximately 70% of NSCLC patients will be diagnosed with unresectable, advanced NSCLC (14-16). NSCLC is associated with a notably poor prognosis in comparison with other tumour types, such as colon, rectal and breast cancer (17, 18).

The overall five-year survival rate for NSCLC (all stages) has increased significantly from 10% (women) and 8% (men) in 1999 to 35% and 27% in 2023 (cancer.dk) This varies by stage at diagnosis from 68%–92% for stage I NSCLC to <1%–10% for stage IV NSCLC (Figure 1).

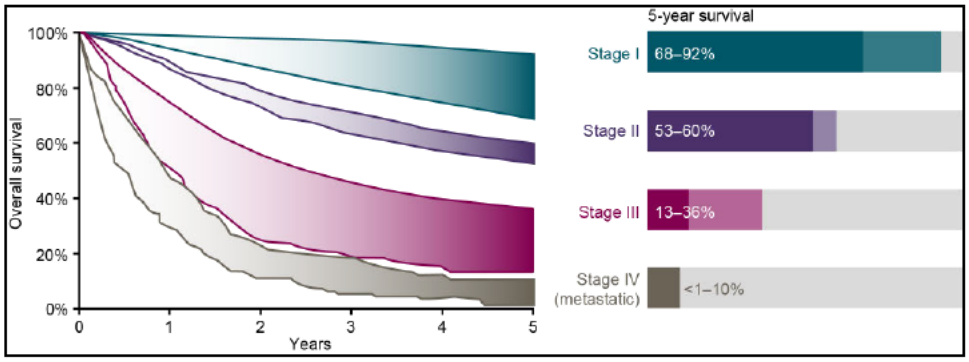


Figure 1. Five-year NSCLC survival rates by clinical stage (AJCC 8th edition) at diagnosis (33).

Despite the curative intent of treatment in early stages, recurrence in patients with stage IB–III NSCLC remains relatively common, regardless of post-operative chemotherapy use.(6) For patients with stage IB–IIIA NSCLC, adjuvant chemotherapy improves overall survival (OS) by ~5% and disease free survival (DFS) by ~6% after five years.(4-6) The five-year NSCLC recurrence rates vary by disease stage, with recurrence seen in approximately 45% of patients with stage IB, which increases to approximately 62% and 76% in patients with stage II and stage III respectively. (6)
Common sites of distant recurrence for NSCLC include the brain, lung, bone and liver (19). Approximately 41% of NSCLC patients develop brain metastases during the course of their disease, making the brain the most common site of distant recurrence in NSCLC.(19) Brain metastases are likely to contribute to the poor survival seen in patients with NSCLC and comprise a substantial symptom burden. (20, 21)

3.2 Patient population

Table 1 Incidence and prevalence in the past 5 years in lung cancer (12)

Year	2019	2020	2021	2022	2023
Incidence in Denmark	4938	5096	5192	5182	5256
Incidence NSCLC	4195	4330	4415	4405	4468

Year	2019	2020	2021	2022	2023
Prevalence in Denmark	13730	14505	15501	16052	16901
Global prevalence *	NA	NA	NA	NA	NA

* For small patient groups, also describe the worldwide prevalence.

Table 1 shows the incidence and prevalence for the past five years in lung cancer according to *Sundhedsdatastyrelsen* (12). The incidence and prevalence relevant for this application is discussed in the section below.

In the initial 2019 application DMC estimated that 340 stage III patients were candidates within the indication. AstraZeneca believe this number is too high for multiple reasons. Some patients will not continue treatment following CRT and more patient than estimated would progress to stage IV. Also, the DMC estimate was based on 2016 numbers with a total of 851 patients in stage IIIa or IIIb. In 2023 that total was 734. [redacted] This is much lower numbers compared to the forecast made by DMC in 2019 based on 2016 numbers. Based on PACIFIC trial data the split between PD-L1 1-24% and above 25% was 47.5%/52.5%.

It is estimated that around 734 NSCLC patients are stage III and 75-80 % of these are unresectable.

Patient-numbers have been discussed between AstraZeneca and DMC in the period following the decision in DMC in 2019. After more than 4 years of experience with the use of durvalumab in stage III NSCLC segment of PD-L1 > 25% and combined with the unpublished data from Region Hovedstaden (22) we have estimated the number of patients that are candidates for durvalumab in the subgroup PD-L1 1 – 24 % (Table 2).

- The numbers are based on 2023 numbers of 734 stage IIIa and IIIb patients.
- Of these, approximately 80% will be candidates for curative intended therapy, and approximately 75% of these will not progress during this treatment.
- Around 60% of these patients will have PD-L1 expression ≥ 1% (if 100 % are tested).
- Based on PACIFIC the split between PD-L1 1-24% and above 25% was 47.5%/52.5%.
- This calculated number assume that 100% of patients will proceed from CRT to durvalumab, which is not the case.

- In total the expected number of patients that will receive durvalumab within the subgroup of patients with PD-L1 1-24% is around 80 annually.

Table 2. Estimated number of patients eligible for treatment ITT and PD-L1 1 – 24 %

Year	2025	2026	2027	2028	2029
Number of patients in Denmark who are eligible for treatment in the coming years	75	77	80	80	80

3.3 Current treatment options

DLCG guideline from 2024 on intended curative treatment of patients with locally advanced disease from NSCLC. (23)

- Patients with unresectable locally advanced non-small cell lung cancer should be considered as candidates for concomitant chemoradiotherapy with 66 Gy/33 F (A)
- Patients with unresectable locally advanced NSCLC in poor general condition or with significant comorbidity should be assessed for radiotherapy 66 Gy/30-33 F without chemotherapy
- Concomitant platinum-containing combination chemotherapy (D) is recommended, rather than sequential chemoradiotherapy, which may be chosen in selected cases for patients who do not tolerate concomitant treatment modality (A)
- Patients who have completed curative chemoradiotherapy for stage III NSCLC with PD-L1 TPS ≥ 25%, should be assessed for 12-month consolidation durvalumab.(23)

3.4 The intervention

Overview of intervention	
Indication relevant for the assessment	The EMA approved indication is for the treatment of locally advanced, unresectable NSCLC in adults whose tumors express PD-L1 ≥ 1% and whose disease has not progressed following platinum based chemoradiation therapy. This application only concerns the subgroup of patients with PD-L1 expression between 1% and 24%
ATMP	NA
Method of administration	Intravenous use. It is to be administered as an intravenous infusion solution over 1 hour

Overview of intervention	
Dosing	10 mg/kg every 2 weeks or 1 500 mg every 4 week until disease progression, unacceptable toxicity, or a maximum of 12 months
Dosing in the health economic model (including relative dose intensity)	NA
Should the medicine be administered with other medicines?	No, monotherapy
Treatment duration / criteria for end of treatment	12 months or until progression or unacceptable toxicity
Necessary monitoring, both during administration and during the treatment period	No
Need for diagnostics or other tests (e.g. companion diagnostics). How are these included in the model?	PD-L1 testing is well established in the lung cancer area but the cut-off of 25% is not standard. The current assays to evaluate PD-L1 expression are maintained. The unique threshold in DK of 25% would be phased out.
Package size(s)	2.4 mL of concentrate in vial containing 120 mg durvalumab. Pack size of 1 vial. 10 mL of concentrate in a vial containing 500 mg durvalumab. Pack size of 1 vial.

3.4.1 The intervention in relation to Danish clinical practice

According to the DLCG clinical guidelines (23), patients with non-resectable stage IIB, IIIA and IIIB NSCLC will be treated with concomitant chemotherapy and radiotherapy or radiotherapy alone with curative intend. Patients with stage III NSCLC who have been treated with curative intended chemoradiotherapy and with a PD-L1 tumor expression ≥ 25% will be evaluated for 12 months of durvalumab treatment.(23) In the ESMO guidelines, durvalumab is recommended for patients with PD-L1 tumor expression ≥ 1% in line with EMA indication for durvalumab. Contrary to international guidelines, in Danish clinical practice, there is no treatment option for patients with PD-L1 tumor expression 1-24%. Hence, the application for this patient population seeks to expand the reimbursement in Denmark to cover patients with PD-L1 tumor expression 1-24% and be in line with the indication for durvalumab. The comparator in the clinical trial is placebo and since there is no other treatment options for this group of patients, the relevant comparator in this application is placebo.

3.5 Choice of comparator(s)

The comparator in the clinical trial is placebo and since there is no other treatment options for this group of patients, the relevant comparator in this application is placebo.

Overview of comparator	
Generic name	NA
ATC code	NA
Mechanism of action	NA
Method of administration	NA
Dosing	NA
Dosing in the health economic model (including relative dose intensity)	NA
Should the medicine be administered with other medicines?	NA
Treatment duration/ criteria for end of treatment	NA
Need for diagnostics or other tests (i.e. companion diagnostics)	NA
Package size(s)	NA

3.6 Cost-effectiveness of the comparator(s)

NA

3.7 Relevant efficacy outcomes

3.7.1 Definition of efficacy outcomes included in the application

In this application, the following efficacy outcomes are used; Overall survival, Progression free survival, and Quality of life. These efficacy endpoints were also used in the first assessment of this indication where durvalumab was approved within a

restricted population. (24, 25) All included efficacy outcomes are described in Table 3 below.

Table 3 Efficacy outcomes measures relevant for the application (PACIFIC PD-L1 1- 24%)

Outcome measure	Time point*	Definition	How was the measure investigated/method of data collection
Overall survival (OS) [PACIFIC ITT and post hoc analyses]		OS was defined as the time from the date of randomization until death due to any cause. OS was calculated using the Kaplan-Meier technique.	OS was calculated using the Kaplan-Meier technique. From baseline until death due to any cause. Assessed until 22 Mar 2018 DCO; up to a maximum of approximately 4 years.
PFS [PACIFIC ITT and post hoc analyses]		PFS was defined as the time from randomization until the date of objective disease progression (RECIST 1.1) or death (by any cause in the absence of progression). Progression was defined using RECIST 1.1 as a 20% increase in the sum of the longest diameter of target lesions, or a measurable increase in a non-target lesion, or the appearance of new lesions.	Tumor scans performed at baseline then every ~8 weeks up to 48 weeks, then every ~12 weeks thereafter until confirmed disease progression. Assessed until 13 Feb 2017 DCO; up to a maximum of approximately 3 years. PFS was calculated using the Kaplan-Meier technique.
PROs/HRQoL [PACIFIC ITT]		Global health status/HRQoL was assessed using the EORTC QLQ-C30 global QoL scale which includes 2 items from the QLQ-C30: "How would you rate your overall health during the past week?" and "How would you rate your overall QoL during the past week?". Scores from 0 to 100 were derived for each item with higher scores indicating a better health status. Time to deterioration for global health status/HRQoL was defined as time from randomization until the date of first clinically meaningful deterioration (a decrease in global health status/HRQoL from baseline of ≥10) or	At baseline, every 4 weeks for first 8 weeks, then every ~8 weeks until 48 weeks, then every ~12 weeks thereafter until confirmed disease progression. Assessed until 22 Mar 2018 DCO; up to a maximum of approximately 4 years.

Outcome measure	Time point*	Definition	How was the measure investigated/method of data collection
		death (by any cause) in the absence of a clinically meaningful deterioration. Time to deterioration was calculated using the Kaplan-Meier technique.	
Safety [PACIFIC ITT]		The occurrence of AEs, SAEs, abnormal laboratory evaluations, vital signs, ECGs, and physical examinations; AEs and serious AEs are reported from the signing of an informed consent form through to the end of the safety follow-up period (90 days after the last dose of study drug)	From signing of an informed consent form through to the end of the safety follow-up period (90 days after the last dose of study drug)

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

4. Health economic analysis

This application follows the 14-week process track and health economic evaluation is not submitted as a part of the application. Thus, this section should be disregarded.

4.1 Model structure

NA

4.2 Model features

NA

Table 4. Features of the economic model

Model features	Description	Justification
NA		

5. Overview of literature

5.1 Literature used for the clinical assessment

The data was obtained from the head-to-head PACIFIC study as the control-arm is aligned with the comparator in this application. Thus, a systematic literature search has not been performed.

Table 5 Relevant literature included in the assessment of efficacy and safety

Reference	Trial name*	NCT identifier	Dates of study (Start and expected completion date, data cut-off and expected data cut-offs)	Used in comparison of*
Durvalumab after Chemoradiotherapy in Stage III Non–Small-Cell Lung Cancer. Antonia S.J., Villegas, A., et al., NEJM, September 8, 2017. (DOI: 10.1056/NEJMoa1709937) (26) Overall Survival with Durvalumab after Chemoradiotherapy in Stage III NSCLC. Antonia S.J., Vilegas, D. et al., NEJM, September 25, 2018 (DOI: 10.1056/NEJMoa1809697) (27) Outcomes with durvalumab by tumour PD-L1 expression in unresectable, stage III non-small-cell lung cancer in the PACIFIC trial. L. Paz-Ares, A. Spira, et al., Annals of Oncology, June 2020 (DOI: 10.1016/j.annonc.2020.03.287) (28) Five-Year Survival Outcomes from the PACIFIC Trial: Durvalumab After Chemoradiotherapy in Stage III Non-Small-Cell Lung Cancer. Spigel DR, Faivre-Finn C, et al., J Clin Oncol. 2022 Apr (DOI: 0.1200/JCO.21.01308.) (29)	PACIFIC	NCT02125461	Start 05.07.2014 and completed 24.08.2023. Primary PFS analysis: February 13, 2017 DCO March 22, 2018 2nd PFS analysis March 20, 2020 Post-hoc OS DCO January 11th, 2021	Durvalumab vs. placebo + BSC

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

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

The health-related quality of life data was obtained from the head-to-head PACIFIC study as the control-arm is aligned with the comparator in this application. Thus, a systematic literature search has not been performed.

Table 6 Relevant literature included for (documentation of) health-related quality of life (See section 10)

Reference	Health state/Disutility	Reference to where in the application the data is described/applied
R. Hui, M. Özgüroğlu, et al. Patient-reported outcomes with durvalumab after chemoradiotherapy in stage III, unresectable non-small-cell lung cancer (PACIFIC): a randomised, controlled, phase 3 study. Lancet Oncol 2019; 20: 1670–80.(30)	EORTC QLQ-C30	Section 10

5.3 Literature used for inputs for the health economic model

This application follows the 14-week process track and health economic evaluation is not submitted as a part of the application. Thus, this section should be disregarded.

Table 7 Relevant literature used for input to the health economic model

Reference (Full citation incl. reference number)	Input/estimate	Method of identification	Reference to where in the application the data is described/applied
NA			

6. Efficacy

6.1 Efficacy of durvalumab compared to placebo for treatment of locally advanced, unresectable NSCLC with PD-L1 ≥ 1% and subgroup PD-L1 between 1 – 24 %. *Post-hoc* survival update. Data cut off January 11, 2021

6.1.1 Relevant studies

The relevant study for this application is PACIFIC. In this section, the trial design and data cut off dates are listed.

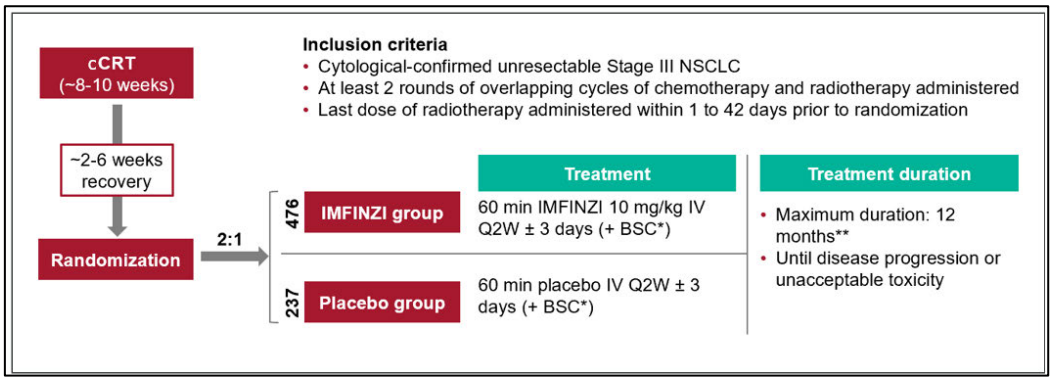


Figure 2 Study design of PACIFIC

Data Cut Off's

- Primary PFS analysis: February 13, 2017
- DCO March 22, 2018
- 2nd PFS analysis March 20, 2020
- *Post-hoc* DCO January 11th, 2021

Table 8 Overview of study design for studies included in the comparison

Trial name, NCT-number (reference)	Study design	Study duration	Patient population	Intervention	Comparator	Outcomes and follow-up time
NCT02125461 (26)	Phase III, Randomised, Double-blind, Placebo-controlled, Multi-centre	Start 05.07.2014 and completed 24.08.2023.	Locally Advanced, Unresectable NSCLC (Stage III) Who Have Not Progressed Following Definitive, Platinum-based, Concurrent Chemoradiation Therapy	Durvalumab intravenously, 10 mg/kg, every 2 weeks until progression er maximum 1 year.	Placebo + BSC intravenously, at a dose of 10 mg per kilogram of body weight, every 2 weeks up to 12 months or until confirmed disease progression, the initiation of alternative cancer therapy, unacceptable toxic events, or withdrawal of consent.	PFS assessed by BICR and evaluated using RECIST 1.1, OS as evaluated by time from randomization until death from any cause. At latest DCO January 11 2021, median follow-up was 34.2 months (all patients) and 61.6 months (censored patients).

6.1.2 Comparability of studies

NA

6.1.2.1 Comparability of patients across studies

Table 9. Baseline characteristics of patients in studies included for the comparative analysis of efficacy and safety (26, 31)

	PACIFIC	
	Durvalumab (N = 476)	Placebo + BSC (N = 237)
Age, median (range)	64.0 (31-84)	64.0 (23-90)
Gender (male)	334 (70.2)	166 (70.0)
Race, n (%)		
White	337 (70.8)	157 (66.2)
Black/African	12 (2.5)	2 (0.8)
Asian	120 (25.2)	72 (30.4)
Other/unknown	7 (1.5)	6 (2.5)
Disease characteristics, n (%)		
Stage IIIA	252 (52.9)	125 (52.7)
Stage IIIB	212 (44.5)	107 (45.1)
Other/unknown	12 (2.4)	5 (2.0)
Histology, n (%)		
Squamous	224(47.1)	102(43.0)
Non-squamous	252(52.9)	135(57.0)
WHO PS, n (%)		
0	234(49.2)	114(48.1)
1	240(50.4)	122(51.5)
Unknown	2(0.4)	1(0.4)
Molecular phenotype, n (%)		
EGFR		
EGFR positive	29 (6.1)	14 (5.9)
EGFR negative	315 (66.2)	165 (69.6)
Unknown	132 (27.7)	58 (24.5)

	PACIFIC	
	Durvalumab (N = 476)	Placebo + BSC (N = 237)
PD-L1		
PD-L1 ≥ 25%	115 (24.2)	44 (18.6)
PD-L1 < 25%	187 (39.3)	105 (44.3)
Unknown	174 (36.6)	88 (37.1)
Smoking history, n (%)		
Non-smoker	43 (9.0)	21 (8.9)
Smoker	433 (91.0)	216 (91.1)
Ex-smoker	354 (74.4)	178 (75.1)
Current smoker	79 (16.6)	38 (16.0)

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

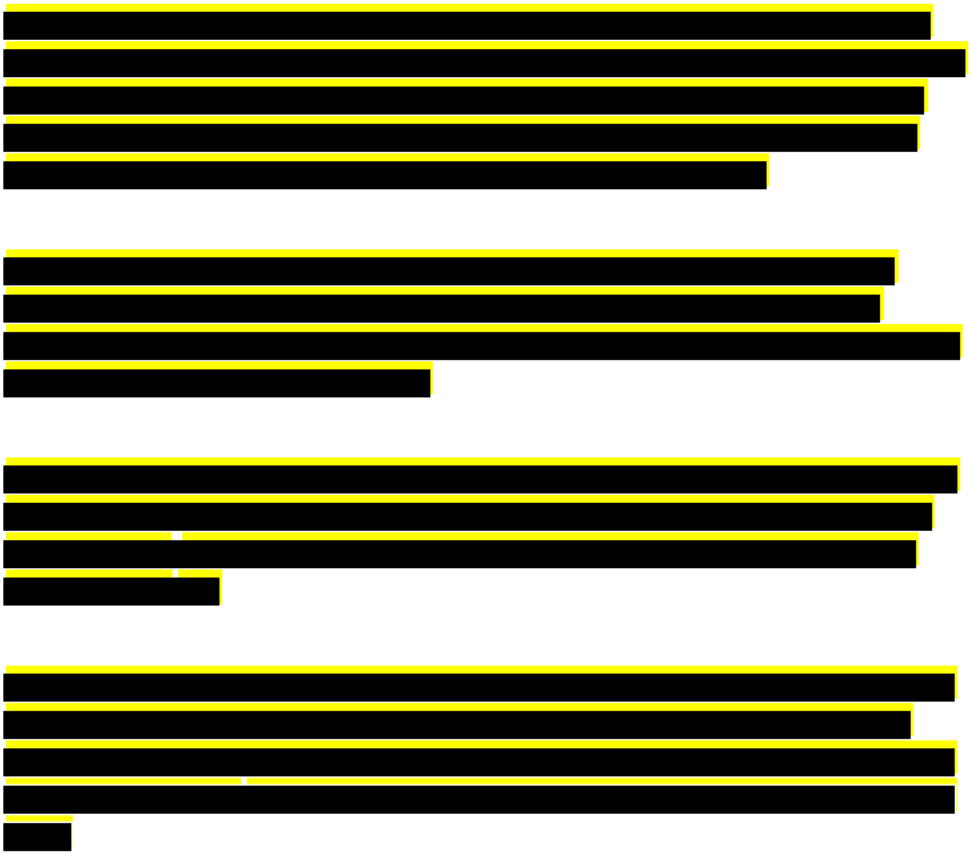


Table 10 Characteristics in the relevant Danish population and in the health economic model based on n=503.

	Value in Danish population (22)	Value used in health economic model (reference if relevant)
[redacted]	[redacted]	
[redacted]	[redacted]	NA
[redacted]	[redacted]	NA
[redacted]	[redacted]	NA
[redacted]	[redacted]	NA
[redacted]	[redacted]	NA
[redacted]	[redacted]	NA
[redacted]	[redacted]	NA

6.1.4 Efficacy – results per PACIFIC.

ITT *Post-hoc*:

709 of 713 randomly assigned patients received durvalumab (473 of 476) or placebo (236 of 237). As of January 11th, 2021 (median follow-up, 34.2 months [all patients]; 61.6 months [censored patients]), updated **OS** (stratified HR, 0.72; 95% CI, 0.59 to 0.89; median, 47.5 v 29.1 months) and **PFS** (stratified HR, 0.55; 95% CI, 0.45 to 0.68; median, 16.9 v 5.6 months) remained consistent with the primary analyses. Estimated 5-year rates (95% CI) for durvalumab and placebo were 42.9% (38.2 to 47.4) versus 33.4% (27.3 to 39.6) for OS and 33.1% (28.0 to 38.2) versus 19.0% (13.6 to 25.2) for PFS. (29)

PD-L1 1 -24 % *post-hoc* analysis

As part of the EMA registration process, a *post hoc* analysis was requested to assess the efficacy of durvalumab treatment (OS and PFS) in PD-L1 negative patients. Therefore, analysis of the PFS and OS was conducted in patients with PD-L1 <1%, PD-L1 ≥1%, PD-L1 25%, PD-L1 ≥25% and unknown PD-L1 status. The PACIFIC study was designed to evaluate the efficacy of durvalumab in an all-comer patient population whose disease

had not progressed after chemoradiation. The *post hoc* analysis was exploratory in nature, based on incomplete and poorly matched data, and therefore, was not powered to detect statistical significance. Thus, the ability to make definitive conclusions in PD-L1 subgroups is limited as is guidance for treatment.

EMA noted in the EPAR that PD-L1 expression could play an important role in the efficacy of durvalumab. They highlight that there is rationale for a benefit driven by PD-L1 ≥1% patients. (31)

Subgroup results PD-L1

In this section results based on PD-L1 status are illustrated. Figure 3 presents OS results for the subgroup PD-L1 status above 1% with a HR of 0.61 (95% CI 0.44-0.85) favoring durvalumab. Figure 3 and Figure 4 shows the OS results in the subgroup with PD-L1 of 1-24% with a HR of 0.73 favoring durvalumab. The survival benefit consistently favored durvalumab versus placebo in the PD-L1 subgroups, with the exception of OS for PD-L1 <1%. The 95% CI for PD-L1 of 1-24% subgroup is overlapping 1 for OS, but as above noted the post-hoc subgroup analyses were not powered to show significance. PFS results for the two subgroups are presented in Figure 5 and Figure 6. In general, the PFS results are consistently showing benefit for all subgroups, although the PFS benefit is not significant for PD-L1 negative patients.

PD-L1 expression level	No. of events / No. of patients (%) IMFINZI	Placebo	Unstratified HR (95% CI)
≥25%	51/115 (44.3%)	27/44 (61.4%)	0.52 (0.32–0.82)
<25%	111/187 (59.4%)	64/105 (61.0%)	0.90 (0.67–1.23)
Unknown	102/174 (58.6%)	64/88 (72.7%)	0.68 (0.50–0.93)
1–24% (post-hoc analysis)	52/97 (53.6%)	29/47 (61.7%)	0.73 (0.46–1.14)
≥1% (post-hoc analysis)	103/212 (48.6%)	56/91 (61.5%)	0.61 (0.44–0.85)
<1% (post-hoc analysis)	59/90 (65.6%)	35/58 (60.3%)	1.15 (0.75–1.75)

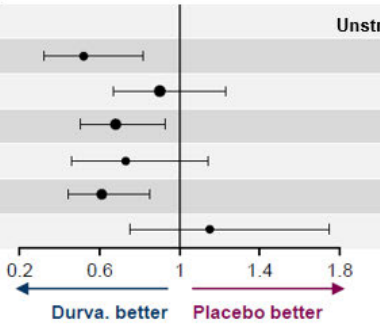


Figure 3. OS result per PD-L1 expression level (29)

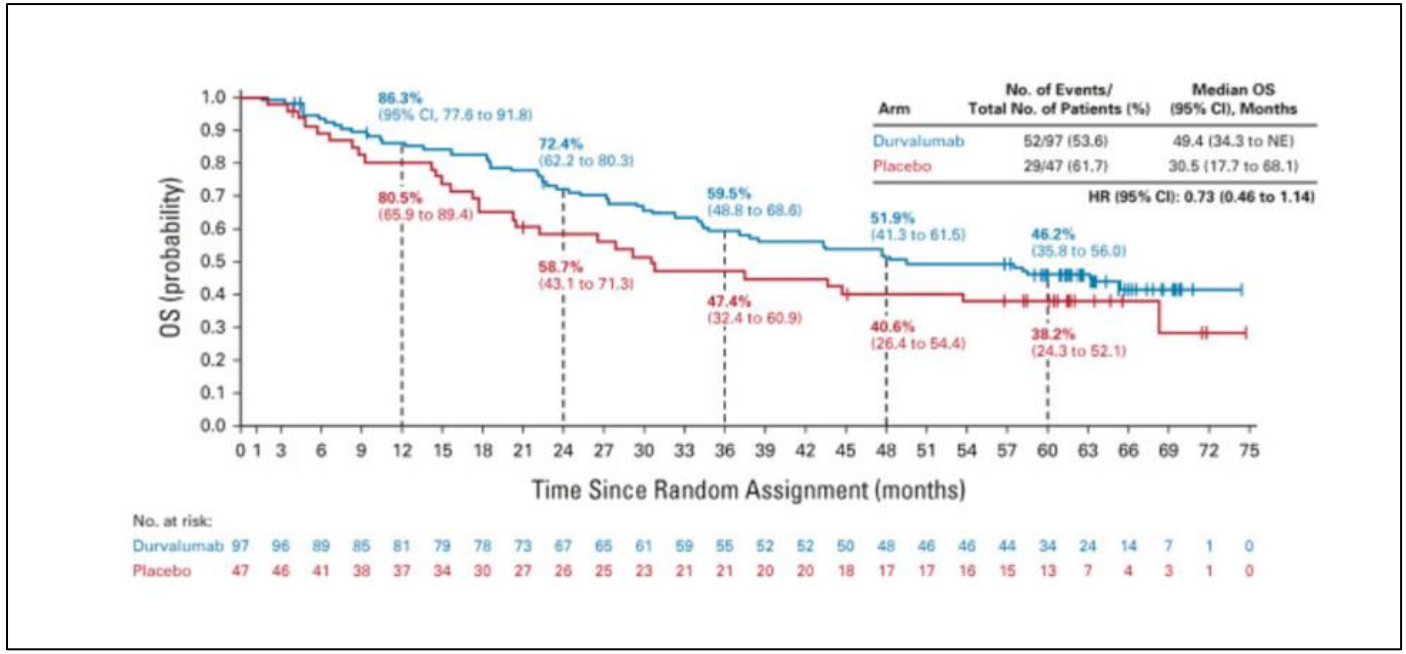


Figure 4. KM OS PD-L1 expression level 1 – 24% (29)

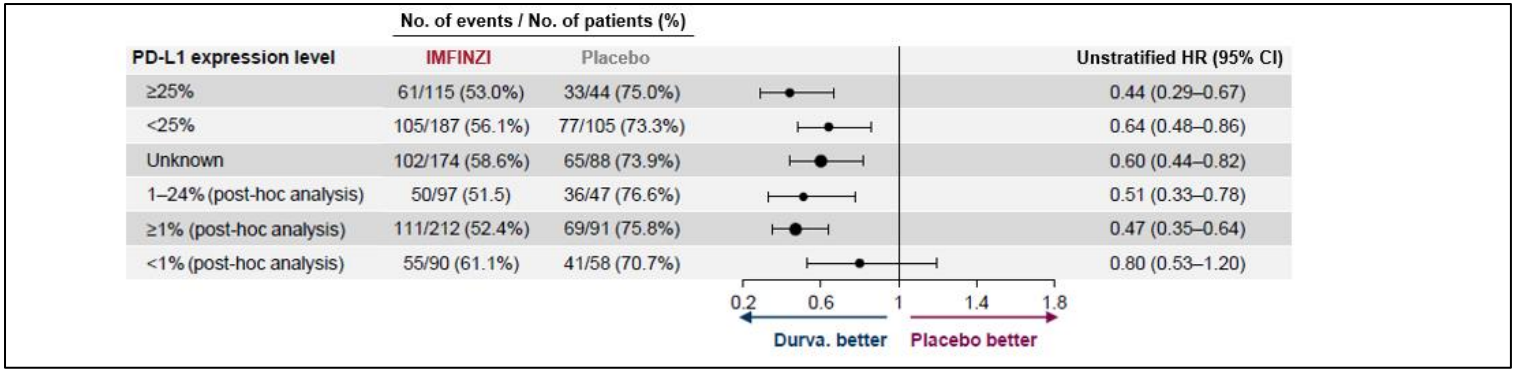


Figure 5. PFS result per PD-L1 expression level (29)

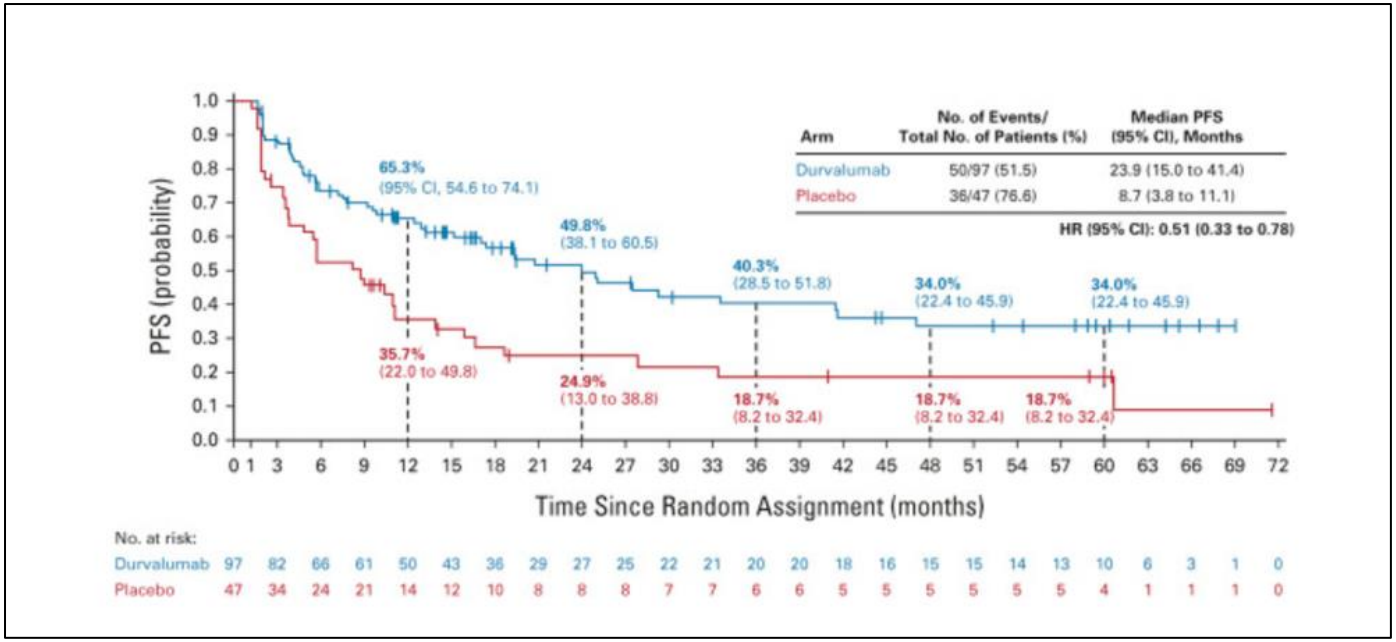
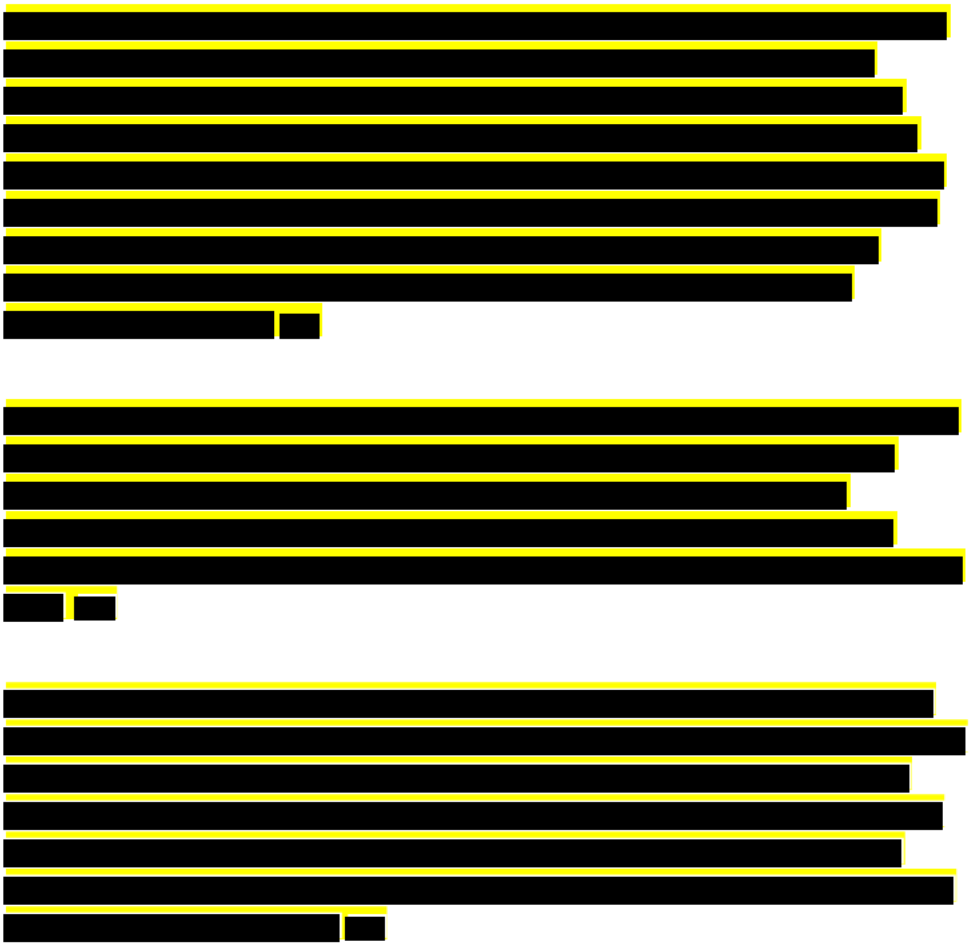


Figure 6. KM PFS PD-L1 expression level 1 – 24% (29)

Real-world evidence



Other RWE studies

Beside the recent Danish real-world evidence study, several real-world evidence (RWE) studies have been published regarding the use of durvalumab in unresectable stage III patients following CRT. Key findings and conclusions are summarized per study in the below section. In summary, they conclude that the efficacy of durvalumab reported in their results are comparable to the PACIFIC study results for patients with PD-L1 >1%.

- Wang et al. concluded from their systematic review and meta-analysis that there is consistency between the efficacy findings in PACIFIC and existing RWE. Thirteen articles were included, and the median PFS (progression-free survival) ranged between 20.1 and 22.5 months. (32)

- PACIFIC-R is an observational study with 1,399 patients treated with at least one dose of durvalumab as part of the early access program (EAP). Data from this study were presented at ESMO in 2021 and are under review. The study reported a median PFS of 21.7 months, which was compared to the 16.9 months PFS in PACIFIC after 5 years. A subgroup analysis showed that PFS was higher in the patient group with PD-L1 >1%. (33)

- Offin et al. analyzed 62 patients between 2017 and 2019 in their single-center study conducted at Memorial Sloan Kettering Cancer Center. Patients were treated according to the PACIFIC regimen. The conclusions were that 12-month OS (overall survival) was comparable to PACIFIC, and there was better loco-regional tumor control compared to historical data. PD-L1 expression levels of >1% versus >50% were not predictive of poor PFS. (34)

- Faehling et al. published data from their multicenter study across 56 German centers as part of the EAP for durvalumab. A total of 126 patients from 2017-2018 were included on the basis that they had not progressed following CRT. Patients in the EAP study had more advanced disease compared to PACIFIC, based on a more advanced stage and presence of oligometastases. PFS for patients in this study was 20.1 months, and the median OS was not reached after 24 months. PD-L1 expression was not predictive of OS. (35)

Subsequent therapy ITT

Overall, 48.5% and 58.6% of patients randomly assigned to durvalumab and placebo, respectively, received ≥ 1 subsequent, disease-related, anticancer therapy (after discontinuing study treatment), most commonly chemotherapy (durvalumab, 33.0%; placebo, 35.9%; Table2). Subsequent immunotherapy was less commonly used among patients randomly assigned to durvalumab (12.6%) versus placebo (29.1%). TFST (stratified HR, 0.65; 95% CI, 0.53 to 0.79) and TSST (stratified HR, 0.65; 95% CI, 0.53 to

0.80) were improved with durvalumab versus placebo and consistent with the previous analyses of these end points.(29) (29).

Table 11. Subsequent therapies (ITT) (29)

Type of therapy	Durvalumab (N=476)	Placebo (N=237)
Any therapy, No. and (%)	**231 (48.5)**	**139 (58.6)**
Radiotherapy	97 (20.4)	61 (25.7)
Immunotherapy	60 (12.6)	69 (29.1)
chemotherapy	157 (33.0)	85 (35.9)
Other systemic therapies	53 (11.1)	35 (14.8)
Other	2 (0.4)[c]	0

NA

7. Comparative analyses of efficacy

7.1.1 Differences in definitions of outcomes between studies

NA

7.1.2 Method of synthesis

NA

7.1.3 Results from the comparative analysis

Table 12. Results from the comparative analysis of durvalumab vs. placebo for ITT populations (26, 27)

ITT Outcome measure	Durvalumab (N=476)	Placebo (N=237)	Result
mOS (DCO Jan 11th, 2021)	47.5m	29.1m	HR=0.72 (0.59-0.89)

ITT Outcome measure	Durvalumab (N=476)	Placebo (N=237)	Result
mPFS (DCO Jan 11th, 2021)	16.9m	5.6m	HR=0.55 (0.45-0.68)
TTDM (DCO 22nd Mar 2018)	28.3m	16.2m	HR=0.53(0.41-0.68) p<.0001
ORR (DCO 22nd Mar 2018)	30% Median not reached (27.4-NR)	17.8% 18.4 months (6.7-24.5)	

Table 13. Results from the comparative analysis of durvalumab vs. placebo for PD-L1 1 – 24 % population (29)

PD-L1 1 – 24 % Outcome measure	Durvalumab (N=97)	Placebo (N=47)	Result
mOS (DCO Jan 11th, 2021)	49.4(34.3-NE)	30.5(17.7-68.1)	HR=0.73 (0.46-1.14)
mPFS (DCO Jan 11th, 2021)	23.9(15.0-41.4)	8.7(3.8-11.1)	HR=0.51 (0.33-0.78)
PD-L1 ≥1%	**Durvalumab (n=212)**	**Placebo (n=91)**	**Result***
Outcome measure			
OS (DCO Jan 11th, 2021), number of events	103(48.6%)	56(61.5%)	HR=0.61 (0.44-0.85)
PFS (DCO Jan 11th, 2021), number of events	111(52.4%)	69(75.8%)	HR=0.47 (0.35-0.64)

***Unstratified HR**

7.1.4 Efficacy – results per [outcome measure]

NA

8. Modelling of efficacy in the health economic analysis

This submission follows Medicinrådets 14-week process. Thus, this section is not filled in.

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

8.1.1 Extrapolation of efficacy data

NA

8.1.1.1 Extrapolation of [effect measure 1]

Table 14. Summary of assumptions associated with extrapolation of [effect measure]

Method/approach	Description/assumption
NA	

8.1.1.2 Extrapolation of [effect measure 2]

NA

8.1.2 Calculation of transition probabilities

Table 15. Transitions in the health economic model

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

8.2 Presentation of efficacy data from [additional documentation]

NA

8.3 Modelling effects of subsequent treatments

NA

8.4 Other assumptions regarding efficacy in the model

NA

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

NA

Table 16. Estimates in the model

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

Table 17. Overview of modelled average treatment length and time in model health state, undiscounted and not adjusted for half cycle correction (adjust the table according to the model)

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

9. Safety

9.1 Safety data from the clinical documentation

As part of the final PFS analysis (IA1), safety and tolerability were assessed in 475 and 234 patients treated with durvalumab and placebo, respectively. The pivotal safety analysis set included patients who received at least 1 infusion of durvalumab 10 mg/kg IV Q2W or at least 1 infusion of placebo. The median total treatment duration was 44.0 and

31.7 weeks with a median of 20.0 and 14.0 infusions in the durvalumab and placebo arm, respectively. (31)

Safety outcomes from PACIFIC were reported with the primary analyses and were not updated for the 5-year follow-up analysis presented in this submission as no patients remained on the 12-month study treatment beyond the time of the primary OS analysis (March 22, 2018 DCO). (26) At the time of the primary OS analysis, all-causality AEs of maximum toxicity grade 3/4 occurred in 32.0% and 27.8% (and fatal AEs in 4.4% and 6.0%) of patients receiving durvalumab and placebo, respectively; 15.4% and 9.8% discontinued durvalumab and placebo because of AEs, mostly pneumonitis, radiation pneumonitis, and pneumonia. (26, 31)

Patients were enrolled in the pivotal study regardless of their PD-L1 expression. However, the type, incidence, and severity of AEs were comparable across PD-L1 status in both treatment arms. Overall, there was no observable pattern that would suggest a different safety profile of durvalumab based on PD L1 status (approximately 39% had PD-L1 <25%, 24.2% had PD-L1 > 25 and 36 % had an unknown status). (31) Exploratory analyses from PACIFIC demonstrated broadly consistent results for safety outcomes irrespective of PD-L1 expression level and CRT-related variables, suggesting that durvalumab treatment is well managed regardless of these baseline factors. (27)

Data are shown for the ITT population (Table 18). Dose reduction is not included as dose escalation or reduction is not recommended according to EPAR. Dose withholding or discontinuation may be required based on individual safety and tolerability. (31)

The safety profile of durvalumab was as expected for PD-L1 inhibitors. Cough, fatigue, dyspnea, pneumonitis, diarrhea, and lung infections were observed. Most of the toxicity was clinically manageable and treatment-related deaths were rare. The discontinuation rate was 15.4% in the durvalumab arm, which is considered acceptable in this patient population. (31)

Overall, the safety profile of durvalumab seems acceptable and in line with other PD-L1 inhibitors. (31)

Table 18. Overview of safety events. Safety analysis set: March 22, 2018 DCO. (31)

	Durvalumab (N=475) (31)	Placebo (N=234) (31)	Difference, % (95 % CI)
Number and proportion of	460 (96.8)	222 (94.9)	2.0% (-1.3-5.2)

	Durvalumab (N=475) (31)	Placebo (N=234) (31)	Difference, % (95 % CI)
patients with ≥1 adverse events, n (%)			
Number and proportion of patients with ≥ 1 serious adverse events*, n (%)	136 (28.6)	53 (22.6)	6.0% (-0.7-12.7)
Number and proportion of patients with ≥ 1 CTCAE grade ≥ 3 events§, n (%)	152 (32.0)	65 (27.8)	4.2% (-2.9-11.3)
Number and proportion of patients with ≥ 1 Immune mediated AE, n (%)	166 (34.9)	39 (16.7)	18.3% (11.9-24.7)
Number and proportion of patients who had a dose delay due to AE, n (%)	202 (42.5)	72 (30.8)	11.8% (4.4-19.2)
Number and proportion of patients who discontinue treatment due to adverse events, n (%)	73 (15.4)	23 (9.8)	5.5% (0.5-10.5)
Number and proportion of patients with any AE with outcome of dead, n (%)	21 (4.4)	14 (6.0)	-1.6% (-5.1-2.0)

* A serious adverse event is an event or reaction that at any dose results in death, is life-threatening, requires hospitalisation or prolongation of existing hospitalisation, results in persistent or significant disability or incapacity, or results in a congenital anomaly or birth defect (see the ICH's complete definition).

§ CTCAE v. 5.0 must be used if available.

Table 19. Serious adverse events (Safety analysis set: March 22, 2018 DCO): Most common CTCAE Grade 3 or 4 AEs (frequency of >1%) (31)

Adverse events	Durvalumab (N=475)		Placebo (N=234)	
	Number of patients with adverse events	Number of adverse events	Number of patients with adverse events	Number of adverse events
Patients with any AE of CTCAE Grade 3 or 4, n (%)	125 (32.0)		65 (27.8)	
Pneumonia, n (%)	21 (4.4)		10 (4.3)	
Anemia, n (%)	14 (2.9)		8 (3.4)	
Hypertension, n (%)	10 (2.2)		2 (0.9)	
Pneumonitis, n (%)	8 (1.7)		5 (2.1)	
Dyspnea, n (%)	7 (1.5)		6 (2.6)	
Radiation pneumonitis, n (%)	7 (1.5)		1 (0.4)	
Aspartate aminotransferase increased, n (%)	6 (1.3)		0	
Lung infection, n (%)	6 (1.3)		2 (0.9)	

Adverse events	Durvalumab (N=475)	Placebo (N=234)
Hyperglycemia, n (%)	5 (1.1)	1 (0.4)
Hypokalemia, n (%)	5 (1.1)	5 (2.1)
Sepsis, n (%)	4 (0.8)	3 (1.3)
Diarrhea, n (%)	3 (0.6)	3 (1.3)
Fatigue, n (%)	1 (0.2)	3 (1.3)

* A serious adverse event is an event or reaction that at any dose results in death, is life-threatening, requires hospitalisation or prolongation of existing hospitalisation, results in persistent or significant disability or incapacity, or results in a congenital anomaly or birth defect (see the ICH's complete definition).

Table 20 Adverse events used in the health economic model

Adverse events	Intervention	Comparator
NA		

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

This submission follows Medicinrådets 14-week process. Thus, this part is not filled in.

Table 21. Adverse events that appear in more than X % of patients

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

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

This submission follows Medicinrådets 14-week process. Thus, parts of this section are not filled in.

EORTC QLQ-C30 was a secondary endpoint in PACIFIC assessing symptoms and health-related quality of life in patients treated with durvalumab compared with placebo.

PACIFIC evaluated patient-reported symptoms, functioning, and global health status or quality of life with two questionnaires that were developed by the European Organisation for Research and Treatment of Cancer (EORTC) Study Group on quality of life: the Quality of Life Questionnaire-Core 30 (QLQ-C30) version 3 and its lung cancer module, the Quality of Life.

Table 22. Overview of included HRQoL instruments

Measuring instrument	Source	Utilization
EORTC QLQ-C30	PACIFIC	Clinical effectiveness

10.1 Health-related quality of life (EORTC QLQ-C30)

10.1.1 Study design and measuring instrument

The EORTC-QLQ-C30 consists of 30 questions which can be combined to produce 5 functional scales (physical, role, cognitive, emotional, social), 3 symptom scales (fatigue, pain, nausea/vomiting), 5 individual symptom items (dyspnoea, insomnia, appetite loss, constipation, diarrhoea) and a global measure of health status. The EORTC-QLQ-C30 will be scored according to the EORTC scoring manual (36). An outcome variable consisting of a score from 0 to 100 will be derived for each of the symptom scales/items, the functional scales and the global health status scale in the EORTC-QLQ-C30 according to the EORTC-QLQ-C30 Scoring Manual. Higher scores on the global health status and functioning scales indicate better health status/function but higher scores on symptom scales/items represent greater symptom severity. Baseline will be defined as the last non-missing assessment prior to randomization for symptoms and summaries.

10.1.2 Data collection

PROs were assessed with paper-based questionnaires at the time of random allocation to groups, week 4, week 8, every 8 weeks until week 48, then every 12 weeks until

disease progression (30). The EORTC QLQ-C30 is a self-administered questionnaires and can be completed by the patient without the assistance of the investigational site personnel. When the patient completes the questionnaires, study coordinators review the questionnaires for missing responses and then ask the patient to date and sign at places specified in the questionnaire.

For each subscale, if <50% of the subscale items are missing, then the subscale score will be divided by the number of non-missing items and multiplied by the total number of items on the subscales. If at least 50% of the items are missing, then that subscale will be treated as missing. Missing single items are treated as missing. The reason for any missing questionnaire will be identified and recorded. If there is evidence that the missing data are systematic, missing values will be handled to ensure that any possible bias is minimized (26, 30).

Table 23. Pattern of missing data and completion

Time point	HRQoL population N	Missing N (%)	Expected to complete N	Completion N (%)
	Number of patients at randomization	Number of patients for whom data is missing (% of patients at randomization)	Number of patients "at risk" at time point X	Number of patients who completed (% of patients expected to complete)
Durvalumab				
Baseline	476	0 (0.0%)	476	474 (99.6%)
Week 4	476	5 (1.1%)	471	440 (93.4%)
Week 8	476	17 (3.6%)	459	399 (86.9%)
Week 16	476	61 (12.8%)	415	349 (84.1%)
Week 24	476	107 (22.5%)	369	315 (85.4%)
Week 32	476	133 (27.9%)	343	283 (82.5%)
Week 40	476	150 (31.5%)	326	258 (79.1%)
Week 48	476	172 (36.1%)	304	254 (83.6%)
Placebo				
Baseline	237	0 (0.0%)	237	232 (97.9%)

Time point	HRQoL population N	Missing N (%)	Expected to complete N	Completion N (%)
Week 4	237	5 (2.1%)	232	214 (92.2%)
Week 8	237	14 (5.9%)	223	199 (89.2%)
Week 16	237	48 (20.3%)	189	164 (86.8%)
Week 24	237	80 (33.8%)	157	132 (84.1%)
Week 32	237	102 (43.0%)	135	111 (82.2%)
Week 40	237	120 (50.6%)	117	101 (86.3%)
Week 48	237	135 (57.0%)	102	88 (86.3%)

10.1.3 HRQoL results

According to the final PFS analysis (IA1), compliance with completing the questionnaires was very high and similar between treatment groups (approximately 83% for durvalumab patients and 85% for placebo patients) up to week 48 (from week 60 compliance rate dropped to <65%).

Baseline QoL scores of PACIFIC patients were similar to the EORTC reference values for lung cancer and NSCLC populations. Additionally, no differences in QoL scores were observed between durvalumab and placebo treatment groups at baseline. In the global QoL and functioning scales, patients reported high baseline scores (>66 points and >76 points on a scale of 0-100, respectively), indicating a good health status given the disease burden. On the symptoms scale, low baseline scores (<35 points) were observed for the majority of symptoms with some symptoms scores reported as low as 8 points (nausea, diarrhea, hemoptysis and sore mouth) suggesting patients had a low burden of symptoms.

Treatment with durvalumab resulted in no meaningful difference in global health/physical functioning compared to placebo, ensuring that the realized PFS improvement for durvalumab is not outweighed by a negative impact on QoL (figure 9). In addition, improvements in appetite loss (EORTC QLQ-LC30) were observed in both groups over time, with statistically significant improvement rates in favor of durvalumab. These results demonstrate that treating patients with durvalumab, an active drug, does not have a detrimental effect on patient QoL, ensuring that realized PFS improvements for durvalumab are not outweighed by any negative impact on QoL.

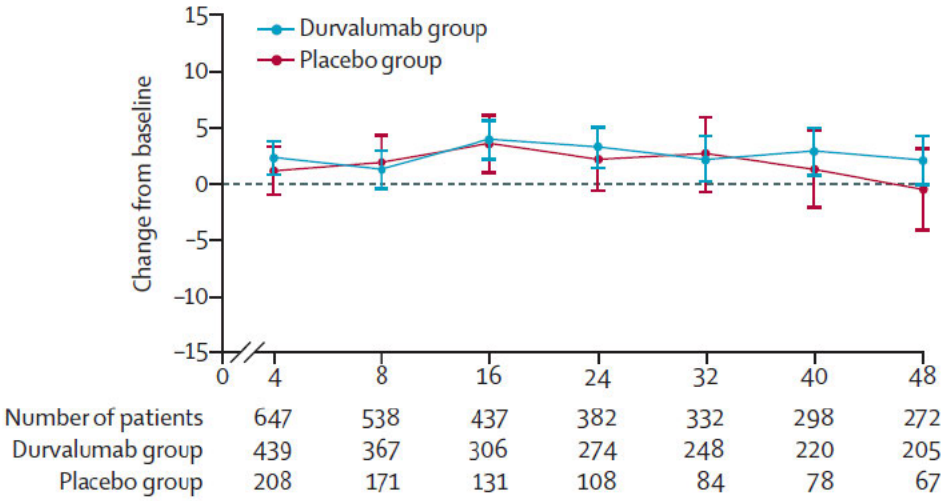


Figure 8. Changes in Global Health Status (EORTTC QLQ-C30) between baseline and week 48 (30)

Table 24. HRQoL [EORTC QLQ-C30] summary statistics (30)

	Durvalumab		Placebo		Durvalumab vs. placebo
	N	Mean (SE)	N	Mean (SE)	Difference (95% CI)
Baseline	439	66.8 (19.9)	208	68.0 (17.4)	-1.2 (-4.4; 2.0); p = 0.46
Week 48	205	70.2 (19.9)	67	68.5 (18.0)	1.7 (-3.8; 7.2); p = 0.54

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

10.2.1 HSUV calculation

NA

10.2.1.1 Mapping

NA

10.2.2 Disutility calculation

NA

10.2.3 HSUV results

Table 25. Overview of health state utility values [and disutilities]

	Results [95% CI]	Instrument	Tariff (value set) used	Comments
NA				

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

10.3.1 Study design

NA

10.3.2 Data collection

NA

10.3.3 HRQoL Results

NA

10.3.4 HSUV and disutility results

NA

Table 26. Overview of health state utility values [and disutilities]

	Results [95% CI]	Instrument	Tariff (value set) used	Comments
NA				

Table 27. Overview of literature-based health state utility values

	Results [95% CI]	Instrument	Tariff (value set) used	Comments
NA				

11. Resource use and associated costs

This submission follows Medicinrådets 14-week process. Thus, this section is not filled in.

11.1 Medicines - intervention and comparator

Table 28. Medicines used in the model.

Medicine	Dose	Relative dose intensity	Frequency	Vial sharing
NA				

11.2 Medicines– co-administration

NA

11.3 Administration costs

Table 29. Administration costs used in the model

Administration type	Frequency	Unit cost [DKK]	DRG code	Reference
NA				

11.4 Disease management costs

Table 30. Disease management costs used in the model.

Activity	Frequency	Unit cost [DKK]	DRG code	Reference
NA				

11.5 Costs associated with management of adverse events

Table 31. Cost associated with management of adverse events.

	DRG code	Unit cost/DRG tariff
NA		

11.6 Subsequent treatment costs

Table 32. Medicines of subsequent treatments.

Medicine	Dose	Relative dose intensity	Frequency	Vial sharing
NA				
NA				

11.7 Patient costs

Table 33. Patient costs used in the model.

Activity	Time spent [minutes, hours, days]
NA	

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

NA

12. Results

This submission follows Medicinrådets 14-week process. Thus, this section is not filled in.

12.1 Base case overview

Table 34. Base case overview

Feature	Description
NA	

12.1.1 Base case results

Table 35. Base case results, discounted estimates

	[Intervention]	[Comparator]	Difference
NA			

12.2 Sensitivity analyses

12.2.1 Deterministic sensitivity analyses

Table 36. One-way sensitivity analyses results

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

12.2.2 Probabilistic sensitivity analyses

NA

13. Budget impact analysis

This submission follows Medicinrådets 14-week process. Thus, this section is not filled in.

Number of patients (including assumptions of market share)

Table 37. Number of new patients expected to be treated over the next five-year period if the medicine is introduced (adjusted for market share)

	Year 1	Year 2	Year 3	Year 4	Year 5
NA					

Budget impact

Table 38. Expected budget impact of recommending the medicine for the indication

	Year 1	Year 2	Year 3	Year 4	Year 5
NA					

14. List of experts

NA

15. References

1. TLV. Underlag för beslut i landstingen. Imfinzi (durvalumab). TLV; 2018 [Available from: https://www.tlv.se/download/18.13634819166e2df86244c71e/1541598097880/bes_underlag181106_imfinzi.pdf.

2. NOMA. Hurtig metodevurdering for legemidler finansiert i spesialisthelsetjeneste: Durvalumab (Imfinzi) til behandling av ikke-småcellet lungekreft: Nyemetoder; 2019 [Available from: https://www.nyemetoder.no/4a88f3/siteassets/documents/rapporter/durvalumab-imfinzi_id2018_022----hurtig-metodevurdering.pdf.

3. NICE. Technology appraisal guidance: Durvalumab for maintenance treatment of unresectable non-small-cell lung cancer after platinum-based chemoradiation: NICE; 2022 [Available from: https://www.nice.org.uk/guidance/ta798/chapter/1-Recommendations.

4. Douillard JY, Rosell R, De Lena M, Carpagnano F, Ramlau R, Gonzáles-Larriba JL, et al. Adjuvant vinorelbine plus cisplatin versus observation in patients with completely resected stage IB-IIIA non-small-cell lung cancer (Adjuvant Navelbine International Trialist Association [ANITA]): a randomised controlled trial. The Lancet Oncology. 2006;7(9):719-27.

5. Arriagada R, Bergman B, Dunant A, Le Chevalier T, Pignon JP, Vansteenkiste J. Cisplatin-based adjuvant chemotherapy in patients with completely resected non-small-cell lung cancer. The New England journal of medicine. 2004;350(4):351-60.

6. Pignon JP, Tribodet H, Scagliotti GV, Douillard JY, Shepherd FA, Stephens RJ, et al. Lung adjuvant cisplatin evaluation: a pooled analysis by the LACE Collaborative Group. Journal of clinical oncology : official journal of the American Society of Clinical Oncology. 2008;26(21):3552-9.

7. Zhang Y-L, Yuan J-Q, Wang K-F, Fu X-H, Han X-R, Threapleton D, et al. The prevalence of EGFR mutation in patients with non-small cell lung cancer: a systematic review and meta-analysis. Oncotarget. 2016;7(48):78985-93.

8. Suidan AM, Roisman L, Belilovski Rozenblum A, Ilouze M, Dudnik E, Zer A, et al. Lung Cancer in Young Patients: Higher Rate of Driver Mutations and Brain Involvement, but Better Survival. Journal of Global Oncology. 2019;5:1-8.

9. Rasmussen TR, Jakobsen E, Rasmussen C. Dansk Lunge Cancer Register Indikatorrapport til National årsrapport 2018. Dansk Lunge Cancer Gruppe (DLCG) og Dansk Lunge Cancer Register (DLCR); 2019 7/11 2019.

10. Postmus PE, Kerr KM, Oudkerk M, Senan S, Waller DA, Vansteenkiste J, et al. Early and locally advanced non-small-cell lung cancer (NSCLC): ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up†. Annals of Oncology. 2017;28:iv1-iv21.

11. Yilmaz A, Damadoglu E, Salturk C, Okur E, Tuncer LY, Halezeroglu S. Delays in the diagnosis and treatment of primary lung cancer: are longer delays associated with advanced pathological stage? Upsala Journal of Medical Sciences. 2008;113(3):287-96.

12. Sundhedsdatastyrelsen. Nye kræfttilfælde i Danmark 2023. Sundhedsdatastyrelsen; 2024.

13. Birring SS, Peake MD. Symptoms and the early diagnosis of lung cancer. Thorax. 2005;60(4):268-9.

14. Cagle PT, Allen TC, Olsen RJ. Lung cancer biomarkers: present status and future developments. Archives of Pathology & Laboratory Medicine. 2013;137(9):1191-8.

15. Datta D, Lahiri B. Preoperative Evaluation of Patients Undergoing Lung Resection Surgerya. Chest. 2003;123(6):2096-103.

16. Le Chevalier T. Adjuvant chemotherapy for resectable non-small-cell lung cancer: where is it going? Annals of Oncology. 2010;21:vii196-vii8.

17. Allemani C, Weir HK, Carreira H, Harewood R, Spika D, Wang X-S, et al. Global surveillance of cancer survival 1995-2009: analysis of individual data for 25,676,887 patients from 279 population-based registries in 67 countries (CONCORD-2). Lancet (London, England). 2015;385(9972):977-1010.

18. Rosen JE, Keshava HB, Yao X, Kim AW, Detterbeck FC, Boffa DJ. The Natural History of Operable Non-Small Cell Lung Cancer in the National Cancer Database. The Annals of Thoracic Surgery. 2016;101(5):1850-5.

19. Chouaid C, Danson S, Andreas S, Siakpere O, Benjamin L, Ehness R, et al. Adjuvant treatment patterns and outcomes in patients with stage IB-IIIA non-small cell lung cancer in France, Germany, and the United Kingdom based on the LuCaBIS burden of illness study. Lung Cancer. 2018;124:310-6.

20. Eichler AF, Kahle KT, Wang DL, Joshi VA, Willers H, Engelman JA, et al. EGFR mutation status and survival after diagnosis of brain metastasis in nonsmall cell lung cancer. Neuro-Oncology. 2010;12(11):1193-9.

21. McTyre E, Scott J, Chinnaiyan P. Whole brain radiotherapy for brain metastasis. Surg Neurol Int. 2013;4(Suppl 4):S236-S44.

22. Pøhl M. Real world treatment of Locally advanced NSCLC with patient characteristic, treatment patterns, and overall survival among patients treated in the capital Region of Denmark 2016-2023. 2025.

23. Danske Multidisciplinære Cancer Grupper. Kurativ behandling af lokal avanceret ikke-småcellet lungekræft - DMCG [Available from: https://www.dmcg.dk/Kliniske-retningslinjer/kliniske-retningslinjer-opdelt-paa-dmcg/lungecancer/kurativ-behandling-af-lokal-avanceret-ikke-smacellet-lungekraft/.

24. Medicinrådet. Medicinrådets anbefaling vedrørende durvalumab som mulig standardbehandling til ikke-småcellet lungekræft stadie III. Medicinrådet, Dampfærgevej 27-29, 3. th., 2100 København Ø; 2019 19. june 2019.

25. Medicinrådet. Baggrund for Medicinrådets anbefaling vedrørende durvalumab som mulig standardbehandling til ikke-småcellet lungekræft stadie III. Medicinrådet, Dampfærgevej 27-29, 3. th., 2100 København Ø; 2019 19. june 2019.

26. Antonia SJ, Villegas A, Daniel D, Vicente D, Murakami S, Hui R, et al. Durvalumab after Chemoradiotherapy in Stage III Non-Small-Cell Lung Cancer. The New England journal of medicine. 2017;377(20):1919-29.

27. Antonia SJ, Villegas A, Daniel D, Vicente D, Murakami S, Hui R, et al. Overall Survival with Durvalumab after Chemoradiotherapy in Stage III NSCLC. The New England journal of medicine. 2018;379(24):2342-50.

28. Paz-Ares L, Spira A, Raben D, Planchard D, Cho BC, Özgüroğlu M, et al. Outcomes with durvalumab by tumour PD-L1 expression in unresectable, stage III non-small-cell lung cancer in the PACIFIC trial. Annals of Oncology: Official Journal of the European Society for Medical Oncology. 2020;31(6):798-806.

29. Spigel DR, Faivre-Finn C, Gray JE, Vicente D, Planchard D, Paz-Ares L, et al. Five-Year Survival Outcomes From the PACIFIC Trial: Durvalumab After Chemoradiotherapy in Stage III Non-Small-Cell Lung Cancer. Journal of Clinical Oncology: Official Journal of the American Society of Clinical Oncology. 2022;40(12):1301-11.

30. Hui R, Özgüroğlu M, Villegas A, Daniel D, Vicente D, Murakami S, et al. Patient-reported outcomes with durvalumab after chemoradiotherapy in stage III, unresectable non-small-cell lung cancer (PACIFIC): a randomised, controlled, phase 3 study. The Lancet Oncology. 2019;20(12):1670-80.

31. European Medicines Agency. Assessment report Imfinzi. International non-proprietary name: durvalumab Procedure No. EMEA/H/C/004771/0000. Committee for Medicinal Products for Human Use (CHMP); 2018 26 July 2018.

32. Wang Y ZT, Huang Y, Li W, Zhao J, Yang Y, Li C, Wang L, Bi N. Real-World Safety and Efficacy of Consolidation Durvalumab After Chemoradiation Therapy for Stage III Non-small Cell Lung Cancer: A Systematic Review and Meta-analysis. Int J Radiat Oncol Biol Phys 2022;112(5):1154-64.

33. N. Girard HJMS, A. Sibille, F. McDonald, F. Mornex, M.C.C. Garassino, A.R. Filippi, S. Peters, J.K. Field, D.C. Christoph, R. Fietkau, V.D. Haakensen, J. Bar, C. Chouaid, V. Bray, S. Kao, W. Sawyer, A. Allen, M. Licour, P. Garrido. 1171MO PACIFIC-R real-world study: Treatment duration and interim analysis of progression-free survival in unresectable stage III NSCLC patients treated with durvalumab after chemoradiotherapy. Annals of Oncology. 2021;32:s939-s40.

34. Michael Offin NS, Andreas Rimner, Stephanie Lobaugh, Annemarie F. Shepherd, Charles B. Simone, Daphna Y. Gelblum, Abraham J. Wu, Nancy Lee, Mark G. Kris, Charles M. Rudin, Zhigang Zhang, Matthew D. Hellmann, Jamie E. Chaft, Daniel R. Gomez Clinical outcomes, local–regional control and the role for metastasis-directed therapies in stage III non-small cell lung cancers treated with chemoradiation and durvalumab. Radiotherapy and Oncology. 2020;149:205-11.

35. Martin Faehling CS, Petros Christopoulos, Petra Hoffknecht, Jürgen Alt, Marlitt Horn, Stephan Eisenmann, Anke Schlenska-Lange, Philipp Schütt, Felix Steger, Wolfgang M. Brückl, Daniel C. Christoph. Durvalumab after definitive chemoradiotherapy in locally advanced unresectable non-small cell lung cancer (NSCLC): Real-world data on survival

and safety from the German expanded-access program (EAP). Lung Cancer. 2020;150:114-22.

36. Peter Fayers NKA, Kristin Bjordal, Desmond Curran, Mogens Gronvold. EORTC QLQ–C30 Scoring Manual. 2nd ed: European Organization for Research and Treatment of Cancer; 1999.

37. Antonia SJ, Balmanoukian A, Brahmer J, Ou S-HI, Hellmann MD, Kim S-W, et al. Clinical Activity, Tolerability, and Long-Term Follow-Up of Durvalumab in Patients With Advanced NSCLC. Journal of Thoracic Oncology: Official Publication of the International Association for the Study of Lung Cancer. 2019;14(10):1794-806.

Appendix A. Main characteristics of studies included

Table 39. Main characteristic of studies included

Trial name: PACIFIC study	NCT number: NCT02125461
Objective	To determine the efficacy and tolerability of Durvalumab as consolidation therapy with placebo in patients with stage III, locally advanced, unresectable NSCLC that had not progressed after platinum-based chemoradiotherapy.
Publications – title, author, journal, year	Durvalumab after Chemoradiotherapy in Stage III Non–Small-Cell Lung Cancer. Antonia S.J., Villegas, A., et al., NEJM, September 8, 2017. (DOI: 10.1056/NEJMoa1709937) (26) Overall Survival with Durvalumab after Chemoradiotherapy in Stage III NSCLC. Antonia S.J., Vilegas, D. et al., NEJM, September 25, 2018 (DOI: 10.1056/NEJMoa1809697) (27) Outcomes with durvalumab by tumour PD-L1 expression in unresectable, stage III non-small-cell lung cancer in the PACIFIC trial. L. Paz-Ares, A. Spira, et al., Annals of Oncology, June 2020 (DOI: 10.1016/j.annonc.2020.03.287) (28) Five-Year Survival Outcomes from the PACIFIC Trial: Durvalumab After Chemoradiotherapy in Stage III Non-Small-Cell Lung Cancer. Spigel DR, Faivre-Finn C, et al., J Clin Oncol. 2022 Apr (DOI: 0.1200/JCO.21.01308.) (29) Patient-reported outcomes with durvalumab after chemoradiotherapy in stage III, unresectable non-small-cell lung cancer (PACIFIC): a randomised, controlled, phase 3 study. (30)
Study type and design	The PACIFIC study is an international, multicenter, phase III, randomized, double-blind, placebo-controlled study to evaluate the safety, tolerability, PK, immunogenicity, and patient-reported outcomes (PROs) of durvalumab following at least two cycles of platinum-based concurrent CRT in patients with locally advanced, unresectable, stage III NSCLC. A total of 983 patients with stage III, locally advanced, unresectable, stage III NSCLC (according to Version 7 of the IASLC Staging Manual in Thoracic Oncology) were enrolled, and 713 patients, of which 377 were stage IIIa and 319 were stage IIIb, were randomized at 235 sites globally (IASLD 2010). Patients were in either complete response (CR) or partial response (PR) or had stable disease (StD) following treatment with platinum-based, concurrent CRT. The study is not restricted to any biomarker-defined patient sub-population, however the roles of potential biomarkers in NSCLC (including PD-L1 expression) are being evaluated as exploratory endpoints during this study. Patients were randomized in a 2:1 ratio (durvalumab to placebo) to one of two arms:

Trial name: PACIFIC study	NCT number: NCT02125461
	• durvalumab (10 mg/kg Q2W via IV infusion for up to 12 months) • placebo (matching placebo for infusion Q2W IV for up to 12 months). Randomization was stratified by age at randomization (<65 vs ≥65 years of age), sex (male vs female), and smoking history (smoker vs non-smoker). The Quadruple masking method was used.
Sample size (n)	The total number of patients randomized were 713, 476 in the durvalumab arms and 237 in the placebo arm
Main inclusion criteria	• Age at least 18 years. • Documented evidence of NSCLC (locally advanced, unresectable, Stage III) • Patients must have received at least 2 cycles of platinum-based chemotherapy concurrent with radiation therapy. • World Health Organisation (WHO) Performance Status of 0 to 1. • Estimated life expectancy of more than 12 weeks.
Main exclusion criteria	• Prior exposure to any anti-PD-1 or anti-PD-L1 antibody. • Active or prior autoimmune disease or history of immunodeficiency. • Evidence of severe or uncontrolled systemic diseases, including active bleeding diatheses or active infections including hepatitis B, C and HIV. • Evidence of uncontrolled illness such as symptomatic congestive heart failure, uncontrolled hypertension or unstable angina pectoris. • Any unresolved toxicity CTCAE >Grade 2 from the prior chemoradiation therapy. • Active or prior documented inflammatory bowel disease (eg, Crohn's disease, ulcerative colitis).
Intervention	The recommended dose of IMFINZI is 10 mg/kg administered as an intravenous infusion over 60 minutes every 2 weeks, until disease progression or unacceptable toxicity, or a maximum of 12 months.
Comparator(s)	Patients in the placebo group were to receive matching placebo for intravenous infusion Q2W for up to 12 months.
Follow-up time	5-year follow up:

Trial name: PACIFIC study	NCT number: NCT02125461
	As of January 11, 2021 median follow-up was 34.2 months [all patients] and 61.6 months [censored patients].
Is the study used in the health economic model?	This application follows the fast-track process track meaning that health economics is not a part of the submission.
Primary, secondary and exploratory endpoints	The coprimary endpoints were progression-free survival (according to the Response Evaluation Criteria in Solid Tumors [RECIST], version 1.1, as assessed by means of blinded independent central review) and overall survival. Progression-free survival was defined as the time from randomization (which occurred up to 6 weeks after chemoradiotherapy) to the date of the first documented event of tumor progression or death in the absence of disease progression. Overall survival was defined as the time from randomization until death from any cause. Progression-free survival was assessed by the investigators, according to RECIST, version 1.1, as a predefined sensitivity analysis. The secondary endpoints were the percentage of patients who were alive without disease progression at 12 and 18 months, the objective response rate, the duration of response, and the time to death or distant metastasis (all assessed by means of blinded independent central review); and overall survival at 24 months, the safety and side-effect profile (graded with the use of the CTCAE, version 4.03), health-related quality of life, pharmacokinetic characteristics, and immunogenicity. Efficacy was assessed every 8 weeks for the first 12 months and every 12 weeks thereafter.
Method of analysis	For time-to-event end points, analyses comparing durvalumab with placebo (ITT population) were performed using log-rank tests stratified using the same factors used to stratify patients at random assignment; this was for consistency with the original analyses. (31). Unstratified Cox regression models (with no adjustment for multiple comparisons) were used for subgroup analyses. Medians and landmark rates (eg, 5-year OS) were estimated by Kaplan-Meier method. The prognostic association of baseline factors (other than assigned study treatment) with OS and PFS was analyzed using univariate and multivariable Cox regression models. Analyses of the efficacy end points included all the patients who underwent randomization, according to the intention-to-treat principle. For time-to-event end points, such as progression-free survival and overall survival, the effect of durvalumab as compared with placebo was estimated by the hazard ratio (together with its corresponding confidence interval of 100 [1 – α] %, with adjustment for the interim analysis, or with a 95% confidence interval and P value) in the intention-to- treat population. Between-group comparisons were performed by a stratified log-rank test; the stratification factors were those that had been used for randomization (age, sex, and smoking history). The Kaplan–Meier method was used to calculate medians and their associated 95% confidence intervals. Sensitivity analyses for

Trial name: PACIFIC study	NCT number: NCT02125461
	overall survival included the assessment of attrition bias. For all the planned analyses of overall survival in prespecified subgroups, an unstratified Cox regression model was used to calculate hazard ratios and 95% confidence intervals. No adjustment for multiple comparisons was planned for these subgroup analyses. Response rates were estimated with the use of the Clopper Pearson method and compared with the use of Fisher's exact test. The type I error was controlled for the primary end points, the overall survival rate at 24 months, and the objective response rate, as described previously, 18 but not for other secondary end points; therefore, P values are not reported.
Subgroup analyses	As part of the registration process, a post-hoc analysis was requested to assess the efficacy of durvalumab treatment (OS and PFS) in the PD-L1 <1% patients. Therefore, analysis of the PFS and OS was conducted in patients with PD-L1 <1% and PD-L1 ≥1%. and tumor samples were required to be re-stratified to enable analysis of the PDL1 ≥1% and <1% subgroups. The PACIFIC study enrolled patients regardless of their PD-L1 expression and therefore, tumor tissue collection was not mandatory. While approximately 37% of those included in the trials had 'unknown' PD-L1 status, it is likely that this will be significantly lower in the real world setting when PD-L1 testing is conducted more frequently, and potentially repeated when tests are inconclusive, increasing the pool of patients eligible for durvalumab. Expression of tumor cell PD-L1 in archival tissue samples obtained prior to chemoradiation was assessed retrospectively using the VENTANA PD-L1 (SP263) IHC assay. Of the 713 patients randomized in the PACIFIC study, information on PD-L1 expression was available for 451 patients (63%; durvalumab: 302; placebo: 149). A total of 262 patients (37%; durvalumab: 174; placebo: 88) had an unknown PD-L1 expression status. Based on data from Study 1108 (37) [8] that became available during the course of the PACIFIC study, a PD-L1 TC expression ≥25% (ie, 25% or more TCs expressing PD-L1 at any intensity) cut-off was established as optimal in the durvalumab NSCLC program. Therefore, the statistical analysis plan (SAP) for PACIFIC planned a subgroup analysis of durvalumab efficacy (PFS and OS) using the PD-L1 TC 25% cut-off. As part of the ongoing durvalumab registration application with global Health Authorities, AstraZeneca was requested to assess the efficacy of durvalumab treatment (PFS and OS) in the PD-L1 negative/<1% patients. Therefore, an additional, post hoc exploratory analysis of PFS and OS at the PD-L1 TC 1% cut-off was conducted. The SP263 stained tumor samples were re-scored after completing validation of the PD-L1 TC 1% cut off and were evaluated by pathologists trained and certified specifically at this cut off. The rescoring at the PD-L1 TC 1% cut-off showed that of the 713 patients randomized, only 148 had PD-L1 TC expression <1% (durvalumab: 90; placebo: 58), and 303 had PD-L1 TC expression ≥1% (durvalumab: 212; placebo: 91). As previously noted, the PD-L1 expression was unknown for 262 patients (durvalumab: 174; placebo: 88)

Trial name: PACIFIC study	NCT number: NCT02125461
	The PD-L1 subgroup analyses reported here were based on the following data cut-off (DCO) dates: 13 February 2017 (DCO for the primary analysis of PFS) for PFS and related secondary efficacy end points (ORR, DoR, ongoing response, and TTDM); 22 March 2018 for OS and safety (DCO for the primary analysis of OS and an updated analysis of safety for patients completing the initial 12 months of treatment); and 31 January 2019 for updated OS. Pre-specified analyses of PFS and ORR were carried out for the PD-L1 TC 25% and <25% patient subgroups (and for patients with unknown PD-L1 status); exploratory, post hoc analyses of OS, DoR, and TTDM were also carried out for these subgroups. Additional analyses were carried out for the exploratory, post hoc TC 1% and <1% subgroups (PFS, OS, ORR, DoR, and TTDM) and a TC 1% - 24% subgroup (PFS and OS only). Adverse event (AE) data was summarised for all subgroups. For time-to-event end points, the treatment effect of durvalumab versus placebo within each subgroup was estimated by an HR (and corresponding 95% CI) using unstratified Cox proportional hazards; no adjustment for multiple comparisons was planned. The Kaplan Meier method was used to estimate medians and associated 95% CIs. Response rate CIs were estimated using the ClopperPearson method. AEs and post-discontinuation, diseaserelated, anticancer therapy was descriptively summarised. SAS® version 9.2 was used for all aforementioned analyses. An exploratory, multiple-imputation model was used to impute missing data (using SAS® version 9.4) and estimate the OS treatment effect (HR and 95% CI) for the TC 1% and <1% subgroups, based on the DCO for the primary analysis. Limitations include the unplanned nature of this analysis and the small sample size of the TC <1% subgroup. The number of OS events (n ¼ 60) in the TC <1% subgroup was inadequate to sufficiently power this analysis, which, based on the trial's pre-specified statistical analysis plan, would have required a high benefit target (HR ¼ 0.43) to demonstrate meaningful results.
Other relevant information	

Appendix B. Efficacy results per study

Results per study

Table 40. Results per study

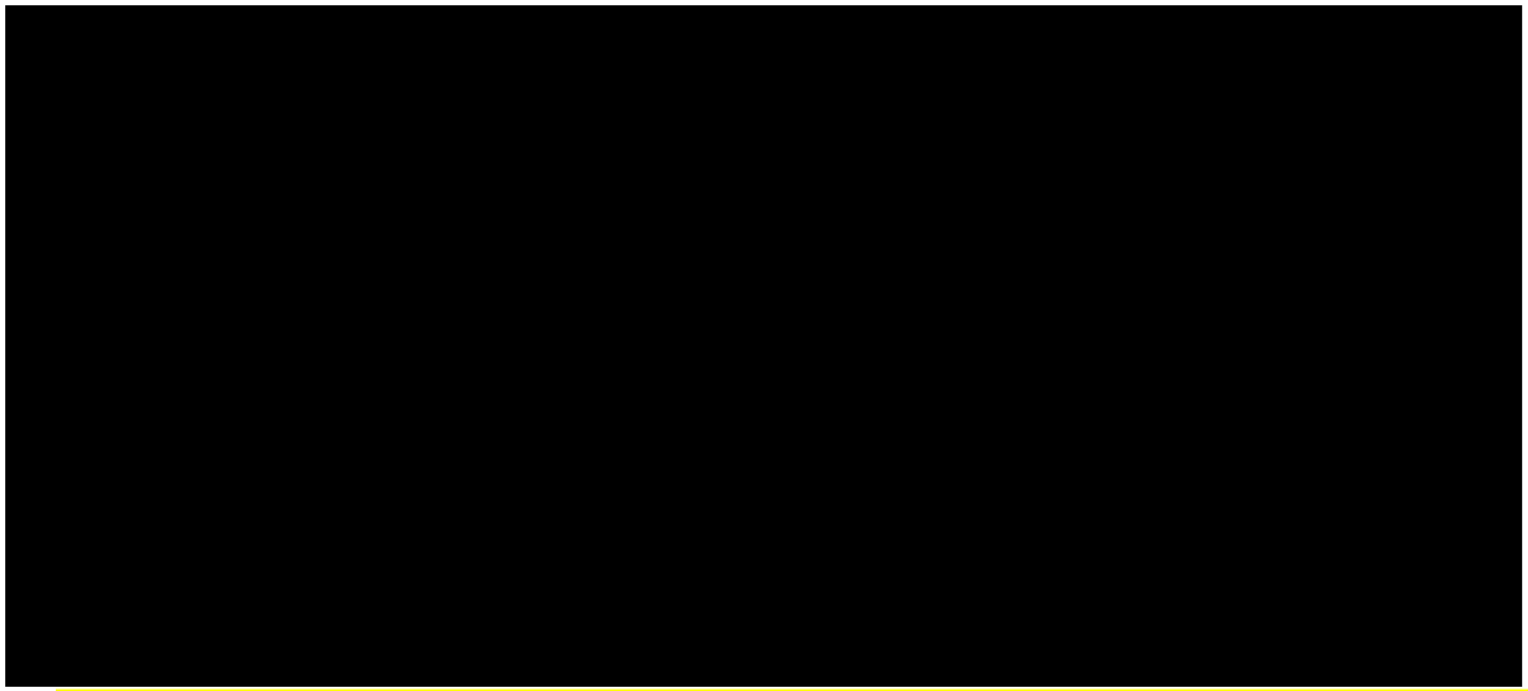
Results of PACIFIC											
				Estimated absolute difference in effect			Estimated relative difference in effect			Description of methods used for estimation	References
Outcome	Study arm	N	Result (CI)	Difference	95% CI	*P* value	Difference	95% CI	*P* value		
5-year survival, Median OS, ITT	Durvalumab	476	47.5 (38.1-52.9)	NA	NA	NA	HR: 0.72	0.59–0.89	NA	DCO January 11, 2021, Between-group comparisons were performed by a stratified log-rank test; the stratification factors were those that had been used for randomization (age, sex, and smoking history). The Kaplan–Meier method was used to calculate medians and the associated 95% confidence intervals. Sensitivity analyses for overall survival included the assessment of attrition bias.	Spigel et al, 2022
	Placebo	237	29.1 (22.1-35.1)								

Results of PACIFIC											
				Estimated absolute difference in effect			Estimated relative difference in effect			Description of methods used for estimation	References
Outcome	Study arm	N	Result (CI)	Difference	95% CI	*P* value	Difference	95% CI	*P* value		
5-year survival, Median OS, PD-L1 TC ≥1%	Durvalumab	212	63.1 (43.7-NE)	NA	NA	NA	HR: 0.61	0.44–0.85	NA	DCO January 11, 2021, Between-group comparisons were performed by a stratified log-rank test; the stratification factors were those that had been used for randomization (age, sex, and smoking history). The Kaplan–Meier method was used to calculate medians and the associated 95% confidence intervals. Sensitivity analyses for overall survival included the assessment of attrition bias.	Spigel et al, 2022
	Placebo	91	29.6 (17.7-44.7)								
5-year survival, Median OS,	Durvalumab	97	49.4 (34.3-NE)	NA	NA	NA	HR: 0.73	0.46–1.14	NA	DCO January 11, 2021, Between-group comparisons were performed by a stratified log-rank test; the stratification factors were	Spigel et al, 2022
	Placebo	47	30.5 (17.7-68.1)								

Results of PACIFIC											
				Estimated absolute difference in effect			Estimated relative difference in effect			Description of methods used for estimation	References
Outcome	Study arm	N	Result (CI)	Difference	95% CI	*P* value	Difference	95% CI	*P* value		
PD-L1 TC 1-24%										those that had been used for randomization (age, sex, and smoking history). The Kaplan–Meier method was used to calculate medians and the associated 95% confidence intervals. Sensitivity analyses for overall survival included the assessment of attrition bias.	
Median PFS, ITT	Durvalumab	476	16.9 (13.0-23.9)	NA	NA	NA	0.55	0.45-0.68	NA	Assessed until January 11 2021 DCO; up to a maximum of approximately 3 years. PFS was calculated using the Kaplan-Meier technique.	Spigel et al, 2022
	Placebo	237	5.6 (4.8-7.7)								
Median PFS, PD-L1 TC ≥1%	Durvalumab	212	24.9 (16.9-38.7)	NA	NA	NA	0.47	0.35-0.64	NA	Assessed until January 11 2021 DCO; up to a maximum of approximately 3 years.	Spigel et al, 2022

Results of PACIFIC											
				Estimated absolute difference in effect			Estimated relative difference in effect			Description of methods used for estimation	References
Outcome	Study arm	N	Result (CI)	Difference	95% CI	*P* value	Difference	95% CI	*P* value		
										PFS was calculated using the Kaplan-Meier technique.	
	Placebo	91	5.5 (3.6-10.3)								
Median PFS, PD-L1 TC 1-24%	Durvalumab	97	23.9 (15.0-41.4)	NA	NA	NA	0.51	0.33-0.78	NA	Assessed until January 11 2021 DCO; up to a maximum of approximately 3 years. PFS was calculated using the Kaplan-Meier technique.	Spigel et al, 2022
	Placebo	47	8.7 (3.8-11.1)								

[redacted]



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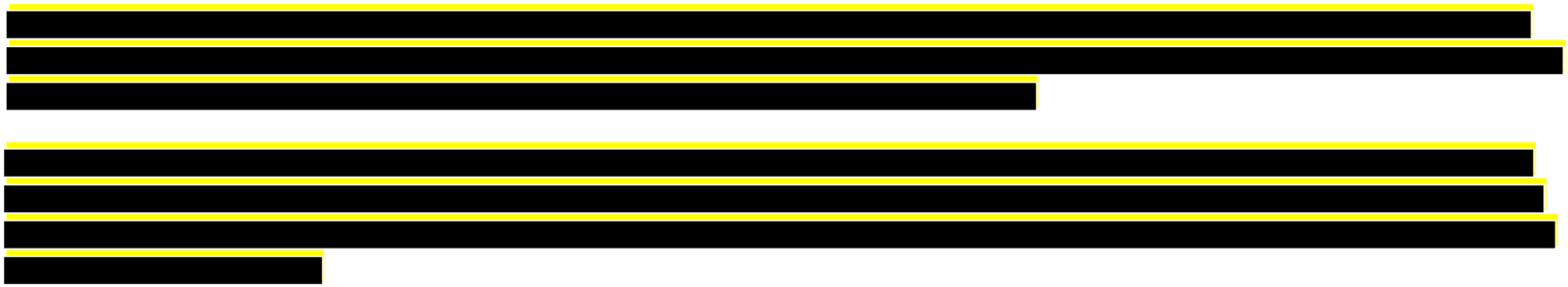

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Appendix C. Comparative analysis of efficacy

Table 41. Comparative analysis of studies comparing durvalumab to placebo for patients with unresectable stage III NSCLC (DCO Jan 11th, 2021)

Outcome		Absolute difference in effect			Relative difference in effect			Method used for quantitative synthesis	Result used in the health economic analysis?
	Studies included in the analysis	Difference	CI	P value	Difference	CI	P value		
Median PFS, PD-L1 1-24%	PACIFIC	15.2	NA	NA	0.51	0.33-0.78	NA	Unstratified Cox regression models (with no adjustment for multiple comparisons) were used for subgroup analyses. Medians and landmark rates (eg, 5-year OS) were estimated by Kaplan-Meier method.	NA
Median OS, PD-L1 ≥1%	PACIFIC	18.9	NA	NA	0.73	0.46-1.14	NA		NA
PFS, number of events, PD-L1 1-24%	PACIFIC	NA	NA	NA	0.47	0.35-0.64)	NA		NA
OS, number of events, PD-L1 ≥1%	PACIFIC	NA	NA	NA	0.61	0.44-0.85	NA		NA
Changes in Global Health Status, Mean SD, Week 48, EORTC QLQ-C30	PACIFIC	1.7	3.8-7.2	p=0.54	NA	NA	NA		NA

Appendix D. Extrapolation

This submission follows Medicinrådets 14-week process. Thus, this section is not filled in.

D.1 Extrapolation of [effect measure 1]

D.1.1 Data input

D.1.2 Model

D.1.3 Proportional hazards

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

D.1.5 Evaluation of visual fit

D.1.6 Evaluation of hazard functions

D.1.7 Validation and discussion of extrapolated curves

D.1.8 Adjustment of background mortality

D.1.9 Adjustment for treatment switching/cross-over

D.1.10 Waning effect

D.1.11 Cure-point

D.2 Extrapolation of [effect measure 2]

Appendix E. Serious adverse events

Table 42. Serious adverse events (Safety analysis set: March 22, 2018 DCO): Most common CTCAE Grade 3 or 4 AEs (frequency of >1%) (31)

Adverse events	Durvalumab (N=475)		Placebo (N=234)	
	Number of patients with adverse events	Number of adverse events	Number of patients with adverse events	Number of adverse events
Patients with any AE of CTCAE Grade 3 or 4, n (%)	125 (32.0)		65 (27.8)	
Pneumonia, n (%)	21 (4.4)		10 (4.3)	
Anemia, n (%)	14 (2.9)		8 (3.4)	
Hypertension, n (%)	10 (2.2)		2 (0.9)	
Pneumonitis, n (%)	8 (1.7)		5 (2.1)	
Dyspnea, n (%)	7 (1.5)		6 (2.6)	
Radiation pneumonitis, n (%)	7 (1.5)		1 (0.4)	
Aspartate aminotransferase increased, n (%)	6 (1.3)		0	

Adverse events	Durvalumab (N=475)	Placebo (N=234)
Lung infection, n (%)	6 (1.3)	2 (0.9)
Hyperglycemia, n (%)	5 (1.1)	1 (0.4)
Hypokalemia, n (%)	5 (1.1)	5 (2.1)
Sepsis, n (%)	4 (0.8)	3 (1.3)
Diarrhea, n (%)	3 (0.6)	3 (1.3)
Fatigue, n (%)	1 (0.2)	3 (1.3)

Appendix F. Health-related quality of life

This submission follows Medicinrådets 14-week process. Thus, this section is not filled in.

Appendix G. Probabilistic sensitivity analyses

This submission follows Medicinrådets 14-week process. Thus, this section is not filled in.

Table 43. Overview of parameters in the PSA

Input parameter	Point estimate	Lower bound	Upper bound	Probability distribution
NA				

Appendix H. Literature searches for the clinical assessment

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

This submission follows Medicinrådets 14-week process with H2H data only included. Thus, this section is not filled in.

Table 44. Bibliographic databases included in the literature search

Database	Platform/source	Relevant period for the search	Date of search completion
NA			

Abbreviations:

Table 45. Conference material included in the literature search

Conference	Source of abstracts	Search strategy	Words/terms searched	Date of search
NA				

H.1.1 Search strategies

Table 46. of search strategy table for [name of database]

No.	Query	Results
NA		

H.1.2 Systematic selection of studies

Table 47. Inclusion and exclusion criteria used for assessment of studies

Clinical effectiveness	Inclusion criteria	Exclusion criteria	Changes, local adaption
NA			

Table 48. Overview of study design for studies included in the analyses

Study/ID	Aim	Study design	Patient population	Intervention and comparator (sample size (n))	Primary outcome and follow-up period	Secondary outcome and follow-up period
NA						

H.1.3 Excluded fulltext references

NA

H.1.4 Quality assessment

NA

H.1.5 Unpublished data

NA

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

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

This submission follows Medicinrådets 14-week process with H2H data only included. Thus, this section is not filled in.

Table 49. Bibliographic databases included in the literature search

Database	Platform	Relevant period for the search	Date of search completion
NA			

Table 50. Other sources included in the literature search

Source name	Location/source	Search strategy	Date of search
NA			

Table 51. Conference material included in the literature search

Conference	Source of abstracts	Search strategy	Words/terms searched	Date of search
NA				

I.1.1 Search strategies

Table 52. Search strategy for [name of database]

No.	Query	Results
NA		

I.1.2 Quality assessment and generalizability of estimates

NA

I.1.3 Unpublished data

NA

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

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

This submission follows Medicinrådets 14-week process. Thus, this section is not filled in.

J.1.1 Example: Systematic search for [...]

Table 53. Sources included in the search

Database	Platform/source	Relevant period for the search	Date of search completion
NA			

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

Table 54. Sources included in the targeted literature search

Source name/ database	Location/source	Search strategy	Date of search
NA			

Medicinrådet