Horizon Scanning in Oncology

Durvalumab (Imfinzi™) for the treatment of patients with stage III non-small cell lung cancer after prior chemoradiotherapy

Ludwig Boltzmann Institut
Health Technology Assessment

DSD: Horizon Scanning in Oncology No. 76
ISSN online 2076-5940

Horizon Scanning in Oncology

Durvalumab (Imfinzi™) for the treatment of patients with stage III non-small cell lung cancer after prior chemoradiotherapy

Ludwig Boltzmann Institut
Health Technology Assessment

Vienna, December 2017

Institute for Health Technology Assessment
Ludwig Boltzmann Gesellschaft

Authors: Lynda McGahan, MSc
Internal review: Priv.-Doz. Dr. phil. Claudia Wild; Dr. med. Eleen Rothschedl; Nicole Grössmann, MSc
External review: OA Dr. Maximilian J. Hochmair
Onkologische Ambulanz und Tagesklinik, Otto Wagner Spital Wien

CONTACT INFORMATION

Publisher:

Ludwig Boltzmann Gesellschaft GmbH
Nußdorferstr. 64, 6 Stock, A-1090 Vienna
http://www.lbg.ac.at/de/lbg/impressum

Responsible for Contents:

Ludwig Boltzmann Institute for Health Technology Assessment (LBI-HTA)
Garnisongasse 7/20, A-1090 Vienna
http://hta.lbg.ac.at/

Decision support documents of the LBI-HTA do not appear on a regular basis and serve to publicise the research results of the Ludwig Boltzmann Institute of Health Technology Assessments.

Decision support documents of the LBI-HTA are only available to the public via the Internet at http://eprints.hta.lbg.ac.at

DSD: Horizon Scanning in Oncology No. 76
ISSN-online: 2076-5940

http://eprints.hta.lbg.ac.at/view/types/

Abstract

Introduction

Non-small cell lung cancer (NSCLC) arises when epithelial cells lining the bronchial tubes undergo aberrant cell growth due to up-regulation of the programmed death ligand (PD-L1). A Marketing Authorisation Application for durvalumab was recently submitted to the European Medicines Agency for the treatment of patients with stage III, unresectable NSCLC whose disease did not progress following platinum-based chemotherapy. By inhibiting PD-1, durvalumab restores T-cell activation, enabling the effective detection and destruction of tumour cells.

Methodology

Published and grey literature were identified by searching the Cochrane Library, CRD Database, Embase, Ovid Medline, PubMed, Internet sites and contacting the manufacturer. Quality assessment was conducted to assess the risk of bias at the study level based on the EUnetHTA internal validity for randomized controlled trials. Furthermore, the magnitude of clinically meaningful benefit that can be expected from durvalumab was evaluated based on, both the original and an adapted version of the Magnitude of Clinical Benefit Scale developed by the European Society for Medical Oncology.

Results of the PACIFIC trial

In the phase III, PACIFIC study, 713 patients with stage III, unresectable NSCLC, without progression following platinum-based chemotherapy, were randomised 2:1 to durvalumab (10 mg/kg IV every 2 weeks) or matching placebo for up to 12 months. At a median follow-up of 14.5 months, durvalumab increased the median progression-free survival (PFS) by 11.2 months, compared to placebo, irrespective of PD-L1 expression level prior to chemoradiotherapy. Durvalumab also increased the overall response rate (ORR) by 12.4%, duration of response (DOR) (>13.8 months), time to death or distant metastasis (TTDM) by 9 months, and reduced the incidence of new brain metastases by 5.5% compared with placebo. Immune-mediated, treatment-related adverse events (AEs) requiring glucocorticoids or endocrine therapy were more commonly reported in the durvalumab group; pneumonitis and pneumonia resulted in discontinuation in 6.3% and 1.1% of durvalumab recipients, respectively.

Conclusion

Overall, durvalumab increases PFS, ORR, DOR, and TTDM in patients with stage III NSCLC, regardless of PD-L1 expression level prior to chemoradiation or histology, compared to placebo. However, overall survival (OS), quality of life (QoL) and long-term safety data are awaited, and study participants may not be representative of those in clinical practice. Direct comparison trials are lacking, to other immunotherapies (e.g. pembrolizumab), and cross-trial comparisons are cautioned due to differences in patient selection based on different PD-L1 assays. Further research is needed regarding the duration and timing of immunotherapy, the best regimen of chemoradiation for combination, and patient selection for greatest benefit based on predictive markers of efficacy and resistance.

Table of contents

List of tables

1 Research questions

The HTA Core Model® for Rapid Relative Effectiveness Assessment of Pharmaceuticals was used for structuring this report [1]. The Model organises HTA information according to pre-defined generic research questions. Based on these generic questions, the following research questions were answered in the assessment.

EUnetHTA HTA Core Model®

Element ID	Research question
Description of the technology	
B0001	What is durvalumab?
A0022	Who manufactures durvalumab?
A0007	What is the target population in this assessment?
A0020	For which indications has durvalumab received marketing authorisation?
Health problem and current use	
A0002	What is NSCLC?
A0004	What is the natural course of NSCLC?
A0006	What are the consequences of NSCLC for the society?
A0023	How many people belong to the target population?
A0005	What are the symptoms and the burden of NSCLC?
A0003	What are the known risk factors for NSCLC?
A0024	How is NSCLC currently diagnosed according to published guidelines and in practice?
A0025	How is NSCLC currently managed according to published guidelines and in practice?
Clinical effectiveness	
D0001	What is the expected beneficial effect of durvalumab on mortality?
D0005	How does durvalumab affect symptoms and findings (severity, frequency) of NSCLC?
D0006	How does durvalumab affect progression (or recurrence) of NSCLC?
D0011	What is the effect of durvalumab on patients' body functions?
D0012	What is the effect of durvalumab on generic health-related quality of life?
D0013	What is the effect of durvalumab on disease-specific quality of life?
Safety	
C0008	How safe is durvalumab in relation to the comparator(s)?
C0002	Are the harms related to dosage or frequency of applying durvalumab?
C0005	What are the susceptible patient groups that are more likely to be harmed through the use of durvalumab?
A0021	What is the reimbursement status of durvalumab?

2 Drug description

Generic/Brand name/ATC code:

Durvalumab/Imfinzi™/MEDI4736

B0001: What is durvalumab?

anti-PD-L1 antibody, immune checkpoint inhibitor

Up-regulation of the programmed death ligand 1 (PD-L1) in patients with tumours increases the propensity for cancer cells to evade immune surveillance. Durvalumab, a monoclonal antibody, is an immune checkpoint inhibitor. By blocking PD-L1 from binding to PD-1 and CD80 receptors, durvalumab restores T-cell activation, enabling the effective detection and destruction of tumour cells.

10 mg/kg IV over 60 minutes every 2 weeks

Durvalumab is available in 120 mg/2.4 ml (50 mg/ml) and 500 mg/10 ml (50 mg/ml) single-use vials. It is administered as an intravenous infusion over 60 minutes, at a dose of 10 mg/kg, every 2 weeks starting within 6 weeks after chemoradiotherapy until disease progression or unacceptable toxicity [2].

monitor thyroid, liver and renal function; interrupt/discontinue for immune-mediated AEs

During treatment, patients require periodic monitoring for blood glucose, thyroid, liver and renal function. Dose interruption or discontinuation may be required in patients that develop immune-mediated pneumonitis, hepatitis, colitis, nephritis, endocrinopathies, infections, infusion-related reactions, or intolerance due to adverse events (AEs) [2].

A0022: Who manufactures durvalumab?

MedImmune LLC, a subsidiary of AstraZeneca

3 Indication

A0007: What is the target population in this assessment?

stage III NSCLC patients previously treated with chemoradiotherapy

Durvalumab is indicated for the treatment of patients with stage III non-small cell lung cancer (NSCLC) after prior chemoradiotherapy [3].

4 Current regulatory status

A0020: For which indications has durvalumab received marketing authorisation?

FDA: licensed for MUC in May 2017

In May 2017, the US Food and Drug Administration (FDA) issued accelerated approval of durvalumab for the treatment of patients with locally advanced or metastatic urothelial carcinoma (MUC) with disease progression during or within 12 months of neoadjuvant or adjuvant platinum-based chemotherapy. The VENTANA PD-L1 (SP263) Assay (Ventana Medical Systems, Inc.) was approved as a complementary diagnostic for assessing PD-L1 protein expression. Initial approval was based on the objective response rate (ORR) and duration of response (DOR) reported in patients with PD-L1-expressing tumours in a single-arm, open-label, phase I/II, Study 1108 trial. Continued approval is contingent upon verification through confirmatory trials [2, 4].

FDA: priority review for stage III NSCLC in October 2017

In July 2017, the FDA granted durvalumab breakthrough therapy designation for the treatment of patients with stage III NSCLC whose disease had *not* progressed following platinum-based chemoradiotherapy [5]. By October 2017, durvalumab was granted a priority review for a supplemental biologics license application based on progression-free survival (PFS) results from the phase III PACIFIC trial [6].

EMA: MMA for stage III NSCLC in October 2017

Durvalumab does not currently have marketing authorisation in Europe for any indication. However, in October 2017, a Marketing Authorisation Application (MAA) for durvalumab was submitted to the European Medicines Agency (EMA) for the treatment of patients with stage III, unresectable NSCLC whose disease had not progressed following platinum-based chemoradiotherapy [7, 8].

5 Burden of disease

A0002: What is NSCLC?

NSCLC accounts for 80–85% of all lung cancers

NSCLC is the most common epithelial lung cancer and accounts for approximately 80–85% of all lung cancers. The most common histological types of NSCLC are squamous (25–30%), adenocarcinomas (40%) and large cell carcinomas (10–15%). Squamous cell, also known as epidermoid, carcinoma is typically centrally located, characterized by keratin, more common in males and tobacco smokers, and has a 10% survival rate at 5 years [9, 10]. Adenocarcinoma and large cell carcinoma are typically peripherally located and have survival rates of approximately 5–6% at 5 years. Approximately 7–35% of NSCLC patients have driver gene alterations in the epidermal growth factor receptor (EGFR), anaplastic lymphoma kinase (ALK) or ROS1, while 1–3% have BRAF mutations. NSCLC tumours express the immune checkpoint PD-L1 that negatively regulates T-cell proliferation and induces cell death in tumour-specific T-cells. PD-L1 expression ranges from 23–27% in non-squamous NSCLC and from 19–56% in squamous NSCLC [11].

PD-L1 expression in NSCLC
non-squamous: 23–27%
squamous: 19–56%

A0004: What is the natural course of NSCLC?

staged I–IV by invasiveness

metastasize to bone, liver, brain, lymph nodes

Lung cancer typically arises when epithelial cells lining the bronchial tubes undergo aberrant cell growth. To facilitate treatment, lung cancer is staged from I through IV based on tumour size, and presence or absence of lymph node involvement and metastases (TNM). Stage I lung cancer is <3 cm and localized to one lobe; stage II has spread to other parts of the lung or lymph nodes; stage III may be large or spread to lymph nodes between the lungs; and stage IV has metastasized to the adjacent lung, brain, liver or bones [9, 12]

A0006: What are the consequences of NSCLC for the society?

52–58% present with advanced cancer; relapse and metastasize early

Lung cancer is the second most commonly diagnosed cancer. While the implementation of smoking cessation programs and multidisciplinary treatments have reduced the incidence and mortality, 52–58% of lung cancer patients present with advanced-stage disease when curative treatment is no longer feasible. PD-L1 is a poor prognostic factor in NSCLC [13], leading to a high rate of relapse and early formation of micro-metastases [14].

A0023: How many people belong to the target population?

4,716 Austrians were diagnosed with NSCLC in 2014

average age at diagnosis ~70 years

Lung cancer is the leading cause of cancer-related death in men and the second in women worldwide. The age standardized incidence rate for the European Standard Population was 56.9 per 100,000 persons per year in 2014. In Austria, 2,894 men and 1,822 women were newly diagnosed with lung cancer in 2014; and 2,450 men and 1,458 women died due to lung cancer (47.3 per 100,000 persons per year) [15]. Approximately 6.5% of people will be diagnosed with lung cancer during their lifetime and approximately one-third of patients with NSCLC have a stage III presentation. Assuming this about 1,550 patients in Austria (2014) had stage III NSCLC at the time of diagnosis. The average age at diagnosis is approximately 70 years [10].

A0005: What are the symptoms and the burden of NSCLC?

NSCLC symptoms: cough, chest pain, weight loss, shortness of breath

Many lung cancers are not symptomatic until they have spread. Symptoms of NSCLC include incessant cough, bloody sputum, chest pain, wheezing or hoarseness, weight loss or loss of appetite, shortness of breath, fatigue, and recurrent bronchitis or pneumonia. Lung cancer may metastasize to bone, brain, liver or lymph nodes causing pain, headaches, improper balance, seizures, jaundice or lumps near the body's surface [9].

A0003: What are the known risk factors for NSCLC?

main risk factor: smoking

The risk of lung cancer increases with age, tobacco use, radiation exposure, air pollution, and occupational exposure to asbestos, arsenic, chromium beryllium, nickel, second-hand smoking and other agents. The risk of developing lung cancer is tenfold higher in smokers compared to lifetime non-smokers. Smoking cessation decreases precancerous lesions and reduces the risk of developing lung cancer [9].

A0024: How is NSCLC currently diagnosed according to published guidelines and in practice?

diagnosis: x-ray, CT, and biopsy

While some lung cancers may be found through screening, most are identified when they become symptomatic. Following a clinical history and physical exam, a chest x-ray may be done to identify any abnormal areas in the lungs. A computed tomography (CT) scan may show the size, shape and location of any lung tumours or enlarged lymph nodes, and guide a needle biopsy if a suspected area is identified. Lung cancer is diagnosed by examining cells derived through biopsy or sputum sampling for the presence of cancer cells. Immunohistochemical (IHC), molecular tests, and liquid biopsy may be conducted to identify specific changes in the gene expression of cancer cells to target first-line treatment for NSCLC patients with genetic aberrations in EGFR, BRAF, ALK or ROS1 genes. In addition to tumour genotyping, all patients may be assessed for PD-L1 expression on tumour cells and tumour-infiltrating immune cells using the Ventana PD-L1 (SP142) IHC assay [12]

PD-L1 status: IHC assay

6 Current treatment

A0025: How is NSCLC currently managed according to published guidelines and in practice?

treatment by stage: surgery, radiation therapy, chemotherapy

Depending on the tumour stage, histology, and the patient's overall health, surgery, radiation therapy and/or platinum-based chemotherapy may be used alone or in combination to treat NSCLC. Treatment per NSCLC stages involves the following options [12]:

- Stage I and II NSCLC patients typically undergo surgery to remove the cancer. Stage II patients may benefit from postoperative adjuvant chemotherapy.
- Patients with stage I or II cancers that are not surgical candidates, due to co-morbidities or limited lung function, may undergo local radiation therapy.
- Stage III NSCLC patients are highly heterogeneous and may undergo a combination of treatments depending on the extent and localization of disease as well as prior treatments.
- Patients with stage IV disease are treated with systemic therapy or a symptom-based palliative approach.

In appropriately selected patients, chemotherapy, molecularly targeted therapy, and/or immunotherapy may extend survival in stage III NSCLC:

optimal chemotherapy regimen for use with concurrent radiotherapy is not known

- While the optimal chemotherapy regimen for use with concurrent radiotherapy is not known, cisplatin plus etoposide, carboplatin, or vinorelbine and paclitaxel are commonly used. The combination of pemetrexed and cisplatin has also emerged as an option for stage III patients with non-squamous histology [12].
- The standard dose fractionation regimen of radiotherapy with chemotherapy for stage III NSCLC is 60 Gy in 30 daily fractions. Intensity-modulated radiation therapy is preferred over 3D radiotherapy due to the reduced risk for pneumonitis.

targeted therapies

- NSCLC patients with genetic alterations in EGFR may benefit from tyrosine kinase inhibitors such as erlotinib, gefitinib, afatinib, or osimertinib. Patients with ALK translocations may benefit from crizotinib, ceritinib, alectinib, or brigatinib therapy. First-line therapy for ROS1-translocated NSCLC is crizotinib; carbozantinib may be effective for crizotinib-resistant cancers. First-line therapy for stage IV patients with BRAF V600E is combination dabrafenib plus trametinib [12].

immunotherapies

- Pembrolizumab, nivolumab, and atezolizumab block PD-L1 on T-lymphocytes and are used as second-line therapies for advanced NSCLC [12] .
- No targeted therapies or immunotherapies were available for stage III NSCLC patients until durvalumab was approved.

7 Evidence

systematic literature search in 5 databases: 112 hits

A literature search was conducted on 19 October 2017 in five databases: the Cochrane Library, CRD Database, Embase, Ovid Medline and PubMed. Search terms were “durvalumab”, “Imfinzi”, “NSCLC” and “non-small cell lung cancer”. The manufacturer was also contacted and submitted a reference and a supplemental appendix that had already been identified by systematic literature search. A manual search yielded three FDA approval documents [2, 5, 6], an EMA marketing authorization application notification [7], five clinical guidance documents [9, 11, 12, 14, 16], three mechanism of action articles [17-19], a phase II study report [20], a phase III protocol [21], a supplementary appendix [22], two statistical documents [10, 15] and two cost editorials [23, 24]. Ongoing trials information was found on www.clinicaltrials.gov. Overall, 131 references were identified.

manual search: 19 additional references

overall: 131 references included: 3 studies

A phase III study, a phase I/II study, and a phase II study contributed to the evidence regarding efficacy and safety of durvalumab for patients with stage III NSCLC after prior chemoradiotherapy. Included in this report are:

- PACIFIC, phase III [3, 22]
- Study 1108, phase I/II [25, 26]
- ATLANTIC, phase II [20, 27]

study level risk of bias assessed based on EUnetHTA internal validity for RCTs

To assess the risk of bias at the study level, the assessment of the methodological quality of the evidence was conducted based on the EUnetHTA internal validity for randomised controlled trials (RCTs) [28]. Evidence was assessed based on the adequate generation of the randomisation sequence, allocation concealment, blinding of patient and treating physician, selective outcome reporting and other aspects that may increase the risk of bias. Study quality details are reported in Table 5 of the Appendix.

magnitude of clinically meaningful benefit assessed based on ESMO-MCBS

To evaluate the magnitude of "clinically meaningful benefit" that can be expected from a new anti-cancer treatment, the Magnitude of Clinical Benefit Scale developed by the European Society for Medical Oncology (ESMO-MCBS v1.1) was used [29, 30]. Additionally, an adapted version (due to perceived limitations) of the ESMO-MCBS was applied [31]. Details of the magnitude of the clinically meaningful benefit scale are reported in Table 3.

7.1 Clinical efficacy and safety – phase III study

PACIFIC: durvalumab versus placebo in 713 unresected, stage III NSCLC patients following platinum-based chemoradiotherapy

PACIFIC (NCT02125461) is a multicentre, randomised, placebo-controlled, phase III study involving 713 patients with stage III, unresectable NSCLC without progression following concurrent platinum-based chemoradiotherapy [3, 22]. Efficacy analyses were based on all randomly assigned patients comprising the intent-to-treat (ITT) population. Safety analyses involved 709 patients who received at least one dose of study drug as consolidation therapy (as-treated population). While patients provided optional archived tumour-tissue samples for PD-L1 testing, enrolment was not restricted by level of PD-L1 expression.

ITT stratified by age, sex, and smoking history

Study participants were adults (≥18 years) with histologically or cytologically confirmed stage III, locally advanced, unresectable NSCLC; World Health Organization (WHO) performance status 0–1; who had received two or more cycles of platinum-based chemotherapy concurrent with radiotherapy, with a life expectancy greater than 12 weeks. Patients were excluded if they were previously exposed to anti-PD-1 or PD-L1 antibodies; received immunotherapy or a study drug within four weeks of first dose; had active or prior autoimmune disease or immunodeficiency; uncontrolled concurrent illness or active infections; unresolved toxic effects or pneumonitis from prior chemoradiotherapy (grade ≥2, Common Terminology Criteria for Adverse Events [CTCAE]).

durvalumab 10 mg/kg IV versus placebo every 2 weeks

Patients were randomized 2:1 to receive durvalumab (10 mg/kg IV) or matching placebo every 2 weeks for up to 12 months, disease progression or unacceptable toxicity. They were stratified according to age (<65 years versus ≥65 years), sex, and smoking history (current or former smoker versus never smoked). The study drug was administered within 42 days after receiving two or more cycles of platinum-based chemotherapy. Patients received chemotherapy containing etoposide, vinblastine, vinorelbine, pemetrexed, paclitaxel or docetaxel concurrently with definitive radiation therapy (54-66 Gy), in which the mean dose to lung was <20 Gy, the volume of lung parenchyma that received >20 Gy was <35%, or both. At interim analysis February 13, 207 (median follow-up of 14.5 months), the median number of infusions received was 20 (range, 1–27) for durvalumab and 14 (range, 1–26) for

placebo. The median relative dose intensity, defined as the ratio of delivered to planned, was 100% in each group (range, 29–100%) for duvalumab and for placebo (range, 50–100%).

co-primary endpoints: PFS and OS secondary endpoints: 12 and 18-month PFS rates, ORR, DOR, TTDM and safety

The co-primary endpoints were PFS according to the Response Evaluation Criteria in Solid Tumours (RECIST version 1.1) as assessed by blinded independent central review (BICR) and overall survival (OS). Secondary endpoints included the percentage of patients who were alive without disease progression at 12 and 18 months, the ORR, DOR, and the time to death or distant metastasis (TTDM), as assessed by BICR, OS at 24 months, and safety. Efficacy was assessed every 8 weeks for the first 12 months and every 12 weeks thereafter.

ITT: median age 64 years, 53% stage IIIA, 91% smokers, 41% PD-L1 expression <25% on tumour cells

The ITT population (n = 713) had a median age of 64 years (range 23–90), 70% were male, 69% were Caucasian, 53% were stage IIIA at entry, 54% had non-squamous histology, and 91% were current or former smokers. Approximately 54% had prior cisplatin-based chemotherapy and 42% had prior carboplatin-based chemotherapy concurrently with radiation (54–66 Gy). EGFR mutations were observed in 6% of patients (6.1% durvalumab versus 5.9% placebo). Approximately 22.3% of patients had PD-L1 expression of ≥25% on tumour cells (24.2% durvalumab versus 18.6% placebo), 41.0% of patients had PD-L1 expression of <25% on tumour cells (39.3% durvalumab versus 44.3% placebo), and PD-L1 status was unknown in 36.7% of patients. Detailed patient characteristics, including inclusion and exclusion criteria are reported in Table 4 and study quality is described in Table 5 of the appendix, respectively. Clinical efficacy data are presented in Table 1 and AEs are listed in Table 2.

7.1.1 Clinical efficacy

D0001: What is the expected beneficial effect of durvalumab on mortality?

OS: not planned for interim analysis

Due to the low maturity of data, an analysis of OS was not planned at the time of the interim analysis for PFS. The first OS interim analysis will be at the time of final analysis for PFS.

D0006: How does durvalumab affect progression (or recurrence) of NSCLC?

median PFS in ITT: 16.8 months for durvalumab vs 5.6 months for placebo

At interim analysis, February 13, 2017, 371 patients had disease progression (214/476 durvalumab versus 157/237 placebo). At a median follow-up of 14.5 months (range 0.2–29.9), durvalumab patients had a BICR-assessed median PFS of 16.8 months (95% CI 13.0–18.1) compared to 5.6 months (95% CI 4.6–7.8) for stage III NSCLC patients treated with placebo. Compared with placebo, durvalumab improved BICR-assessed PFS (stratified hazard ratio [HR] for disease progression or death 0.52 [95% CI 0.42–0.65]; two-sided $p<0.001$).

APF12: durvalumab: 56% placebo: 35%

The proportion alive and progression-free rate at 12 months (APF12), as assessed by BICR, was 55.9% (95% CI 51.0–60.4) with durvalumab versus 35.3% (95% CI 29.0–41.7) with placebo. At 18 months, the proportion alive and progression-free (APF18) was 44.2% (95% CI 37.7–50.5) with durvalumab versus 27.0% (95% CI 19.9–34.5) with placebo.

Patients receiving durvalumab demonstrated greater PFS than placebo recipients regardless of their PD-L1 expression prior to chemoradiotherapy (HR 0.59 [95% CI 0.43–0.82] for PD-L1 expression <25% and 0.41 [95% CI 0.26-0.65] for PD-L1 expression ≥25%). While the majority of patients were smokers, durvalumab recipients who were non-smokers exhibited greater PFS over placebo recipients who were smokers.

PFS benefit irrespective of PD-L1 expression level

D0005: How does durvalumab affect symptoms and findings (severity, frequency) of NSCLC?

The ORR, as assessed by BICR, was 28.4% (126/443) for durvalumab versus 16.0% (34/213) for placebo (p<0.001) (treatment effect [TE] 1.78 [95% CI 1.27–2.51]; p<0.001). The median DOR was not reached (NR) in the durvalumab group and 13.8 months (95% CI 6.0–NR) in the placebo group (TE 0.43 [95% CI 0.22–0.84]). Of the patients that responded to durvalumab, 72.8% had an ongoing response at 12 and 18 months compared with 56.1% and 46.8%, respectively, of placebo recipients.

ORR:
durvalumab: 28.4%
placebo: 16.0%

DOR:
durvalumab: NR
placebo: 13.8 months

The TTDM was 23.2 months (95% CI 23.2–NR) with durvalumab versus 14.6 months (95% CI 10.6–18.6) with placebo (HR 0.52 [95% CI 0.39–0.69]; two-sided p<0.001). The frequency of BICR-assessed new lesions was 20.4% with durvalumab and 32.1% with placebo. The incidence of new brain metastases was 5.5% in durvalumab recipients and 11.0% in placebo recipients.

TTDM:
durvalumab: 23.2 months
placebo: 14.6 months

D0011: What is the effect of durvalumab on patients' body functions?

Durvalumab may cause immune-mediated AEs including pneumonitis, hepatitis, colitis, nephritis, endocrinopathies, immunogenicity and infection [2]. Immune-mediated AEs, of any cause and grade, were observed in 115/475 (24.2% of) patients in the durvalumab group and 19/234 (8.1% of) patients in the placebo group. Grade 5 immune-mediated AEs were reported in 4 (0.8% of) durvalumab recipients and 3 (1.3% of) placebo recipients. Grade 3 or 4 AEs occurred in 3.4% of durvalumab-treated patients and 2.6% of placebo-treated patients. Treatments for immune-mediated AEs were issued to 14.3% and 5.6% of patients receiving durvalumab and placebo, respectively; including high-dose glucocorticoids (8.2% and 4.3%), endocrine therapy (10.7% and 1.3%), and other immunosuppressive agents (0.4% both groups) [3].

treatment for immune-mediated AEs:
durvalumab: 14.3%
placebo: 5.6%

D0012: What is the effect of durvalumab on generic health-related quality of life?

No evidence was reported regarding the effect of durvalumab on generic health-related quality of life (QoL).

generic health-related QoL: no evidence

D0013: What is the effect of durvalumab on disease-specific quality of life?

No evidence was reported regarding the effect of durvalumab on disease-specific QoL.

disease-specific QoL: no evidence

Table 1: Efficacy results of PACIFIC [3]

Descriptive statistics and estimate variability	**Treatment group**	**Durvalumab**	**Placebo**
	Number of subjects	476	237
	OS, n (%)	NA	NA
	Median PFS, months	16.8 (95% CI 13.0–18.1)	5.6 (95% CI 4.6–7.8)
	PFS, n (%) (follow-up: 14.5 months)	214/476 (45)	157/237 (66)
	APF12, %	55.9 (95% CI 51.0–60.4)	35.3 (95% CI 29.0–41.7)
	APF18, %	44.2 (95% CI 37.7–50.5)	27.0 (95% CI 19.9–34.5)
	ORR, n (%) 12-month response, n (%) 18-month response, n (%)	126 (28.4) (95% CI 24.3–32.9) 347 (72.8) 347 (72.8)	34 (16.0) (95% CI 11.3–21.6) 133.2 (56.1) 110 (46.8)
	Best overall response, n (%) CR PR SD PD UE	 6 (1.4) 120 (27.1) 233 (52.6) 73 (16.5) 10 (2.3)	 1 (0.5) 33 (15.5) 119 (55.9) 59 (27.7) 1 (0.5)
	Median DOR, months	NR	13.8 6.0–NR
	Median TTDM	23.2 (95% CI 23.2–NR)	14.6 (95% CI 10.6–18.6)
	Frequency of new lesions, n (%) New brain metastases, n (%)	97 (20.4) 26 (5.5)	76 (32.1) 26 (11.0)
Effect estimate per comparison	*Comparison groups*		*Durvalumab versus placebo*
	OS Co-primary endpoint	NA	NA
	BICR-assessed PFS Co-primary endpoint	Stratified HR	0.52
		95% CI	0.42–0.65
		Two-sided p value	<0.001
	Investigator-assessed PFS	Stratified HR	0.61
		95% CI	0.50–0.76
		Two-sided p value	P<0.001
	PFS PD-L1 <25%	HR	0.59
		95% CI	0.43–0.82
		p value	NA
	PFS PD-L1 ≥25%	HR	0.41
		95% CI	0.26–0.65
		p value	NA
	ORR Secondary endpoint	TE	1.78
		95% CI	1.27–2.51
		p value	<0.001
	DOR	TE	0.43
		95% CI	0.22–0.84
		p value	NA
	TTDM	HR	0.52
		95% CI	0.39–0.69
		Two-sided p value	<0.001

Abbreviations: BICR = blinded independent review committee; CI = confidence interval; CR = complete response; DOR = duration of response; HR = hazard ratio; NA = not analysed; NR = not reached; OS = overall survival; PD = progressive disease; PR = partial response; SD = stable disease; TE = treatment effect; TTDM = time to death or distant metastasis; UE = unable to evaluate

7.1.2 Safety

C0008: How safe is durvalumab in relation to the comparator(s)?

Treatment-related AEs were reported in 322/475 (67.8% of) patients in the durvalumab group and 125/234 (53.4% of) patients in the placebo group. Serious AEs occurred in 136/475 (28.6% of) durvalumab recipients and 53/234 (22.6% of) placebo recipients. Death due to AEs occurred in 4.4% and 5.6% of durvalumab and placebo patients, respectively. Grade 5 treatment-related AEs occurred in seven (1.5% of) durvalumab recipients (n = 4 [0.8%] with pneumonitis, n = 2 [0.4%] with cardiac arrest, and n = 1 [0.2%]) each with cardiomyopathy, right ventricular failure, respiratory distress, respiratory failure, increased brain natriuretic peptide, and radiation pneumonitis right ventricular failure, increased level of brain natriuretic peptide, and unknown cause) and three (1.3% of) placebo recipients (n = 2 [0.9%] with pneumonitis and 1 [0.4%] cause unknown]. Grade 3 or 4 AEs of any cause were reported in 29.9% of durvalumab recipients and 26.1% of placebo recipients. Pneumonia and anaemia, the most common grade 3 or 4 AE, were observed in 4.4% and 2.9% of patients receiving durvalumab, and 3.8% and 3.4% of patients receiving placebo, respectively. The most common AEs of any cause and grade in the durvalumab group were cough (35.4%), pneumonitis (33.9%), fatigue (23.8%), dyspnoea (22.3%), diarrhoea (18.3%), and pyrexia (14.7%).

treatment-related AEs:
durvalumab: 68%
placebo: 53%

AE-related deaths:
durvalumab: 4.4%
placebo: 5.6%

most common AEs:
cough, pneumonitis, fatigue, dyspnoea, diarrhoea and pyrexia

AEs of special interest, regardless of cause, were reported in 66.1% of patients receiving durvalumab and 48.7% of patients receiving placebo; most frequently diarrhoea (18.3% and 18.8%), pneumonitis (12.6% and 7.7%), rash (12.2% and 7.3%), and pruritus (12.2% and 4.7%). Concomitant treatments for AEs of special interest were issued to 42.1% of durvalumab recipients and 17.1% of placebo recipients, including glucocorticoids (15.2% and 6.8%), high-dose glucocorticoids (8.8% and 5.1%), endocrine therapy (11.6% and 1.3%, respectively) and other immunosuppressive agents (0.4% both groups).

AEs of special interest:
diarrhoea, pneumonitis, rash and pruritus

C0002: Are the harms related to dosage or frequency of applying durvalumab?

Severe infusion-related reactions have been reported in patients receiving durvalumab. It is necessary to interrupt or infuse slowly in patients with mild or moderate infusion reactions and discontinue use in patients with grade 3 or 4 reactions [2]. By interim analysis, the number of infusions received by study participants was 20 (range 1–27) in the durvalumab group and 14 (range 1–26) in the placebo group; 6.3% and 5.1% of patients were still receiving durvalumab at the time of data cut-off, respectively. The median relative dose intensity was 100% in each group (range 29–100% for durvalumab, 50–100% for placebo) with an overall median follow-up of 14.5 months [3].

infusion reactions:
interrupt, infuse slowly, or discontinue

Durvalumab may be withheld and corticosteroids administered to manage moderate pneumonitis, hepatitis, colitis, diarrhoea, nephritis, or dermatitis. Moderate hypothyroidism, adrenal insufficiency, hypophysitis, type 1 diabetes mellitus, or infections may require withholding of durvalumab and administration of hormone replacement therapies, insulin or anti-infective agents. Treatment may be resumed when AEs return to grade 1 severity and

moderate AEs:
discontinue, administer corticosteroids
severe AE: discontinue

the corticosterioid dose has been reduced to <10 mg/day of prednisone or equivalent. Durvalumab may be discontinued to manage grade 3 or 4 AEs based on the severity of the adverse reaction [2].

leading causes of discontinuation: pneumonitis and pneumonia

Approximately 73/476 (15.4% of) durvalumab patients and 23/237 (9.8% of) placebo patients discontinued treatment due to AEs. Pneumonitis and pneumonia, the most frequent AEs leading to discontinuation of durvalumab and placebo, were reported in 6.3% and 1.1% of patients receiving durvalumab, and 4.3% and 1.3% of patients receiving placebo, respectively. Grade 3 or 4 pneumonitis and pneumonia occurred in 3.4% and 4.4% of durvalumab recipients and 2.6% and 3.8% of placebo recipients, respectively [3].

C0005: What are the susceptible patient groups that are more likely to be harmed through the use of durvalumab?

susceptibles: elderly, immune compromised, comorbid, reduced functional status

Study participants had a median age of 64 years (range, 23–90 years) and good performance status (WHO 0–1). Patients with a history of autoimmune disease, immunodeficiency, active infections or uncontrolled illnesses were excluded from study. While PFS benefit was observed across age subgroups (<65 years versus ≥65 years) [3], clinical specificity of elderly patients with comorbidities, co-medications, reduced functional reserve, and immunosenescence may affect the efficacy and or toxicity of immune-checkpoint inhibitors [32, 33]. The safety and efficacy of durvalumab has not been established in pediatric patients and the pharmacokinetics are unknown in patients with severe renal impairment (CLcr 15–29 ml/min), moderate (bilirubin >1.5–3.0 times ULN and any AST) or severe hepatic impairment (bilirubin >3.0 times ULN and any AST) [2].

durvalumab may cause foetal harm

Based on its mechanism of action durvalumab may cause foetal harm and adverse reactions in breastfed infants, females are advised to use effective contraception and not to breast feed for at least three months following the last dose of durvalumab [2].

Table 2: Most frequent adverse events of any cause of PACIFIC [3]

Adverse Event (according to CTCAE version 4.03)	**Durvalumab** (n = 475)		**Placebo** (n = 234)	
	Any Grade n (%)	Grade 3 or 4 n (%)	Any Grade n (%)	Grade 3 or 4 n (%)
Any event	460 (96.8)	142 (29.9)	222 (94.9)	61 (26.1)
Cough	168 (35.4)	2 (0.4)	59 (25.2)	1 (0.4)
Pneumonitis or radiation pneumonitis	161 (33.9)	16 (3.4)	58 (24.8)	6 (2.6)
Fatigue	113 (23.8)	1 (0.2)	48 (20.5)	3 (1.3)
Dyspnoea	106 (22.3)	7 (1.5)	56 (23.9)	6 (2.6)
Diarrhoea	87 (18.3)	3 (0.6)	44 (18.8)	3 (1.3)
Pyrexia	70 (14.7)	1 (0.2)	21 (9.0)	0 (0)
Decreased appetite	68 (14.3)	1 (0.2)	30 (12.8)	2 (0.9)
Nausea	66 (13.9)	0 (0)	31 (13.2)	0 (0)
Pneumonia	62 (13.1)	21 (4.4)	18 (7.7)	9 (3.8)
Arthralgia	59 (12.4)	0 (0)	26 (11.1)	0 (0)
Pruritus	58 (12.2)	0 (0)	11 (4.7)	0 (0)
Rash	58 (12.2)	1 (0.2)	17 (7.3)	0 (0)
Upper respiratory tract infection	58 (12.2)	1 (0.2)	23 (9.8)	0 (0)
Constipation	56 (11.8)	1 (0.2)	20 (8.5)	0 (0)
Hypothyroidism	55 (11.6)	1 (0.2)	4 (1.7)	0 (0)
Headache	52 (10.9)	1 (0.2)	21 (9.0)	2 (0.9)
Asthenia	51 (10.7)	3 (0.6)	31 (13.2)	1 (0.4)
Back pain	50 (10.5)	1 (0.2)	27 (11.5)	1 (0.4)
Musculoskeletal pain	39 (8.2)	3 (0.6)	24 (10.3)	1 (0.4)
Anaemia	36 (7.6)	14 (2.9)	25 (10.7)	8 (3.4)

Abbreviations: CTCAE = common terminology for cancer adverse events

7.2 Clinical effectiveness and safety – further studies

Study 1108: 304 NSCLC patients given durvalumab 10 mg/kg IV every 2 weeks, median 6 doses

Study 1108 (NCT01693562) is an ongoing, multicentre, open-label, phase I/II study to evaluate the safety and clinical activity of durvalumab mono-therapy in subjects with multiple advanced solid tumours, including NSCLC [25]. Patients received 10 mg/kg of durvalumab intravenously every 2 weeks until disease progression or unacceptable toxicity, for up to 12 months. Clinical response is based on investigator-assessment (RECIST v1.1) at 6, 12, and 16 weeks, then every 8 weeks. Retreatment was permitted only upon progression after 12 months of therapy in patients with disease control. Safety was evaluated prior to each dose (CTCAE v4.03) through 90 days after the last dose. Tumour PD-L1 expression was assessed using the Ventana PD-L1 (SP263) assay.

ORR:
PD-L1-positive: 25%
PD-L1-negative: 6%

As of April 2016, 304 NSCLC patients received durvalumab, 144 (45%) had non-squamous and 160 (53%) had squamous histology, median age was 65 years (range, 26–87), ECOG performance status was 0 in 24% and 1 in 76%, and 85% were smokers. Durvalumab monotherapy was associated with improved ORR and OS in PD-L1-positive treatment naïve NSCLC of squamous or non-squamous histology [25, 26]. At a median of 6 doses (range 1-27), the ORR was 25% for PD-L1-positive patients versus 6% for PD-L1-negative patients. The ORR was 29%, 26%, and 22% as first-, second-, and third-line therapy, respectively, for the PD-L1-positive subgroup, and 11%, 4%, and 6% for the PD-L1-negative subgroup. The median OS in PD-L1-positive and PD-L1-negative subgroups was 17.8 months and 8.2 months as second-line; and 13.0 months and 7.1 months as ≥ third-line, respectively.

12-month OS rate:
PD-L1-positive: 55.8%
PD-L1-negative: 38.8%

The 12-month OS rate in PD-L1-positive and PD-L1-negative subgroups was 55.8% and 38.8% as second-line; and 51.1% and 36.8% as ≥ third-line, respectively. Durvalumab-related AEs, of any grade, were reported in 57% of patients, most commonly fatigue (17%), decreased appetite (9%), and diarrhoea (9%). Grade ≥3 drug-related AEs were reported in 10% of patients; most frequently fatigue, hyponatremia, and colitis (1% each). Pneumonitis and colitis, the most frequent AEs leading to discontinuation of durvalumab in 5% of patients, occurred in 6 (3%) and 5 (2%) of patients, respectively [25].

5% discontinue due to pneumonitis and colitis

ATLANTIC: durvalumab 10 mg/kg IV every 2 weeks as 3rd line for NSCLC who progress on ≥2 therapies

ATLANTIC (NCT02087423) is an ongoing, multicentre, single-arm, open-label, phase II study assessing the efficacy and safety of durvalumab (10 mg/kg IV every 2 weeks) as third-line treatment for patients with locally advanced or metastatic NSCLC with known PD-L1 status, who progress following two or more previous therapies, including platinum-based chemotherapy [34]. While the study contains three cohorts, final results were reported for cohort 2 and 3 that had EGFR/ALK wild-type or unknown status. Patients in cohort 3 expressed PD-L1 on at least 90% or more tumour cells, as assessed by Roche Ventana SP263 assay; while 61% of patients in cohort 2 expressed PD-L1 on at least 25% or more tumour cells and 39% had less than 25% PD-L1 expression.

ORR:
PD-L1<25%: 7.5%
PD-l1≥25%: 16.4%
PD-L1≥90%: 30.9%

Overall, 265 patients with a median age of 62 years were included in cohort 2, and 68 patients with a median age of 61 years in cohort 3 [34]. The ORR was 7.5%, 16.4%, and 30.9% in patients with tumour PD-L1 expression of <25%, ≥25%, and ≥90%, respectively. In cohort 2, the median PFS was 3.3 months and 1.9 months in patients with high and low/negative PD-L1 expression, respectively. In cohort 3, the median PFS was 2.4 months. In cohort 2, the 12-month OS rate was 47.7% and 34.5% for patients with high and low/negative PD-L1 expression, respectively. In cohort 3, the 12-month OS rate was 50.8%. Overall, 10.2% of patients had grade ≥3 treatment-related AEs, and 2.7% of treatment-related AEs lead to drug discontinuation.

PFS:
PD-L1<25%: 1.9 months
PD-l1≥25%: 3.3 months
PD-L1≥90%: 2.4 months

8 Estimated costs

A0021: What is the reimbursement status of durvalumab?

Currently, there are no price estimates for Europe. Durvalumab costs approximately US $15,000 per month [24], or US $180,000 per year [23].

estimate: US $15,000/month
Austria: no price estimate available

9 Ongoing research

Several studies are ongoing to investigate durvalumab as monotherapy or in combination with immune checkpoint inhibitors, tyrosine kinase inhibitors, or other anti-cancer agents to treat advanced NSCLC. In November 2017, searches of www.clinicaltrials.gov and http://www.clinicaltrialsregister.eu using the search terms "durvalumab" and "NSCLC" yielded 40 registered studies (eight phase III, 18 phase II, eight phase I/II, and six phase I). Most studies were industry-sponsored or conducted in collaboration with industry.

40 registered studies

8 industry sponsored ongoing phase III

Selected ongoing phase III studies evaluating durvalumab as monotherapy (MYSTIC, PEARL, ARCTIC, PACIFIC), in combination with tremelimumab (MYSTIC, NEPTUNE, ARCTIC) in first-line (PEARL, MYSTIC, NEPTUNE), second-line (PACIFIC), third-line (ARCTIC) settings for NSCLC, or the addition of durvalumab plus tremelimumab to standard care (POSEIDON) for metastatic NSCLC:

- **NCT03003962:** PEARL is a randomised, open-label, multicentre study to determine the efficacy and safety of durvalumab versus platinum-based chemotherapy in the first-line treatment of advanced NSCLC in patients with wild-type EGFR and ALK and high expression of PD-L1. Estimated primary completion date is October 2018.
- **NCT02453282:** MYSTIC is a randomised, open-label, multicentre study to evaluate the efficacy and safety of durvalumab plus tremelimumab combination therapy and durvalumab monotherapy versus platinum-based chemotherapy in the first-line treatment of patients with EGFR and ALK wild-type locally advanced or metastatic NSCLC. Estimated primary completion date is June 2018.
- **NCT02542293:** NEPTUNE is a randomised, open-label, multicentre study to assess the efficacy of durvalumab plus tremelimumab versus platinum-based chemotherapy in the first-line treatment of patients with EGFR and ALK wild-type advanced or metastatic NSCLC. Estimated primary completion date is October 2018.
- **NCT02352948:** ARCTIC is a randomised, open-label, multicentre study to evaluate the safety and efficacy of durvalumab monotherapy or in combination with tremelimumab determined by PD-L1 expression versus standard care in patients with locally advanced or

metastatic NSCLC. Estimated primary completion date is November 2017.

- **NCT03164616:** POSEIDON is a randomised, open-label, multicentre study to determine the efficacy of durvalumab or durvalumab plus tremelimumab in combination with platinum-based chemotherapy for first-line treatment of patients with metastatic NSCLC. Estimated primary completion date is July 2019.
- **NCT02273375:** ADJUVANT is a randomised, double-blind, placebo controlled study to find out whether it is better to receive durvalumab or to receive no further treatment following surgery and possibly chemotherapy for NSCLC that is PD-L1 positive. Estimated primary completion date is January 2025.
- **NCT02454933:** CAURAL is a randomised, open-label, multicentre study to assess the safety and efficacy of osimertinib in combination with durvalumab versus osimertinib monotherapy in patients with locally advanced or metastatic EGFR T790 mutation-positive NSCLC who have received prior EGFR tyrosine kinase inhibitor therapy. Estimated primary completion date is August 2017.

10 Discussion

FDA: licensed for MUC; granted priority review for NSCLC

EMA: MAA submitted for stage III NSCLC in October 2017

In May 2017, the FDA approved durvalumab, and a complementary diagnostic assay for PD-L1 expression (VENTANA PD-L1 (SP263) Assay), for treating locally advanced or MUC with disease progression following platinum-based chemotherapy. In July 2017, durvalumab was granted FDA-breakthrough therapy designation as consolidation therapy within 42 days after chemoradiotherapy for patients with stage III NSCLC whose disease had *not* progressed following platinum-based chemoradiotherapy [5]. In October 2017, durvalumab was granted priority review for a supplemental biologics license application based on PFS results from the phase III PACIFIC study [6]. Durvalumab does not currently have market authorisation in Europe for any indication. However, in October 2017, an MAA for durvalumab was submitted to the EMA for the treatment of patients with stage III, unresectable NSCLC whose disease had *not* progressed following platinum-based chemoradiotherapy [7, 8].

PACIFIC, a randomised, placebo-controlled phase III study compared the safety and efficacy of durvalumab (10 mg/kg IV every 2 weeks) versus matching placebo in 713 patients with stage III, unresectable NSCLC without progression following platinum-based chemoradiotherapy [3]. OS data were not mature at the time of interim analysis for PFS. Compared with placebo, durvalumab increased BICR-assessed median PFS by 11.2 months at a median follow-up of 14.5 months. The PFS benefit of durvalumab over placebo was observed irrespective of PD-L1 expression level prior to chemoradiotherapy or smoking status. BICR-assessed ORR was 28.4% for durvalumab versus 16.0% for placebo; while the median DOR was 13.8 months for placebo, it was not reached in the durvalumab group. Of those who responded to durvalumab, 72% had an ongoing response at 18-months, compared with 46.8% of placebo recipients, respectively. Durvalumab increased the TTDM by 9 months compared to placebo and lowered the incidence of new brain metastases by 5.5%.

PACIFIC: durvalumab increased PFS, ORR, TTDM compared to placebo

durvalumab increased median PFS +11.2 month irrespective of prior PD-L1 expression or smoking status

durvalumab response was durable at 12- and 18-months

Treatment-related AEs occurred in 68% of durvalumab recipients and 53.4% of placebo recipients. Durvalumab patients reported more immune-mediated AEs than placebo recipients (24% versus 8%), and required more high-dose glucocorticoids (8.2% versus 4.3%) and endocrine therapies (10.7% versus 1.3%) as treatment. Pneumonitis and pneumonia, the leading causes of discontinuation, were reported in 6.3% and 1.1% of durvalumab patients and 4.3% and 1.3% of placebo patients.

durvalumab resulted in immune-mediated AEs

Results of the PACIFIC study hold some limitations. The first interim analysis for the co-primary endpoint of OS will be conducted at the time of final analysis for PFS. Evaluating PFS, ORR, TTDM, and discontinuation data are useful outcomes in clinical trials; however, follow-up is insufficient to evaluate OS and potential antibody formation, and 14.3% of durvalumab patients required treatment for immune-mediated AEs. No evidence was reported regarding the effect of durvalumab on generic or disease-specific QoL. Generalizability of the results may be limited in that while the PACIFIC study participants were a median age of 64 years and had good performance status, the average age at diagnosis is 70 years, the clinical specificity in elderly patients with comorbidities, reduced functional reserve and immunosenescence may affect the efficacy and or toxicity of durvalumab. While study participants received durvalumab after concurrent chemoradiotherapy, it is not clear whether the same outcomes could be derived following sequential chemoradiotherapy.

PACIFIC: first phase III demonstrating benefit in PFS, ORR, TTDM; lack OS and QOL data, susceptibles

The clinical efficacy results of PACIFIC are consistent with phase I/II data from Study 1108 and ATLANTIC in that durvalumab monotherapy improves ORR and PFS in patients with squamous or non-squamous histology. However, in contrast to Study 1108 and ATLANTIC where higher PD-L1 expression conferred increased OS, PFS and ORR, the PFS and ORR benefits of durvalumab observed in PACIFIC occurred irrespective of baseline PD-L1 expression on tumour cells. While durvalumab may be an effective adjuvant therapy in stage III patients following chemoradiotherapy, further evaluation is needed regarding the relation between PD-L1 expression and response, and the mechanism of action between immunotherapy and chemoradiotherapy.

PACIFIC results contrast phase II data as PFS and ORR benefits of durvalumab occur irrespective of baseline PD-L1 expression

low risk of bias: randomised, double-blind, placebo-controlled, industry funded

The PACIFIC is a randomised, double-blind, placebo-controlled, trial with few methodological limitations. There is no risk of bias in the generation of randomisation sequence or allocation concealment. Patients were stratified by age, sex and smoking status, and block-randomised 2:1 to durvalumab versus placebo via a centralised interactive web-based/voice-based randomisation system. Efforts were made to minimise the time between randomisation and starting the drug. Patients, physicians and outcome assessors were blinded as the placebo was identical in appearance, study centre staff were blinded to allocation and only the dispensing pharmacist and the independent data monitoring committee were aware of unblinded data. Selective outcome reporting is unlikely as all outcomes were reported as specified in the protocol with the exception of QoL and immunogenicity. The risk of bias may be increased by industry involvement in the study design, data analysis and reporting, however, the overall risk of bias at the study level is low.

ESMO-MCBS original: 4 adapted: 3

Given the non-curative setting of durvalumab and the statistically significant primary endpoint PFS we applied form 2b of the ESMO-MCBS v1.1 in order to assess whether durvalumab satisfies the criteria for a "meaningful clinical benefit" (score 4 or 5). Both the original as well as the adapted version of the MCBS were applied [29-31]. The application of the ESMO-MCBS to the PACIFIC study resulted in a grade 4 and 3 in the original and the adapted version of the ESMO-MCBS, respectively (Table 3). Therefore, durvalumab only leads to a meaningful clinical benefit in the original scale, but not in the adapted framework. Differences in scores occur due to the higher implication of a plateau in the PFS curve and an improvement in the one year PFS in the original ESMO-MCBS. However, it needs to be taken into account that the calculation of the scores is only based on the analysis of the PACIFIC trial.

lack of comparative trials; results of durvalumab alone or combined with tremelimumab in first line will define use

While several studies are ongoing, trials are needed that directly compare the safety and efficacy of durvalumab with other immunotherapies such as nivolumab, pembrolizumab or atezolizumab, a PD-L1 antibody recently approved for pre-treated NSCLC irrespective of PD-L1 assessment. While comparison studies are lacking, cross-trial comparisons are cautioned due to differences in patient selection based on the different PD-L1 assays used across trials. The results of durvalumab alone or combined with tremelimumab, in first-line settings (NEPTUNE and MYSTIC) will define how durvalumab compares with pembrolizumab and nivolumab studies regarding first-line immunotherapy for advanced NSCLC.

estimate: US $15,000/month Austria: no price estimate available

The cost of durvalumab is approximately US$ 15,000 per month, or US $180,000 per year. Currently, there are no cost estimates for Europe. There are approximately 4,716 new cases of lung cancer being diagnosed each year in Austria, and at least one third have stage III, locally advanced disease at diagnosis.

Overall, PACIFIC is the first fully published phase III randomised, placebo-controlled trial to report that durvalumab increases PFS, ORR, DOR, and TTDM in patients with stage III NSCLC regardless of PD-L1 expression and histology, compared to placebo (at the time of interim analysis). While durvalumab provided durable PFS and ORR, OS and QoL data are awaited. Results from PACIFIC may hold limited external validity as participants are not entirely generalizable to clinical practice. Ongoing trials investigating durvalumab alone or in combination with tremelimumab are likely to inform how durvalumab compares with pembrolizumab and nivolumab as first-line immunotherapy for NSCLC. Further research is needed regarding the duration and timing of immunotherapy, the best regimen of chemoradiation for combination and patient selection for greatest benefit based on predictive markers of efficacy and resistance [35].

PACIFIC: first phase III RCT reporting benefit in PFS, ORR, DOR and TTDM in stage III NSCLC (interim analysis)

OS and QoL data is missing

further research is needed: e.g. duration and timing of immunotherapy

Table 3: Benefit assessment based on the original ESMO-MCBS v1.1 and the adapted ESMO-MCBS [29-31]

ESMO-MCBS	Active substance	Indication	Intention	PE	Form	MG-ST	Efficacy				Safety		AJ	FM
							MG months	*HR (95% CI)*	*Score calculation*	*PM*	*Toxicity*	*QoL*		
Adapted ESMO-MCBS	durvalumab	NSCLC	NC	OS & **PFS**[A]	2b	≤6 m	OS: NA **PFS: 11.2**[1]	OS: NA **PFS: 0.52 (0.42–0.65)**	HR ≤0.65 AND Gain ≥1.5 m	3	+3.8% grade 3–4 AEs, +5.6% discontinuation rate	NA	x	**3**
Original ESMO-MCBS	durvalumab	NSCLC	NC	OS & **PFS**[A]	2b	≤6 m	OS: NA **PFS: 11.2**[1]	OS: NA **PFS: 0.52 (0.42–0.65)**	HR ≤0.65 AND Gain ≥1.5 m	3	x	NA	+1[2]	**4**

Abbreviations: [A] = co-primary endpoints; AE = adverse event; AJ = Adjustments; CI = confidence interval; FM = final adjusted magnitude of clinical benefit grade; HR = hazard ratio; m = months; MG = median gain; NA = not available; NSCLC = non-small cell lung cancer; OS = overall survival; PE = primary endpoint; PFS = progression-free survival; PM = preliminary magnitude of clinical benefit grade; QoL = quality of life; ST = standard treatment

DISCLAIMER

The scores achieved with the ESMO Magnitude of Clinical Benefit Scale are influenced by several factors: by the specific evaluation form used, by the confidence interval (CI) of the endpoint of interest, and by score adjustments due to safety issues. Ad form: Every individual form measures a different outcome. The meaning of a score generated by form 2a is not comparable to the exact same score resulting from the use of form 2c. To ensure comparability, we report the form that was used for the assessment. Ad CI: The use of the lower limit of the CI systematically favours drugs with a higher degree of uncertainty (broad CI). Hence, we decided to avoid this systematic bias and use the mean estimate of effect. Ad score adjustments: Cut-off values and outcomes that lead to an up- or downgrading seem to be arbitrary. In addition, they are independent of the primary outcome and, therefore, a reason for confounding. Hence, we report the adjustments separately.

[1] results are based on interim analysis

[2] 1 level upgrade due to a long term plateau in the PFS curve and a ≥10% improvement in PFS at 1 year (+20.6%)

11 References

[1] European Network for Health Technology Assessment (EUnetHTA). HTA Core Model® for Rapid Relative Effectiveness Assessment of Pharmaceuticals.Version 3.0. 2013 [cited 2017-10-25]; Available from: http://meka.thl.fi/htacore/model/HTA%20Core%20Model%20for%20Rapid%20REA%20of%20Pharmaceuticals%203.0.pdf.

[2] U.S. Food and Drug Administation Drugs@FDA Imfinzi™ Label Information. 2017 [cited 2017-11-16];Available from: https://www.accessdata.fda.gov/drugsatfda_docs/label/2017/761069s000lbl.pdf.

[3] 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. New England Journal of Medicine. 2017;377:1919-29.

[4] Syed YY. Durvalumab: First Global Approval. Drugs. 2017;77(12):1369-76.

[5] AstraZeneca. Imfinzi granted breakthrough therapy designation by US FDA for patients with locally-advanced unresectable non-small cell lung cancer. 2017 [cited 2017-11-17];Available from: https://www.astrazeneca.com/media-centre/press-releases/2017/us-fda-accepts-supplemental-biologics-license-application-for-imfinzi-in-locally-advanced-unresectable-non-small-cell-lung-cancer-171017.html.

[6] RT for decision makers in respiratory care. FDA grants priority review to durvalumab for locally advanced unresectable NSCLC. 2017 [cited 2017-11-17];Available from: http://www.rtmagazine.com/2017/10/fda-priority-review-imfinzi-advanced-nsclc/.

[7] AstraZeneca. The European Medicines Agency accepts marketing authorisation application for imfinzi in locally-advanced unresectable non-small cell lung cancer. 2017 [cited 2017-11-17];Available from: https://www.astrazeneca.com/media-centre/press-releases/2017/the-european-medicines-agency-accepts-marketing-authorisation-application-for-imfinzi-in-locally-advanced-unresectable-non-small-cell-lung-cancer-09102017.html.

[8] European Medicines Agency. Applications for new human medicines under evaluation by the Committee for Medicinal Products for Human Use. 2017 [cited 2017-12-01];Available from: http://www.ema.europa.eu/docs/en_GB/document_library/Report/2017/10/WC500236155.pdf.

[9] National Cancer Institute. Non-Small Cell Lung Cancer Treatment. [cited 2017-11-22];Available from: https://www.cancer.gov/types/lung/hp/non-small-cell-lung-treatment-pdq/.

[10] National Cancer Institute. SEER Stat Fact Sheeets: Lung and Bronchus Cancer. [cited 2017-11-22];Available from: https://seer.cancer.gov/statfacts/html/lungb.html.

[11] Leventakos K, Mansfield AS. Advances in the Treatment of Non-small Cell Lung Cancer: Focus on Nivolumab, Pembrolizumab, and Atezolizumab. BioDrugs. 2016;30(5):397-405.

[12] Midthun D E. Overview of the initial evaluation, treatment and prognosis of lung cancer. In: Lilenbaum R C SSE, Vora S R, editor. UpToDate. Waltham, MA. (cited 20.11.2017): UpToDate; 2017.

[13] Seetharamu N, Budman DR, Sullivan KM. Immune checkpoint inhibitors in lung cancer: past, present and future. Future Oncol. 2016;12(9):1151-63.

[14] Doholaria B, Hammond W, Shreders A, Lou Y. Emerging therapeutic agents for lung cancer. Journal of Hematology & Oncology 2017;9(138).

[15] Statistik Austria. Krebserkrankungen-Luftrohre, Bronchien, Lunge. . 2014 [cited 2017-11-20];Available from: http://www.statistik.at/web_en/statistics/PeopleSociety/health/cancer_incidence/cancer_incidence_overview/index.html.

[16] Soria J-C, Tan D, Chiari R, Wu Y-L, Paz-Ares L, Wolf J. Firt-line ceritinib versus platinum-based chemotherapy in advanced ALK-rearranged non-small-cell lung cancer (ASCEND-4): a randomised, open-label, phase 3 study. Lancet. 2017;389(10072):917-29.

[17] Deng L, Liang H, Burnette B, Beckett M, Darga T, Weichselbaum R, et al. Irradiation and anti-PD-L1 treatment syntergistically promote antitumor immunity in mice. The Journal of Clinical Investigation. 2014;124(2):687-95.

[18] Dovedi S, Adlard AL, Lipowska-Bhalla G, McKenna C, Jones S, Cheadle E, et al. Acquired resistance to fractionated radiotherapy can be overcome by concurrent PD-L1 blockade. Cancer Research. 2014;74(19):5458-68.

[19] Zhang P, Su DM, Liang M, Fu J. Chemopreventive agents induce programmed death-1-ligand 1 (PD-L1) surface expression in breast cancer cells and promote PD-L1-mediated T cell apoptosis. Molecular Immunology. 2008;45(5):1470-6.

[20] Garassino M, Cho B, Gray J. Durvalumab in ≥3rd-line EGFR mutant/ALK+, locally advanced or metastatic NSCLC: results from the phase 2 ATLANTIC study. 2017;ELCC (Abstract #820). Geneva Available from: http://oncologypro.esmo.org/Meeting-Resources/ELCC-2017/Durvalumab-in-3rd-line-EGFR-mutant-ALK-locally-advanced-or-metastatic-NSCLC-Results-from-the-phase-2-ATLANTIC-study.

[21] Antonia SJ, Villegas A, Daniel D, Vicente D, Murakami S, Hui R, et al. A phase III, randomised, double-blind, placebo-controlled, multicentre, international study of MED14736 as sequential therapy in patients with locally advanced, unresectable non-small cell lung cancer (stage III) who have not progressed following definitive, platinum-based, concurrent chemoradiation therapy (PACIFIC)-Protocol New England Journal of Medicine. 2017;377.

[22] Antonia S, Villegas A, Daniel D, al. e. Supplementary Appendix to: Antonia S, Villegas A, Daniel D et al. Durvalumab after chemoradiotherapy in stage III non-small cell lung cancer. . New England Journal of Medicine. 2017;DOI: 10.1056/NEJMoa1709937.

[23] The Economist. Cancer drugs are getting better and dearer. 2017 [cited 2017-11-28];Available from: https://www.economist.com/news/business/21721676-astrazenecas-imfinzi-costs-180000-years-treatment-cancer-drugs-are-getting-better-and.

[24] Reuters. BRIEF-AstraZeneca's durvalumab average monthly cost around $15,000. 2017 [cited 2017-11-28];Available from: https://www.reuters.com/article/brief-astrazenecas-durvalumab-average-mo/brief-astrazenecas-durvalumab-average-monthly-cost-around-15000-idUSL8N1I32KY.

[25] Antonia SJ, Brahmer JR, Khleif S, Balmanoukian AS, Ou SHI, Gutierrez M, et al. Phase 1/2 study of the safety and clinical activity of durvalumab in patients with non-small cell lung cancer (NSCLC). Annals of Oncology. 2016;27((Antonia S.J.) Department of Thoracic Oncology, Moffitt Cancer Center, Tampa, United States).

[26] Antonia SJ, Kim SW, Spira AI, Ahn MJ, Ou SHI, Stjepanovic N, et al. Safety and clinical activity of durvalumab (MEDI4736), an anti-PD-LI antibody, in treatment-naive patients with advanced non-small-cell lung cancer. Journal of Clinical Oncology. 2016;34.

[27] Garassino M, Vansteenkiste J, Kim JH, Léna H, Mazières J, Powderly J, et al. Durvalumab in ≥3rd-line locally advanced or metastatic, EGFR/ALK wild-type NSCLC: Results from the phase 2 atlantic study. Journal of Thoracic Oncology. 2017;12(1):S10-S1.

[28] EUnetHTA - European network for Health Technology Assessment. Internal validity of randomized controlled trials 2013 [cited 2017-10-25]; Available from: https://eunethta.fedimbo.belgium.be/sites/5026.fedimbo.belgium.be/files/Internal_Validity.pdf.

[29] Cherny NI, Dafni U, Bogaerts J, Latino NJ, Pentheroudakis G, Douillard JY, et al. ESMO-Magnitude of Clinical Benefit Scale version 1.1. Annals of Oncology. 2017;28(10):2340-66.

[30] Cherny NI, Sullivan R, Dafni U, Kerst JM, Sobrero A, Zielinski C, et al. A standardised, generic, validated approach to stratify the magnitude of clinical benefit that can be anticipated from anti-cancer therapies: The European Society for Medical Oncology Magnitude of Clinical Benefit Scale (ESMO-MCBS). Annals of Oncology. 2015;26(8):1547-73.

[31] Wild C, Grössmann N, Bonanno PV, Bucsics A, Furst J, Garuoliene K, et al. Utilisation of the ESMO-MCBS in practice of HTA. Annals of Oncology. 2016;27(11):2134-6.

[32] Ferrara R, Mezquita L, Auclin E, Chaput N, Besse B. Immunosenescence and immunecheckpoint inhibitors in non-small cell lung cancer patients: Does age really matter? Cancer Treatment Reviews. 2017;60:60-8.

[33] Sgambato A, Cassaluce F, Gridelli C. The role of checkpoint inhibitors immunotherapy in advanced non-small cell lung cancer in the elderly. Expert Opin Biol Ther. 2017:1-7.

[34] Garassino MC, Barlesi F, Chaft J, Shi K, Ibrahim R, Stockman P, et al. Phase 2 study of medi4736 in patients with PD-l1+ locally advanced or metastatic stage IIIb-IV NSCLC treated with ≥ 2 prior regimens (atlantic). Journal of Thoracic Oncology. 2015;10(9):S429.

[35] Jeanson A, Barlesi F. MEDI 4736 (durvalumab) in non-small cell lung cancer. Expert Opin Biol Ther [Internet]. 2017 [cited YES:[1-7 pp.]. Available from: http://onlinelibrary.wiley.com/o/cochrane/clcentral/articles/361/CN-01394361/frame.html.

12 Appendix

Table 4: Characteristics of the PACIFIC trial

Title: Durvalumab after chemoradiotherapy in stage III NSCLC [3, 22]			
Study identifier	NCT02125461, D4191C00001, EudraCT 2014-000336-42, PACIFIC		
Design	International (26 countries), multicentre (235 centres), randomized, double-blind, placebo-controlled, phase III		
	Duration of main phase:		May 2014-April 2016: 709 of 713 patients randomized received at least one dose of study drug (n=473 durvalumab, n=236 placebo) Interim analysis data cut-off: February 13, 2017 when 371 patients had disease progression (n=214 durvalumab, n=157 placebo) Overall median follow-up: 14.5 months (range 0.2–29.9)
	Duration of Run-in phase:		Not applicable, patients randomly assigned within 1–42 days after chemoradiotherapy
	Duration of Extension phase:		Not applicable
Hypothesis	Interventional The study was designed to evaluate the efficacy and safety of durvalumab compared with placebo as consolidation therapy following concurrent chemoradiation in patients with stage III unresectable NSCLC		
Funding	AstraZeneca		
Treatments groups	Durvalumab (n=476 ITT, n=475 safety population)		10 mg/kg IV, infused over 60 minutes, every 2 weeks as consolidation therapy for up to 12 months
	Placebo (n=237, n=234 safety population)		10 mg/kg IV, infused over 60 minutes, every 2 weeks as consolidation therapy for up to 12 months
	Overall survival (co-primary endpoint)	OS	Time from date of randomization until death due to any cause (baseline to 5 years)
	Progression free survival (co-primary endpoint)	PFS	Time from randomization until date of objective disease progression (RECIST 1.1 assessed by BIRC and investigators) or death by any cause in the absence of progression (baseline to 5 years)
	Overall survival at 24 months (secondary endpoint)	OS24	The number (%) of patients who are alive at 24 months after randomization per the Kaplan-Meier estimate of OS at 24 months (baseline to 5 years)
	Duration of response (secondary endpoint)	DOR	Time from date for first documented response of CR or PR until the first documented response of progression (BIRC-assessed RECIST 1.1) or death in the absence of progression (to 3 years)
	Objective response rate (secondary endpoint)	ORR	The number (%) of patients with at least one visit response of CR or PR (BIRC-assessed RECIST 1.1 to 3 years)
	Proportion alive and progression free at 12 months (secondary endpoint)	APF12	The number (%) of patients who are alive and progression free (BIRC-assessed RECIST 1.1 at 12 months after randomization per Kaplan-Meier estimate of PFS at 12 months to 3 years)
	Proportion alive and progression free at 18 months (secondary endpoint)	APF18	The number (%) of patients who are alive and progression free (BIRC-assessed RECIST 1.1 at 18 months after randomization per Kaplan-Meier estimate of PFS at 18 months to 3 years)
	Time to death or distant metastasis (secondary endpoint)	TTDM	Any new lesion that is outside of the radiation field (BIRC-assessed to 5 years)
	Safety, adverse events	AE	Incidence of adverse events and according to CTCAE (v4.03)
Database lock	Last verified June 2017		

Title: Durvalumab after chemoradiotherapy in stage III NSCLC [3, 22]				
Study identifier	NCT02125461, D4191C00001, EudraCT 2014-000336-42, PACIFIC			
Results and Analysis				
Analysis description	**Primary Analysis** ITT: interim analysis of PFS was planned at approximately 367 events. At interim analysis, 371 patients had disease progression (214 durvalumab, 157 placebo), median follow-up of 14.5 months. At interim analysis, the HR for disease progression or death was estimated using Kaplan-Meier. Between-group comparisons were performed using log-rank test, stratified by age, sex, and smoking history. Sensitivity analyses included assessment of evaluation bias, evaluation-time bias, and attrition bias in the determination of disease progression and adjustment for covariates in the estimating the HR for disease progression or death. A pre-planned analysis of PFS in 35 pre-specified subgroups was performed in which HR and 95% CI were calculated using an un-stratified Cox regression model. There was no multiplicity adjustment as the subgroup analysis was intended to show consistency of the treatment effect. Response rates were estimated using Clopper-Pearson and compared with Fisher's exact test. Type I error was controlled for the co-primary endpoints and key secondary endpoint ORR, but not for other secondary endpoints. Efficacy was assessed in the ITT population, and safety was assessed in the as-treated population. An external independent data and safety monitoring committee is assessing safety in an ongoing analysis.			
Analysis population	Inclusion	❁ Age ≥18 years ❁ Documented evidence of NSCLC (locally advanced, unresectable, stage III) ❁ Patients must have received ≥2 cycles of platinum-based chemotherapy concurrent with radiation therapy ❁ WHO Performance Status of 0 to 1 ❁ Estimated life expectancy of >12 weeks		
	Exclusion	❁ Prior exposure to any atni-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 (e.g. Crohn's disease, ulcerative colitis)		
	Characteristics	Durvalumab (n = 476)	Placebo (n = 237)	Total (n = 713)
	Median age (range), years Age ≥65 years, n (%)	64 (31–84) 215 (45.2)	64 (23–90) 107 (45.1)	64 (23–90) 322 (45.2)
	Male sex, n (%)	334 (70.2)	166 (70.0)	500 (70.1)
	Race, n (%) Caucasian African American Asian Other NR	 337 (70.8) 12 (2.5) 120 (25.2) 6 (1.3) 1 (0.2)	 157 (66.2) 2 (0.8) 72 (30.4) 6 (2.5) 0	 494 (69.3) 14 (2.0) 192 (26.9) 12 (1.68) 1 (0.1)
	Disease stage, n (%) IIIA IIIB Other‡	 252 (52.9) 212 (44.5) 12 (2.5)	 125 (52.7) 107 (45.1) 5 (2.1)	 377 (52.9) 319 (44.7) 17 (2.4)
	WHO performance score, n (%) 0 1 NR	 234 (49.2) 240 (50.4) 2 (0.4)	 114 (48.1) 122 (51.5) 1 (0.4)	 348 (48.8) 362 (50.8) 3 (0.4)
	Tumour histology, n (%) Squamous Non-squamous	 224 (47.1) 252 (52.9)	 102 (43.0) 135 (57.0)	 326 (45.7) 387 (54.3)
	PD-L1 status, n (%) TC <25% TC ≥25% Unknown	 187 (39.3) 115 (24.2) 174 (36.6)	 105 (44.3) 44 (18.6) 88 (37.1)	 292 (83.6) 159 (42.8) 262 (73.7)

Title: Durvalumab after chemoradiotherapy in stage III NSCLC [3, 22]				
Study identifier	NCT02125461, D4191C00001, EudraCT 2014-000336-42, PACIFIC			
Analysis population *(continuation)*	EGFR mutation status, n (%)			
	Positive	29 (6.1)	14 (5.9)	43 (12.0)
	Negative	315 (66.2)	165 (69.6)	480 (135.8)
	Unknown	132 (27.7)	48 (24.5)	180 (52.2)
	Smoking status, n (%)			
	Current smoker	79 (16.6)	38 (16.0)	117 (16.4)
	Former smoker	354 (74.4)	178 (75.1)	532 (74.6)
	Never smoked	43 (9.0)	21 (8.9)	64 (9.0)
	Previous radiotherapy, n (%)			
	<54 Gy	3 (0.6)	0 (0)	3 (0.4)
	≥54 to ≤66 Gy	442 (92.9)	217 (91.6)	659 (92.4)
	>66 to ≤74 Gy	30 (6.3)	19 (8.0)	49 (6.9)
	>74 Gy	0 (0)	0 (0)	0 (0)
	Missing data	1 (0.2)	1 (0.4)	2 (0.3)
	Previous chemotherapy, n (%)			
	Adjuvant	3 (0.6)	1 (0.4)	4 (0.6)
	Induction	123 (25.8)	68 (28.7)	191 (26.8)
	Concurrent with radiation	475 (99.8)	236 (99.6)	711 (99.7)
	Prior chemotherapy regimen, n (%)	266 (55.9)	129 (54.4)	395 (55.4)
	Cisplatin-based	199 (41.8)	102 (43.0)	301 (42.2)
	Carboplatin-based			
	Best response to previous chemo-radiotherapy, n (%)			
	Complete response	9 (1.9)	7 (3.0)	16 (2.2)
	Partial response	232 (48.7)	111 (46.8)	343 (48.1)
	Stable response	222 (46.6)	114 (48.1)	336 (47.1)
	Progression	2 (0.4)	0 (0)	2 (0.3)
	Non-evaluable	9 (1.9)	4 (1.7)	13 (1.8)
	Non-applicable	2 (0.4)	1 (0.4)	3 (0.4)

Abbreviations: APF12 = alive and progression free at 12 months; APF18 = alive and progression free at 18 months; BICR = blinded independent central review; CR = complete response; CTCAE = Common Terminology Criteria for Adverse Events; DOR = duration of response; EGFR = epidermal growth factor receptor; HR = hazard ratio; ITT = intent-to-treat; IV = intravenous; NR = not reported; NSCLC = non-small cell lung cancer; ORR = objective response rate; OS = overall survival; PD-L1 = programmed cell death ligand-1; PFS = progression free survival; PR = partial response; RECIST = Response evaluation Criteria in Solid Tumours; TC = tumour cell; TTMD = time to death or distant metastasis; WHO = World Health Organization, ‡Patients with other disease stages included 12 patients in the durvalumab group (4 with stage IV, 4 with stage IIB, 3 with stage IIA, and 1 with stage IA), and 4 patients in the placebo group (2 with stage IIB, 1 with stage IIA, and 2 with stage IB)

Table 5: Risk of bias assessment on study level is based on EUnetHTA (Internal validity of randomised controlled trials) [28]

Criteria for judging risk of bias		Risk of bias
Adequate generation of randomisation sequence: block-randomised 2:1 durvalumab versus placebo via centralised interactive web-based and voice-based randomisation system; stratified by age (<65 vs ≥65 years) sex, and smoking history (current or former smoker vs never smoked)		no
Adequate allocation concealment: actual study drug given was determined by the centralised randomisation service that incorporates a standard procedure for generating randomisation; numbers; efforts made to minimise time between randomisation and starting study drug; unique code numbers matched kits used only once		no
Blinding	**Patient:** blinded to study drug allocation; centralised randomisation.	no
	Treating physician: placebo was identical in colour and the IV bags for administration were identical in size; study drug was blinded using an opaque sleeve with tamper evident tape over the IV bag prior to dispensing; blinded to drug allocation except for pharmacist preparing study drug.	no
	Outcome assessment: study centre staff blinded to study drug allocation; investigational centres will not have access to randomisation scheme until final data analysis; pharmacists required to dispense study drug at study site; treatment codes kept within industry to safeguard integrity of the blind; IDMC will be provided with un-blinded data for their review.	no
Selective outcome reporting unlikely: with the exception of QoL, pharmacokinetic characteristics, and immunogenicity, outcomes reported as specified in protocol; withdrawals and drop-outs reported		no
No other aspects that increase the risk of bias: study designed by industry and academic advisors; sponsor completed data analyses; authors had full access to the data; sponsor funded medical writing		yes
Risk of bias – study level		low

Abbreviations: IDMC = independent data monitoring committee; QoL = quality of life