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Atezolizumab (Tecentriq®) in previously treated non-small cell lung cancer (NSCLC)

Ludwig Boltzmann Institut
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Abstract

Introduction

Non-small cell lung cancer (NSCLC) arises when epithelial cells lining the bronchial tubes undergo aberrant cell growth. The US Food and Drug Administration (FDA) recently approved atezolizumab for the treatment of patients with metastatic NSCLC, whose disease progressed during or following platinum-based chemotherapy. Patients who progress following treatment for epidermal growth factor receptor (EGFR) or anaplastic lymphoma kinase (ALK) genomic tumour aberrations may also receive atezolizumab. By inhibiting the programmed death ligand 1 (PD-L1), atezolizumab enables T-cell activation, restoring their ability to effectively detect and destroy 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 atezolizumab was evaluated based on, both the original and an adapted version of, the Magnitude of Clinical Benefit Scale (MCBS) developed by the European Society for Medical Oncology (ESMO).

Results of the OAK trial

Between 11 March 2014 and 29 April 2015, an intent-to-treat (ITT) population of 425 patients was randomly assigned to receive either atezolizumab (n = 425) or docetaxel (n = 425). Atezolizumab increased the primary endpoint of overall survival (OS) in the ITT population by 4.2 months and duration of response (DOR) by 10.1 months, compared with docetaxel. Patients with higher PD-L1 expression derived the greatest improvement in median OS (+ 11.6 months) with atezolizumab, 20.5 months versus 8.9 months with docetaxel. Atezolizumab did not improve progression-free survival (PFS) or the proportion of patients with an objective response (OR) compared with docetaxel. While fewer patients had treatment-related AEs with atezolizumab compared to docetaxel, clinically significant immune-related AEs were reported including pneumonitis, hepatitis, colitis and thyroid disease.

Conclusion

Overall, with the exception of those with EGFR mutations, atezolizumab increases OS and DOR in previously treated NSCLC patients regardless of PD-L1 expression or histology, with a favourable safety profile compared to docetaxel. There is no evidence regarding quality of life, patient reported outcome measures or patient reported experience measures to determine whether atezolizumab provides clinically significant improvement in the symptoms or severity of NSCLC. Results from OAK hold limited external validity as participants are not entirely generalizable to clinical practice. Longer trials are needed that directly compare the safety and efficacy of atezolizumab versus other immunotherapies such as nivolumab or pembrolizumab, or docetaxel in combination with nintedanib or ramucirumab.

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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 atezolizumab?
A0022	Who manufactures atezolizumab?
A0007	What is the target population in this assessment?
A0020	For which indications has atezolizumab 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 atezolizumab on mortality?
D0005	How does atezolizumab affect symptoms and findings (severity, frequency) of NSCLC?
D0006	How does atezolizumab affect progression (or recurrence) of NSCLC?
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D0012	What is the effect of atezolizumab on generic health-related quality of life?
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Safety	
C0008	How safe is atezolizumab in relation to the comparator(s)?
C0002	Are the harms related to dosage or frequency of applying atezolizumab?
C0005	What are the susceptible patient groups that are more likely to be harmed through the use of atezolizumab?
A0021	What is the reimbursement status of atezolizumab?

2 Drug description

Generic/Brand name/ATC code:

Atezolizumab/Tecentriq®/MPDL3280A

B0001: What is atezolizumab?

anti-PD-L1 antibody, immune checkpoint inhibitor

Up-regulation of the programmed death ligand 1 (PD-L1) in patients with haematological malignancies and solid tumours increases the propensity for cancer cells to evade immune surveillance. Atezolizumab, a monoclonal antibody, is an immune checkpoint inhibitor. By inhibiting PD-L1, atezolizumab enables T-cell activation, restoring their ability to effectively detect and destroy tumour cells [2].

1,200 mg IV over 60 minutes every 3 weeks

Atezolizumab is available in 1,200 mg/20 mL (60 mg/mL) single-use vials. It is administered as an intravenous infusion over 60 minutes, at a fixed dose of 1,200 mg, every three weeks until disease progression or unacceptable toxicity [2].

A0022: Who manufactures atezolizumab?

Genentech Inc, a subsidiary of F Hoffmann-La Roche Ltd

3 Indication

A0007: What is the target population in this assessment?

previously treated NSCLC patients

Atezolizumab is indicated for previously treated non-small cell lung cancer (NSCLC) patients.

4 Current regulatory status

A0020: For which indications has atezolizumab received marketing authorisation?

FDA: licensed for locally advanced or MUC in May 2016

In May 2016, the US Food and Drug Administration (FDA) issued accelerated approval of atezolizumab for the treatment of patients with locally advanced or metastatic urothelial carcinoma (MUC) with disease progression during or following platinum-based chemotherapy, or within 12 months of neoadjuvant or adjuvant treatment with platinum-based chemotherapy [2].

In October 2016, the US FDA approved atezolizumab for the treatment of patients with metastatic NSCLC whose disease progressed during or following platinum-based chemotherapy. Patients with epidermal growth factor receptor (EGRF) or anaplastic lymphoma kinase (ALK) genomic tumour aberrations who progress following prior therapy for these aberrations may also receive atezolizumab [2].

FDA: licensed for metastatic NSCLC in October 2016

Atezolizumab does not currently have marketing authorisation in Europe for any indication.

EMA: currently not authorised

5 Burden of disease

A0002: What is NSCLC?

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%), adenocarcinoma (40%) and large cell carcinoma (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 [3, 4]. Adenocarcinoma and large cell carcinoma are typically peripherally located and have survival rates of approximately 5–6% at 5 years. A subset of approximately 7–35% of NSCLC patients has driver gene alterations in EGRF or ALK. 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 [5].

NSCLC accounts for 80–85% of all lung cancers

EGFR + ALK alterations in 7–35% of NSCLC patients

A0004: What is the natural course of NSCLC?

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 [3, 6].

staged I–IV by invasiveness

metastasize to bone, liver, brain, lymph nodes

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

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. Patient prognosis is poor due to the high rate of relapse and early formation of micro-metastases [7].

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

A0023: How many people belong to the target population?

4,716 Austrians were diagnosed with NSCLC in 2014

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 2013. In Austria, 2,894 men and 1,822 women were newly diagnosed with lung cancer in 2014; and 3,908 men and 2,450 women died due to lung cancer (47.3 per 100,000 persons per year) [8]. Approximately 6.5% of people will be diagnosed with lung cancer during their lifetime and at least a third of newly diagnosed patients have distant metastases. The average age at diagnosis is approximately 70 years [4].

average age at diagnosis ~70 years

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 [3].

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 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 [3].

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 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) and molecular tests 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 EGRF or ALK genes. PD-L1 expression on tumour cells and tumour-infiltrating immune cells can be assessed using the Ventana PD-L1 (SP142) IHC assay [6].

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.

- Stage I and II NSCLC patients typically undergo surgery to remove the cancer. Stage II patients may benefit from postoperative adjuvant chemotherapy or radiation therapy.
- 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.

Docetaxel: preferred chemotherapy

targeted therapies

immunotherapies

- Docetaxel is the preferred chemotherapy agent for squamous NSCLC and for non-squamous NSCLC patients previously treated with pemetrexed.
- Ramucirumab may be used concurrently, when treating with docetaxel, for patients with a good performance status [6].
- The molecular characterization of tumour tissue in NSCLC patients may guide treatment in those with metastatic disease or relapse following primary therapy [6]. NSCLC patients with driver gene alterations in EGFR or ALK may benefit from tyrosine kinase inhibitors such as erlotinib, gefitinib, afatinib or crizotinib. Afatinib is indicated as second-line treatment for patients with squamous NSCLC based on improved OS and PFS compared with erlotinib [9]. Patients with advanced disease without EGFR or ALK mutations may receive antibody therapy with bevacizumab targeted against the vascular endothelial growth factor (VEGF).
- Pembrolizumab and nivolumab block PD-L on T lymphocytes and are used as second-line therapies for advanced NSCLC. Nivolumab is used for the treatment of patients with advanced squamous NSCLC and non-squamous NSCLC who experience progression on or after standard platinum-chemotherapy regardless of PD-L1 protein expression. Pembrolizumab is used in previously treated advanced NSCLC that expresses PD-L1 [6].

7 Evidence

systematic literature search in 5 databases: 92 hits

A literature search was conducted on 13 March 2017 in five databases: the Cochrane Library, CRD Database, Embase, Ovid Medline and PubMed. Search terms were “Atezolizumab”, “Tecentriq”, “MPDL3280A”, “NSCLC” and “non-small cell lung cancer”. The manufacturer was also contacted and submitted nine references (seven of which had already been identified by systematic literature search). A manual search yielded two FDA approval documents [2, 10], six clinical guidance documents [3, 5-7, 11], two statistical documents [4, 8], and a cost editorial [12]. Ongoing trials information was found on clinicaltrials.gov. Overall, 105 references were identified.

A phase II and three phase III studies contributed to the evidence regarding efficacy and safety of atezolizumab for pre-treated NSCLC patients.

Included in this reported are:

included: 4 studies

- OAK, phase III [13-15]
- POPLAR, phase II [16-18]
- FIR, phase II [19], and
- BIRCH, phase II [20, 21]

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 RCTs [22, 23]. 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) was used [24]. Additionally, an adapted version (due to perceived limitations) of the ESMO-MCBS was applied [25]. Details of the magnitude of the clinically meaningful benefit scale are reported in Table 3.

7.1 Clinical efficacy and safety – Phase III studies

OAK: atezolizumab versus docetaxel in 1,225 previously treated NSCLC patients; ITT = 850

OAK (NCT02008227) [13] is an open-label, randomized, phase III multicentre study involving 1,225 NSCLC patients who progressed following platinum-based chemotherapy. The primary analysis population comprised the first 850 randomized patients; the remaining 375 patients enrolled contributed to the final safety population of 1,225 patients.

Inclusion criteria were stage IIIB or IV squamous or non-squamous NSCLC, age ≥18 year, with measurable disease per Response Evaluation Criteria in Solid Tumours (RECIST; version 1.1) and Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1. Patients with EGFR or ALK aberrations must have received previous tyrosine kinase inhibitor therapy. Patients with a history of autoimmune disease and those previously treated with docetaxel, CD137 agonists, anti-CTLA4, PD-L- or PD-L1-targeted therapies were excluded. Tumour specimens were evaluated prospectively for PD-L1 expression on tumour cells (TC) and tumour-infiltrating immune cells (IC) using the Ventana PD-L1 (SP142) IHC assay. Eligible patients were stratified by PD-L1 expression status, number of prior chemotherapy regimens and histology.

ITT stratified by PD-L1 expression, prior chemotherapy and histology

Patients were randomized 1:1 to receive either atezolizumab 1,200 mg or docetaxel 75 mg/m^2 intravenously over 60 minutes every three weeks until unacceptable toxicity or disease progression. Approximately 609 (21% of) atezolizumab recipients and 578 (2% of) docetaxel recipients had a treatment duration longer than 12 months. Median treatment duration was 3.4 months with atezolizumab and 2.1 months with docetaxel.

Atezolizumab 1,200 mg vs docetaxel 75 mg/m^2 IV every 3 weeks

The primary endpoint was overall survival (OS) compared between treatment groups within the intention-to-treat (ITT) and the PD-L1 TC1/2/3 or IC1/2/3 populations. TC1/2/3 or IC1/2/3 was defined as PD-L1 expression on ≥1% of TC or IC; TC2/3 or IC2/3 was defined as PD-L1 expression on 5% of cells; TC3 was defined as PD-L1 expression on ≥ 50% of tumour cells and IC3 as ≥10% of tumour-infiltrating immune cells; and TC0 as PD-L1 expression on ≤1% of tumour infiltrating immune cells [13]. Secondary endpoints included investigator-assessed objective response rates (ORR), progression-free survival (PFS), duration of response (DOR) and safety. Tumours were assessed every 6 weeks for the first 36 weeks and every 9 weeks thereafter. Patients were followed-up for survival while receiving treatment and every 3 months following treatment discontinuation. The median follow-up was 21 months at the time of primary analysis.

endpoints: OS in ITT and PD-L1 expressing populations, PFS, ORR, DOR and safety

The ITT population (n = 850) had a median age of 64 years (range 33 to 85), 61% were male, 70% were Caucasian, 75% had received one prior platinum-based chemotherapy and 25% had received two prior therapies. Baseline ECOG performance status was 0 (37%) or 1 (63%). Approximately 74% of patients had non-squamous NSCLC, 10% had EGFR mutations, 0.2% had ALK aberrations, and 82% were current or previous smokers. Of the 850 patients, 16% were classified as having high PD-L1 expression (TC3 and IC3). Detailed patient characteristics including inclusion and exclusion criteria are reported in Table 4 of the appendix while study quality is reported in Table 5 of the appendix. Clinical efficacy data are presented in Table 1; adverse events (AEs) are presented in Table 2.

ITT: 75% non-squamous, 82% smokers, 75% had one prior chemotherapy, 16% high PD-L1 expression

7.1.1 Clinical efficacy

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

Atezolizumab improved OS, regardless of histology or PD-L1 expression in both the ITT and TC1/2/3 or IC1/2/3 populations compared with docetaxel. At primary analysis, median follow-up of 21 months, 271 (64% of) atezolizumab recipients and 298 (70% of) docetaxel recipients had died. Median OS in the ITT population was 13.8 months for atezolizumab versus 9.6

median OS in the ITT: 13.8 months for atezolizumab vs 9.6 months for docetaxel

months for docetaxel (HR 0.73 [95% CI 0.62–0.87]; p = 0.0003). In the TC1/2/3/ or IC1/2/3 population, 151 (63% of 241) atezolizumab recipients and 149 (67% of 222) docetaxel recipients had died. Median OS was 15.7 months with atezolizumab versus 10.3 months with docetaxel (HR 0.74 [95% CI 0.58–0.93]; p = 0.0102) in the TC1/2/3/ or IC1/2/3 population [13].

median OS in the PD-L1 expressing population: 20.5 months for atezolizumab vs 8.9 months for docetaxel

Atezolizumab recipients with high PD-L1 expression (TC3 or IC3) derived the greatest benefit, with a median OS of 20.5 months versus 8.9 months in docetaxel recipients (HR 0.41 [95% CI 0.27–0.64; p < 0.0001]). Patients in the low or undetectable subgroup TC0 and IC0 also had improved survival with atezolizumab (median OS 12.6 months versus 8.9 months; HR 0.75 [95% CI 0.59–0.96]; p = 0.0215). Compared with docetaxel (n = 110), atezolizumab (n = 112) improved median OS in both squamous (n = 313, HR 0.73 [95% CI 0.54–0.98]; p = 0.0383) and non-squamous (docetaxel n = 315, atezolizumab n = 313; HR 0.73 [95%CI 0.60–0.89]; p = 0.0015) NSCLC patients [13, 15]. HRs of OS were also in favour of atezolizumab in the predefined subgroups of patients treated with CNS metastases and never smokers (HR 0.54 [95% CI 0.31–0.94] and HR 0.71, [95% CI 0.47–1.08], respectively).

OS benefit consistent across subgroups: histology, CNS metastases, never smokers

NO benefit for patients with EGFR mutation

In contrast, no statistically significant difference in OS was found between groups in patients with EGFR mutations. The median OS for patients with EGFR mutation was 10.5 months in the atezolizumab group vs 16.2 months in the docetaxel group (HR 1.24 [95% CI 0.71–2.18]) [13].

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

PFS similar between treatment groups

No statistically significant difference in PFS was found between treatment groups in the ITT or the TC1/2/3 or IC1/2/3 populations. At primary analysis, 380 (89% of) atezolizumab recipients and 375 (88% of) docetaxel recipients achieved PFS. Median PFS was 2.8 months for atezolizumab versus 4.0 months for docetaxel (HR 0.95 [95% CI 0.82–1.10]; p = 0.49) [13, 14]. Subpopulation analysis showed that the TC3 or IC3 group demonstrated a greater PFS with atezolizumab than docetaxel (HR 0.63 [95% CI 0.43–0.91]; p = 0.0123) [13].

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

ORR similar between treatment groups

No statistically significant difference in ORR was found between treatment groups in the ITT or the TC1/2/3 or IC1/2/3 populations. However, atezolizumab recipients in the ITT population derived longer DOR than docetaxel recipients (16.3 months versus 6.2 months). Responses are ongoing in 30 (52%) of 58 atezolizumab recipients and 10 (18%) of 57 docetaxel recipients [13]. According to subgroup analysis, the proportion of patients with an objective response (OR) improved with atezolizumab versus docetaxel in the TC3 or IC3 group (22/72 patients versus 7/65 patients); lowest for TC0 and IC0 patients (14/180 patients versus 21/199 patients). DOR improvement with atezolizumab versus docetaxel was similar in all PD-L1 expression subgroups [13].

median DOR in the ITT: 16.3 months for atezolizumab vs 6.2 months for docetaxel

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

Atezolizumab may affect body functions by causing immune-mediated adverse events including pneumonitis, hepatitis, colitis, hypothyroidism, hyperthyroidism, pneumonia and infections. The use of therapeutic proteins may result in immunogenicity. Among 135 patients in OAK, 73 (54%) tested positive for treatment-induced anti-therapeutic antibodies (ATA) at one or more post-dose time points. The presence of ATAs did not have a clinically significant impact on pharmacokinetics, safety or efficacy [2].

immune-mediated AEs, immunogenicity

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

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

no evidence: generic health-related QoL

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

No evidence was found regarding the effect of atezolizumab on disease-specific QoL.

no evidence: disease-specific QoL

Table 1: Efficacy results of OAK [13-15]

Descriptive statistics and estimate variability	Treatment group	Atezolizumab	Docetaxel
	Number of subjects	n = 425	n = 425
	Median OS, months (95% CI)		
	ITT	13.8 (11.8–15.7)	9.6 (8.6–11.2)
	TC1/2/3 or IC1/2/3	15.7 (12.6–18.0); n = 241	10.3 (8.8–12.0); n = 222
	TC3 or IC3	20.5 (17.5–NE)	8.9 (5.6–11.6)
	TC0 and IC0	12.6 (9.6–15.2)	8.9 (7.7–11.5)
	Squamous	8.9 (7.4–12.8)	7.7 (6.3–8.9)
	Non-squamous	15.6 (13.3–17.6)	11.2 (9.3–12.6)
	CNS metastases	20.1 (NR)	11.9 (NR)
	Never smokers	16.3 (NR)	12.6 (NR)
	EGFR mutation positive	10.5 (NR)	16.2 (NR)
	PFS events (%)		
	ITT	380 (89)	375 (88)
	TC1/2/3 or IC1/2/3	216/241 (90)	193/222 (87)
	Median PFS, months (95% CI)		
	ITT	2.8 (2.6–3.0)	4.0 (3.3–4.2)
	TC1/2/3 or IC1/2/3	2.8 (2.6–4.0)	4.1 (2.9–4.3)
	TC3 or IC3	4.2 (2.9-7.0)	3.3 (2.7-4.2)
	ORR (%)		
	OR ITT	58 (14)	57 (13)
	OR TC1/2/3 or IC1/2/3	43/241 (18)	36/222 (16)
	Median DOR, months (95% CI)		
	ITT	16.3 (10.0–NE)	6.2 (4.9–7.6)
	TC1/2/3 or IC1/2/3	16.0 (9.7–NE)	6.2 (4.9–9.2)

Effect estimate per comparison	Comparison groups		Atezolizumab vs docetaxel
	Study endpoint	Patient population	HR (95% CI), p-value
	OS (primary endpoint)	ITT (n = 850) TC1/2/3 or CI1/2/3 (n = 463) TC3 or IC3 (n = 137) TC0 and IC0 (n = 379) Squamous (n = 222) Non-squamous (n = 628) CNS metastases (n = 85) Never smokers (n = 156) EGFR mutation positive (n = 85)	0.73 (0.62–0.87), p = 0.0003 0.74 (0.58–0.93), p = 0.0102 0.41 (0.27–0.64), p < 0.0001 0.75 (0.59–0.96), p = 0.0215 0.73 (0.54–0.98), p = 0.0383 0.73 (0.60–0.89), p = 0.0015 0.54 (0.31–0.94), p = NR 0.71 (0.47–1.08), p = NR 1.24 (0.71–2.18), p = NR
	PFS events	ITT TC1/2/3 or CI1/2/3	0.95 (0.82–1.10), p = 0.49 0.91 (0.74–1.12), p = 0.38
	Median PFS	ITT TC3 or IC3	0.95 (0.82–1.10), p = 0.4928 0.63 (0.43-0.91); p=0.0123
	DOR	ITT TC1/2/3 or CI1/2/3	0.34 (0.21–0.55), p < 0.0001 0.38 (0.22–0.65), p = 0.0003

Abbreviations: CI = confidence interval; CNS = central nervous systems, DOR = duration of response; HR = hazard ratio; IC = tumour infiltrating immune cells; ITT = intention-to-treat; NE = not evaluable, NR = not reported; ORR = objective response rate: OS = overall survival; PFS = progression-free survival; TC = tumour cells; vs = versus

7.1.2 Safety

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

most common AEs: fatigue, decreased appetite, cough, asthenia, dyspnoea and nausea

One grade 5 AE was reported in the docetaxel group. Grade 3 or 4 AEs were reported in 227 (37%) of 609 atezolizumab recipients and 310 (54%) of 578 patients treated with docetaxel; out of those 15% (90/609) in the atezolizumab group and 43% in the docetaxel group were reported due to treatment-related grade ≥3 AEs. The most common atezolizumab-related AEs, of any grade, were fatigue (27%), decreased appetite (24%), cough (23%), asthenia (19%), and dyspnoea (19%). Pruritus and musculoskeletal pain were more common in atezolizumab recipients than patients receiving docetaxel. Approximately 8% (46/609) atezolizumab recipients and 19% (108/578) docetaxel recipients discontinued treatment due to AEs and one treatment-related death occurred in the docetaxel group due to a respiratory tract infection [13].

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

infusion reactions: 1.6% of patients; interrupt or infuse slowly

NSCLC patients receive a fixed dose of 1,200 mg atezolizumab intravenously over 60 minutes every three weeks. If the first infusion is tolerated, subsequent infusions may be delivered over 30 minutes. Severe infusion reactions have occurred in 1.6% (16/1027) patients with NSCLC. It is necessary to interrupt or slow the rate of infusion in patients with mild or

moderate infusion reactions and discontinue use in patients with grade ≥3 infusion reactions [2].

Study participants receive a median treatment duration of 3.4 months (range 0–26) with atezolizumab and median treatment duration of 21 months (range 0–23) with docetaxel. Approximately 40% atezolizumab patients were treated with a median treatment duration beyond progression of three cycles (range 1–34). AEs leading to dose modifications, delay or interruption occurred in 25% (152/609) and 36% (210/578) of patients in the atezolizumab and docetaxel group, respectively [13].

median treatment duration: 3.4 months (range 0–26 months)

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

Study participants had a median age of 63 years and a good performance status (ECOG performance 0 or 1). Patients with a history of autoimmune disease or compromised immunity were excluded from the study [13]. While OS benefit was observed across age subgroups (<65, 65–74, 75–84), there were too few patients to estimate OS and PFS for those ≥85 years [15]. Clinical specificity of older patients and those with comorbidities, co-medications, reduced functional reserve, and immunosenescence may affect the efficacy and/or toxicity of immune-checkpoint inhibitors in this population [11].

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

Atezolizumab may impair fertility and cause fetal harm resulting in increased rates of abortion or stillbirth. Females are advised to use effective contraception during treatment and refrain from breast feeding for at least 5 months following the last dose of atezolizumab [2].

atezolizumab may cause fetal harm

Table 2: Most frequent treatment-related adverse events of OAK [13]

Adverse Event (according to CTCAE version 4.0)	**Atezolizumab** (n = 609)		**Docetaxel** (n = 578)	
All AEs any grade, n (%)	390 (64)		496 (86)	
AEs in ≥10% of patients	Any Grade n (%)	Grade 3 or 4 n (%)	Any Grade n (%)	Grade 3 or 4 n (%)
Fatigue	163 (27)	17 (3)	205 (36)	23 (4)
Decreased appetite	143 (24)	2 (<0.5)	136 (24)	9 (2)
Cough	141 (23)	2 (<0.5)	105 (18)	1 (<0.5)
Nausea	108 (18)	4 (1)	131 (23)	2 (<0.5)
Diarrhoea	94 (15)	4 (1)	141 (24)	11 (2)
Asthenia	116 (19)	8 (1)	114 (20)	13 (2)
Dyspnoea	118 (19)	15 (3)	112 (19)	14 (2)
Anaemia	70 (12)	14 (2)	136 (24)	33 (6)
Alopecia	3 (1)	0 (0)	202 (35)	1 (<0.5)
Constipation	107 (18)	2 (<0.5)	82 (14)	1 (<0.5)
Pyrexia	108 (18)	1 (<0.5)	76 (13)	1 (<0.5)
Peripheral edema	54 (9)	1 (<0.5)	82 (14)	3 (1)
Vomiting	74 (12)	2 (<0.5)	62 (11)	4 (1)
Arthralgia	73 (12)	3 (1)	58 (10)	1 (<0.5)
Myalgia	39 (6)	1 (<0.5)	91 (16)	4 (1)
Back pain	67 (11)	7 (1)	42 (7)	4 (1)
Neutropenia	10 (2)	3 (1)	90 (16)	75 (13)
Peripheral neuropathy	24 (4)	0 (0)	65 (11)	7 (1)
Musculoskeletal pain	64 (11)	4 (1)	25 (4)	1 (<0.5)
Stomatitis	19 (3)	1 (<0.5)	63 (11)	11 (2)
Dysgeusia	18 (3)	0 (0)	58 (10)	0 (0)
Febrile neutropenia	1 (<1)	1 (<0.5)	62 (11)	62 (11)

Abbreviations: AE = adverse event; CTCAE = common terminology for cancer adverse events

7.2 Clinical effectiveness and safety – further studies

POPLAR: atezolizumab 1,200 mg vs docetaxel 75 mg/m² IV every 3 weeks; ITT = 287

POPLAR (NCT01903993) is an open-label, randomized, phase II study comparing the safety and efficacy of atezolizumab versus docetaxel in 287 NSCLC patients who progressed on post-platinum chemotherapy [16]. Eligible patients were stratified by PD-L1 expression status, number of prior chemotherapy regimens and histology, and randomized to atezolizumab 1,200 mg (n = 144) or docetaxel 75 mg/m^2 (n = 143) intravenously every three weeks until unacceptable toxicity or disease progression.

OS in the ITT population was 12.6 months for atezolizumab versus 9.7 months for docetaxel (HR 0.73, [95%CI 0.53–0.99]; p = 0.04). Improved OS was associated with increasing PD-L1 expression (TC3 or IC3 HR 0.49 [95% CI 0.22–1.07]; p = 0.068; TC2/3 or IC2/3 HR 0.54 [95% CI 0.33–0.89]; p = 0.014; TC1/2/3 or IC1/2/3 HR 0.59 [95%CI 0.40–0.85]; p = 0.005; TC0 and IC0 HR 1.04 [95%CI 0.62–1.75]; p = 0.871). Patients with pre-existing immunity, defined by high T-effector-interferon-γ-associated gene expression, had improved OS with atezolizumab. Approximately 8% of atezolizumab recipients and 22% of docetaxel recipients discontinued use due to AEs. Results suggest that atezolizumab significantly improved OS compared to docetaxel in previously treated NSCLC. Improvement in OS was correlated to PD-L1 expression and may be predictive for atezolizumab benefit [16]. PFS and ORR did not reflect the OS benefit seen with atezolizumab versus docetaxel suggesting that OS benefit may extend beyond disease progression by RECIST v1.1 [17, 18].

OS ITT: 12.6 for atezolizumab versus 9.7 for docetaxel

OS benefit correlated with increasing PD-L1 expression

Two other non-randomized, single-arm, phase II studies, FIR (NCT01846416) [19] and BIRCH (NCT02031458) [20, 21], assessed the safety and efficacy of PD-L1-positive patients with locally advanced or metastatic NSCLC. Atezolizumab improved OS in both chemotherapy-naïve and previously treated NSCLC. Higher PD-L1 expression (TC3 or IC3) was associated with higher ORR based on RECIST v1.1 [19-21].

FIR and BIRCH: atezolizumab improved ORR in chemo-naïve and previously treated NSCLC; benefit correlated PD-L1 expression

8 Estimated costs

A0021: What is the reimbursement status of atezolizumab?

Currently, no price estimates are available for Austria. Atezolizumab costs approximately US $12,500 per month [12]. Median treatment duration of approximately 3.4 months with atezolizumab would cost US$ 42,500.

estimate: US $12,500; no price estimates available for Austria

9 Ongoing research

Several studies evaluating the use of atezolizumab as monotherapy or in combination as second-line therapy for NSCLC are ongoing. A search of clinicaltrials.gov using search terms “atezolizumab” and “NSCLC” yielded 36 registered studies (nine phase III, 14 phase II, and 13 phase I studies). Most studies were industry-sponsored or conducted in collaboration with industry.

36 registered trials; 8 industry-sponsored ongoing phase III studies

Selected ongoing phase III and II studies for pre-treated NSCLC patients:

- **NCT02813785:** open-label, randomized, controlled trial to evaluate the efficacy and safety of atezolizumab compared with docetaxel in NSCLC after failure with platinum-based chemotherapy. Estimated primary completion date is May 2019.

- **NCT02486718:** open-label, randomized study to evaluate efficacy and safety of atezolizumab with best supportive care following adjuvant cisplatin-based chemotherapy in patients with completely resected stage IB-IIIA NSCLC. Estimated primary completion date is September 2026.
- **NCT03014648:** evaluate the efficacy of PD-l1 inhibition with atezolizumab in advanced squamous and non-squamous NSCLC patients previously treated with anti-PD-1 therapy with either nivolumab or pembrolizumab in three cohorts, progressive disease, stable disease and partial to complete response followed by progressive disease. Estimated primary completion date is October 2022.
- **NCT02630186:** evaluate safety and anti-tumour effects of the combination of rociletinib and atezolizumab in patients with advanced or metastatic EGFR-mutant NSCLC. Estimated primary completion date is December 2016.
- **NCT02716038:** evaluate the effectiveness of nab-paclitaxel + carboplatin + atezolizumab for treating NSCLC. Estimated primary completion date is April 2020.
- **NCT03023423:** comparative effectiveness of daratumumab in combination with atezolizumab versus atezolizumab alone in patients with previously treated NSCLC. Estimated primary completion date is July 2018.
- **NCT02495636:** evaluate the effects of combining atezolizumab and CDX-1401. Estimated primary completion date is July 2017.
- **NCT02174172:** evaluate the safety and tolerability of atezolizumab in combination with other immune-modulating therapies in the treatment of advanced or metastatic NSCLC. Estimated primary completion date is February 2019.

10 Discussion

FDA approved atezolizumab for NSCLC in October 2016; not approved in Europe

In October 2016, the US FDA approved atezolizumab, 1,200 mg IV administered every 3 weeks, for the treatment of patients with metastatic NSCLC, whose disease progressed during or following platinum-based chemotherapy. Patients with driver gene alterations in EGFR or ALK must have disease progression on prior therapy to receive atezolizumab. The approval was based on two international, randomized, open-label trials, OAK (phase III) and POPLAR (phase II) [2]. Atezolizumab does not currently have market authorization in Europe.

OAK: atezolizumab improved OS and DOR, and reduced AEs compared to docetaxel

OAK, a randomized, open-label, phase III study evaluated the comparative efficacy and safety of atezolizumab versus docetaxel in a total of 1,225 NSCLC patients after failure with platinum-based chemotherapy. Compared with docetaxel, atezolizumab increased OS in the ITT population by 4.2 months and DOR by 10.1 months. Patients with high PD-L1 expression (TC3 and IC3) derived the greatest improvement in median OS with atezolizumab, 20.5 months versus 8.9 months with docetaxel (+ 11.6 months). Nevertheless, the efficacy results showed that PD-L1-targeted therapy with atezolizumab resulted in improved OS compared with docetaxel in previously treated NSCLC regardless of PD-L1 expression or histology, and response was durable except for patients with EGFR mutations.

atezolizumab improved OS regardless of PD-L1 expression or histology, with the exception of EGFR-positive patients

atezolizumab did not improve PFS or ORR compared to docetaxel

Compared with docetaxel, atezolizumab did not improve PFS or the proportion of patients with an OR. Investigators suggest that the discordance between PFS and OS may be due to an initial increase in tumour volume from increased immune filtration, delayed anti-tumour activity, or anti-tumour immune activation beyond progression that may be sustained with continued treatment. Post-progression prolongation of survival has been previously noted for EGFR inhibitor therapies and OAK results imply this effect may also occur with atezolizumab treatment [26]. While fewer patients had treatment-related AEs with atezolizumab compared to docetaxel, clinically significant immune-related AEs were reported including pneumonitis, hepatitis, colitis and thyroid disease [13].

atezolizumab resulted in immune-related AEs

OAK results consistent with phase II data from POPLAR, FIR, BIRCH

The clinical efficacy results of OAK are consistent with phase II data from POPLAR where atezolizumab increased the OS of previously-treated NSCLC patients by 2.9 months compared with docetaxel [16]. These results also correspond with phase II data from FIR and BIRCH demonstrating a correlation between increased improvement in OS with increasing PD-L1 expression [16, 19-21].

high risk of bias: open-label, unmasked allocation; industry funded

Several methodological limitations of the OAK study compromise internal validity. While patients were randomized to atezolizumab or docetaxel by permuted-block via a centralized randomization system, allocation concealment was not maintained and may influence how participants were assigned to a given group. Internal validity is compromised in an open-label study, where patients, treating physicians and outcome assessors are aware of which treatment a patient received introducing potential for bias in the estimated effect of an intervention. However, an independent data monitoring committee reviewed safety data.

ESMO-MCBS:
grade A in the original scale
grade C in the adapted framework

Given the non-curative setting of atezolizumab and the statistically significant primary endpoint OS we applied Form 2a of the ESMO-MCBS in order to assess whether atezolizumab 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 [24, 25]. The application of the ESMO-MCBS to the OAK study resulted in a grade 4 and 3 in the original and the adapted version of the ESMO-MCBS, respectively. Therefore, atezolizumab only leads to a meaningful clinical benefit in the original scale, but not in the adapted framework. This difference occurs due to the use of the point estimate of the HR and the higher implication of toxicities in the adapted ESMO-MCBS.

subgroup analysis underpowered

Results of the OAK study hold some limitations. Subgroup analyses were not powered for formal efficacy comparisons and should be interpreted with caution; the EGFR mutation-positive population may warrant further study. Generalizability of results may be limited. While OAK study participants were a median age of 63 with good performance status, this may compromise external validity as the average age at diagnosis for NSCLC is 70 years [4].

poor external validity: clinical specificity in susceptibles may affect efficacy or toxicity

Clinical specificity of older patients and those with comorbidities, higher ECOG scores, and immunosenescence may affect the efficacy and or toxicity of immunotherapies in this population [11]. While evaluating median OS, PFS, ORR, and discontinuation data are useful outcomes in clinical trials, no evidence was reported regarding generic health-related or disease-specific QoL. Patient reported outcomes (PROMs) and patient reported experiences (PREMs) would be useful in determining whether atezolizumab provides adequate clinical benefit in terms of improving the symptoms and severity of NSCLC. While three immunotherapeutics, nivolumab, pembrolizumab, and atezolizumab, are approved for NSCLC based on statistically and clinically significant improvement in OS compared to docetaxel, docetaxel combination standards (nintedanib or ramucirumab) may prove a better comparator [27].

insufficient follow-up to determine effects of developing treatment-induced ATAs

Follow-up may have been insufficient to identify all potential AEs or to assess the long-term effects of developing treatment-induced ATAs.

US $12,500/month
US $42,500/3.4 months

The cost of atezolizumab is approximately US $12,500 per month and is not yet known for Europe. Median treatment duration of approximately 3.4 months with atezolizumab would cost US$ 42,500. There are approximately 4,716 new cases of lung cancer being diagnosed each year in Austria, and at least one third of newly diagnosed patients having distant metastases.

PROMs and PREMs data may inform value of atezolizumab in improving symptoms and severity

Overall, OAK is the first phase III randomized study to report that compared to docetaxel, PD-L1 targeted immunotherapy with atezolizumab increases OS and DOR in previously treated NSCLC patients regardless of PD-L1 expression or histology with a favourable safety profile compared to docetaxel. Although, OS is improved, there is no evidence regarding QoL, PROMs or PREMs to determine whether atezolizumab provides clinically significant improvement in symptoms or severity of NSCLC. Results from OAK hold limited external validity as participants are not entirely generalizable to clinical practice.

improved OS and DOR with a favourable safety profile

While several studies are ongoing, longer trials are needed that directly compare the safety and efficacy of atezolizumab versus other immunotherapies such as nivolumab or pembrolizumab, or docetaxel in combination with nintedanib or ramucirumab.

Table 3: Benefit assessment based on original ESMO-MCBS and adapted benefit assessment based on adapted ESMO-MCBS [34, 35]

ESMO-MCBS	Active substance	Indication	Intention	PE	Form	MG standard treatment	Efficacy				Safety		AJ	FM
							MG months	*HR (95% CI)*	*Score calculation*	*PM*	*Toxicity*	*QoL*		
adapted ESMO-MCBS	atezolizumab	pre-treated NSCLC	Not curative	OS	2a	≤1 year	+4.2	0.73 0.62–0.87	HR >0.65–0.70 OR Gain 1.5–2.4 months	2	-28% grade 3–4 AEs (+1)[1]	-	+1	**3**
ESMO-MCBS	atezolizumab	pre-treated NSCLC	Not curative	OS	2a	≤1 year	+4.2	0.73 0.62–0.87	HR ≤0.65 AND Gain ≥3 months	4	-	-	-	**4**

Abbreviations: AJ = Adjustments, FM = final adjusted magnitude of clinical benefit grade, HR = hazard ratio, m = months, MG = median gain, ND = no difference, NSCLC = non-small lung cancer, OS = overall survival, PE = primary endpoint, PM = preliminary magnitude of clinical benefit grade, QoL = quality of life

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] One level upgrade because <10% grade ≥3 adverse events.

11 References

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12 Appendix

Table 4: Characteristics of the OAK trial

Title: Atezolizumab versus docetaxel in patients with previously treated non-small cell lung cancer [13]			
Study identifier	NCT02008227, GO28915, *EudraCT* 2013-003331-30, OAK		
Design	Open-label, multicentre (31 countries, 194 centres), randomized controlled phase III study		
	Duration of main phase:		Recruited 850 patients to ITT March 11, 2014 to Nov 28, 2014 Enrolled final 375 patients by April 29, 2015 completing safety population. At primary analysis (July 7, 2016), median follow-up was 21 months; 596 patients had died.
	Duration of Run-in phase:		Not applicable
	Duration of Extension phase:		Not applicable
Hypothesis	Superiority The study was designed to evaluate the efficacy and safety of atezolizumab compared with docetaxel in patients with locally advanced or metastatic NSCLC after failure with platinum-containing chemotherapy.		
Funding	F. Hoffmann-La Roche Ltd, Genentech Inc.		
Treatments groups	Atezolizumab (n=425 ITT; n=609 safety population)		1,200 mg IV over 60 minutes every 3 weeks until unacceptable toxicity or disease progression
	Docetaxel (n=425 ITT; n=578 safety population)		75 mg/m² IV over 60 minutes every 3 weeks until unacceptable toxicity or disease progression
Endpoints and definitions	Overall survival	OS	Time from randomization to death Compared between treatment groups within the ITT and the PD-L1 TC1/2/3 or IC1/2/3 populations (4.5 years)
	Progression-free survival	PFS	Time from randomization to first occurrence of RECIST v1.1-defined disease progression or all-cause death Overall response rate determined using RECIST (v1.1) (1 year)
	Objective response rate	ORR	Overall response rate evaluated with RECIST (v1.1) (1 year)
	Duration of response	DOR	Time from first occurrence of objective response to time of RECIST v1.1-defined disease progression or all-cause death Duration of response evaluated with RECIST (v1.1) (1 year)
	Safety, adverse events	AE	Incidence of adverse events according to NCICTAE (v4.0) (up to 1 year)
Database lock	Last verified November 2016		
Results and Analysis			
Analysis description	**Primary Analysis** ITT: OS planned when 70% of ITT patients had died. July 7, 2016, median FU: 21 months; 569 patients had died (271 atezolizumab, 298 docetaxel recipients). OS, PFS, DOR compared between treatment groups; stratified log-rank test at two-sided significance. Median OS by Kaplan-Meier; 95% CI by Brookmeyer-Cowley. HR by Cox regression. Pre-specified analyses of consistency of treatment effect according to baseline characteristics and PD-L1 expression subgroups. ORR by Clopper-Pearson; Cochran-Mantel-Haenszel. Safety population: included final 375 enrolled for a total population of 1225 patients. The funder provided study drugs, was involved in study design, data collection, analysis, interpretation, report writing and provided approval to submit publication. Safety monitored by independent committee.		

Title: Atezolizumab versus docetaxel in patients with previously treated non-small cell lung cancer [13]				
Study identifier	NCT02008227, GO28915, *EudraCT* 2013-003331-30, OAK			
Analysis population	Inclusion	✲ Adult patients ≥18 years of age ✲ LA or metastatic (Stage IIIB, Stage IV, or recurrent) NSCLC ✲ FFPE tumour specimens ✲ Disease progression during or following prior platinum-containing regimen for LA, unresectable/inoperable/metastatic NSCLC or recurrence within 6 months of platinum-based chemo-therapy ✲ Measurable disease, as defined by RECIST v1.1 ✲ ECOG performance status of 0 or 1		
	Exclusion	✲ Active or untreated CNS metastases ✲ Malignancies other than NSCLC within 5 years prior to randomi-zation, except those treated with expected curative outcome or negligible risk of metastasis or death ✲ History of autoimmune disease, idiopathic pulmonary fibrosis, drug-induced or active pneumonitis, or organizing pneumonia ✲ Active hepatitis B or C ✲ Prior treatment with docetaxel, CD137 agonists, anti-CTLA4, or anti-PD-1 pathway-targeting therapeutics		
	Characteristics	Atezolizumab (n=425)	Docetaxel (n=425)	Overall ITT (n=850)
	Median age (range), years	63 (33-82)	64 (34-85)	64 (33-85)
	Ages ≥65 years, (%)	190 (45)	207 (49)	397 (47)
	Male sex, (%)	261 (61)	259 (61)	520 (61)
	Race (%) Caucasian Asian Black Other Unknown	 302 (71) 85 (20) 5 (1) 13 (3) 20 (5)	 296 (70) 95 (22) 11 (3) 9 (2) 14 (3)	 598 (70) 180 (21) 16 (2) 22 (3) 34 (4)
	ECOG performance status (%) 0 1	 155 (36) 270 (64)	 160 (38) 265 (62)	 315 (37) 535 (63)
	Tobacco history (%) Never Current Previous	84 (20) 59 (14) 282 (66)	72 (17) 67 (16) 286 (67)	156 (18) 126 (15) 568 (67)
	EGFR mutation (%) Positive Negative Unknown	 42 (10) 318 (75) 65 (15)	 43 (10) 310 (73) 72 (17)	 85 (10) 628 (74) 137 (16)
	ALK translocation Positive Negative Unknown	 2 (<1) 223 (52) 200 (47)	 0 (0) 201 (47) 224 (53)	 2 (<1) 424 (50) 424 (50)
	Histology Non-squamous Squamous	 313 (74) 112 (26)	 315 (74) 110 (26)	 628 (74) 222 (26)
	PD-L1 subgroups TC3 or IC3 TC2/3 or IC2/3 TC1/2/3 or IC1/2/3 TC0 and IC0	 72 (17) 129 (30) 241 (57) 180 (42)	 65 (15) 136 (32) 222 (52) 199 (47)	 137 (16) 265 (31) 463 (54) 379 (45)
	Previous LA or met-astatic therapies (%) 1 2	 320 (75) 105 (25)	 320 (75) 105 (25)	 640 (75) 210 (25)

Title: Atezolizumab versus docetaxel in patients with previously treated non-small cell lung cancer [13]	
Study identifier	NCT02008227, GO28915, *EudraCT* 2013-003331-30, OAK
	Initially designed to enrol 850 patients, increased to 1300 patients to power for OS comparison in patients with high PD-L1 expression; final enrolment was 1225 patients *- Subgroup analyses were not powered for formal efficacy comparison; interpret with caution* *- Patients were stratified by PD-L1 expression, number of previous chemotherapies, and histology* *- TC1/2/3 or IC1/2/3 was defined as PD-L1 expression on 1% of TC or IC; TC2/3 or IC2/3 as PD-L1 expression on 5% of cells; TC3 as PD-L1 expression on 50% or more TCs and IC3 as 10% or more on IC; TC0 and IC0 as PD-L1 expression on less than1% of TC or IC* *-Permuted block-randomization via interactive voice or web response system; open-label; investigator-assessed PFS* *- ITT population comprises first 850 patients randomized (1:1) to atezolizumab (1200 mg IV) or docetaxel (75 mg/m²) every 3 weeks; safety population comprises 609 atezolizumab recipients and 578 docetaxel recipients* *- Of 425 assigned atezolizumab, 298 discontinued (270 died, 26 withdrew, 2 LFUP); of 425 assigned docetaxel, 347 discontinued (297 died, 48 withdrew, 2 LFUP)*

Abbreviations: ALK = anaplastic lymphoma kinase; CNS = central nervous system; CTLA4 = cytotoxic T-lymphocyte-associated protein 4; ECOG = Eastern Cooperative Oncology Group; EGFR = epidermal growth factor receptor; FFPE = representative formalin-fixed paraffin-embedded; FU = follow-up; ITT = intent-to-treat; IV = intravenous; KRAS = V-Ki-ras2 Kirsten rat sarcoma viral oncogene homolog; LA = locally advanced; LFUP = lost to follow-up; NCICTCAE = National Cancer Institute Common Terminology Criteria for Adverse Events; NSCLC = non-small cell lung cancer; ORR = objective response rate; OS = overall survival; PD-L1 =programmed death ligand-1; PFS: progression-free survival; RECIST = Response Evaluation Criteria in Solid Tumours

Table 5: risk of bias assessment on study level is based on EUnetHTA (Internal validity of randomized controlled trials) [22]

Criteria for judging risk of bias		**risk of bias**
Adequate generation of randomisation sequence: permuted block-randomized (block size of 8) to assign 1:1 ratio atezolizumab vs docetaxel via centralised interactive web-based and voice-based randomisation system		no
Adequate allocation concealment: trial centres enrolled the patients and allocation was specified as unmasked		yes
Blinding	**Patient:** open-label, patients unmasked	yes
	Treating Physician: open-label, unmasked	yes
	Outcome assessment: open-label, investigator-assessed PFS	yes
Selective outcome reporting unlikely: outcomes reported as specified in protocol; withdrawals and drop-outs reported		no
No other aspects which increase the risk of bias: industry funded the study, provided study drugs, and was involved in study design, data collection, analysis, interpretation, writing of the report and provided approval to submit for publication.		high
Risk of bias – study level		high

Abbreviations: PFS = progression-free survival