NICE National Institute for Health and Care Excellence

Single Technology Appraisal

Atezolizumab for adjuvant treatment of resected non-small-cell lung cancer (MA review of TA823) [ID6324]

Committee Papers

NICE National Institute for Health and Care Excellence

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

SINGLE TECHNOLOGY APPRAISAL

Atezolizumab for adjuvant treatment of resected non-small-cell lung cancer (MA review of TA823) [ID6324]

Contents:

The following documents are made available to stakeholders:

Access the **final scope and final stakeholder list** on the NICE website.

1. **Company submission** from Roche:
   a. Full submission
   b. Summary of Information for Patients (SIP)

2. **Clarification questions and company responses**
   a. Additional questions – NMA results

3. **Patient group, professional group, and NHS organisation submission** from:
   a. British Thoracic Oncology Group – written by clinical expert, Jason Adhikaree

4. **Expert personal perspectives** from:
   a. Adam Januszewski – Clinical expert, nominated by Roche (company)

5. **External Assessment Report** prepared by School of Health and Related Research (ScHARR), University of Sheffield

6. **External Assessment Group response to factual accuracy check of EAR**

Any information supplied to NICE which has been marked as confidential, has been redacted. All personal information has also been redacted.

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single technology appraisal

Atezolizumab for adjuvant treatment of resected non-small-cell lung cancer (CDF review of TA823) [ID6324]

Document B

Company evidence submission

December 2024

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B.1 Decision problem, description of the technology and clinical care pathway

B.1.1 Decision problem

The submission covers the technology's full marketing authorisation for this indication: Tecentriq® as monotherapy is indicated as adjuvant treatment following complete resection and platinum-based chemotherapy for adult patients with NSCLC with a high risk of recurrence whose tumours have PD-L1 expression on ≥ 50% of tumour cells (TC) and who do not have EGFR mutant or ALK-positive NSCLC.

Table 1: The decision problem

	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope
Population	Adults with completely resected NSCLC which expressed PD-L1 on 50% or more of tumour cells and has not progressed after platinum based chemotherapy.	Adults with completely resected NSCLC which expressed PD-L1 on 50% or more of tumour cells, who do not have EGFR mutant or ALK-positive NSCLC and has not progressed after platinum based chemotherapy	The existing licenced indication for early stage NSCLC has been updated to align with the European Medicines Agency (EMA) licence, as part of the Windsor Framework. The Windsor Framework is a government agreement, which will come into effect on the 1st January 2025, which ensures medicines supplied to Northern Ireland can be approved and licensed on a UK-wide basis by the Medicines and Healthcare products Regulatory Agency (MHRA).
Intervention	Atezolizumab (as an adjuvant treatment)	Per final scope	N/A
Comparator(s)	• Active monitoring • Adjuvant pembrolizumab (subject to NICE appraisal) • Adjuvant osimertinib (for adults with EGFR mutation positive NSCLC and subject to NICE appraisal)	• Active monitoring	Since the Company will not be seeking reimbursement and will not be licenced in the EGFR-positive and ALK-positive population, adjuvant osimertinib and adjuvant alectinib should not be included in the list of relevant comparators for this CDF review. Additionally, as adjuvant pembrolizumab is not currently

	• Adjuvant alectinib (for adults with ALK mutation positive NSCLC and subject to NICE appraisal)		reimbursed, it should not be included as a comparator for this CDF review.
Outcomes	The outcome measures to be considered include: • Disease-free survival (DFS) • Overall survival (OS) • Adverse effects of treatment • Health-related quality of life	Per final scope	N/A
Economic analysis	The reference case stipulates that the cost effectiveness of treatments should be expressed in terms of incremental cost per quality-adjusted life year. The reference case stipulates that the time horizon for estimating clinical and cost effectiveness should be sufficiently long to reflect any differences in costs or outcomes between the technologies being compared. Costs will be considered from an NHS and Personal Social Services perspective. The availability of any commercial arrangements for the intervention, comparator and subsequent treatment	As per NHS reference case	

	technologies will be taken into account. The availability and cost of biosimilar and generic products should be taken into account.		
Subgroups to be considered	• Disease stage • Presence of biological or genetic markers	None	• **Disease stage:** The Company will not provide a disease stage subgroup analysis because the trial was not designed to compare these subgroups. In addition, the patient population within each subgroup is too small to conduct any meaningful statistical analysis (Stage II n = 58, Stage IIIA n= 48). • **Presence of biological or genetic markers:** The existing licenced indication for atezolizumab has been updated to exclude the subgroup of patients with ALK+ and EGFR+ tumours. Adjuvant atezolizumab has been recommended and made available via the CDF since September 2022. Evidence from the SAC-T data report has shown that ALK-positive and EGFR-positive NSCLC patients would not be treated with adjuvant atezolizumab or any immunotherapy. This finding was also confirmed by clinicians (1). Instead, alectinib is

			considered the appropriate treatment for the ALK-positive subgroup, and osimertinib is recommended for the EGFR-positive subgroup. Therefore, after careful consideration of the evidence, the Company has decided to modify its licence in this indication to align with the EMA licence. Due to the lack of usage in the excluded groups, the impact of the licence restriction is expected be minimal on patient access and outcomes.
Special considerations including issues related to equity or equality	N/A	Per final scope	N/A

B.1.2 Description of the technology being appraised

The technology for appraisal is described in Table 2.

Table 2: Technology being appraised

UK approved name and brand name	Atezolizumab (Tecentriq®)
Mechanism of action	Atezolizumab is a humanised IgG monoclonal antibody which directly and selectively binds to an immune checkpoint protein called programmed death-ligand 1 (PD-L1) on the surface of both tumour cells (TC) and tumour-infiltrating immune cells (IC) (2). PD-L1 binds to PD-1 and B7.1 on activated T cells to inhibit T cell proliferation, cytokine production and cytolytic activity, thereby inhibiting the anti-tumour immune response (3-5). Therefore, by binding PD-L1, atezolizumab may activate the anti-tumour immune response. In addition, interruption of the PD-L1/PD-1 and PD-L1/B7.1 pathway with atezolizumab prevents down regulation of T-cell activity while allowing for the priming of new T cells (3, 6). The PD-L2/PD-1 interaction is left intact, potentially preserving peripheral immune homeostasis (7). Atezolizumab is FcγR-binding deficient; therefore, it cannot bind to Fc receptors on phagocytes and cause antibody dependent cell-mediated cytotoxicity (ADCC). This is important since ADCC-mediated depletion of tumour specific T cells could worsen autoimmunity rather than improve it (4, 8).
Marketing authorisation/CE mark status	On 2nd August 2021, the Innovation, Licensing and Access Steering Group (MHRA, NICE and SMC) awarded atezolizumab the innovative medicine designation, Innovation Passport, for the adjuvant treatment of adult patients with NSCLC whose tumours express PD-L1 on ≥ 1% of tumour cells and whose disease has not progressed following platinum-based adjuvant chemotherapy. On 27th January 2022, under Project Orbis, the MHRA granted a line extension for atezolizumab as monotherapy for the adjuvant treatment of adult patients with Stage II to IIIA NSCLC (as per the 7th edition of the UICC/AJCC staging system), whose tumours have PD-L1 expression on ≥ 50% of tumour cells and whose disease has not progressed following platinum-based adjuvant chemotherapy. As part of the Windsor Framework, the approved MHRA licence was updated on 11th November 24: atezolizumab as monotherapy as adjuvant treatment following complete resection and platinum-based

	chemotherapy for adult patients with NSCLC with a high risk of recurrence whose tumours have PD-L1 expression on ≥ 50% of tumour cells (TC) and who do not have EGFR mutant or ALK-positive NSCLC.
Indications and any restriction(s) as described in the summary of product characteristics (SmPC)	**Atezolizumab is currently approved by the MHRA for administration as an 840 mg and 1,200mg solution for intravenous (IV) infusion, and as a 1,875mg solution for subcutaneous (SC) injection (9-11):** **For early-stage NSCLC:** • As monotherapy, for the adjuvant treatment following complete resection for adult patients with Stage II to IIIA (7th edition of the UICC/AJCC-staging system) NSCLC whose tumours have PD-L1 expression on ≥ 50% of tumour cells (TC), who do not have EGFR mutant or ALK-positive NSCLC, and whose disease has not progressed following platinum-based adjuvant chemotherapy **For metastatic NSCLC:** • In combination with bevacizumab, paclitaxel and carboplatin, for the first-line treatment of adult patients with metastatic non-squamous NSCLC. In patients with EGFR mutant or ALK-positive NSCLC, it is indicated only after failure of appropriate targeted therapies • In combination with nab-paclitaxel and carboplatin, for the first-line treatment of adult patients with metastatic non-squamous NSCLC who do not have EGFR mutant or ALK-positive NSCLC • As monotherapy, for the first-line treatment of adult patients with metastatic NSCLC whose tumours have a PD-L1 expression ≥ 50% TC or ≥ 10% tumour-infiltrating immune cells (IC) and who do not have EGFR mutant or ALK-positive NSCLC • As monotherapy, for the treatment of adult patients with locally advanced or metastatic NSCLC after prior chemotherapy. Patients with EGFR mutant or ALK-positive NSCLC should have received targeted therapies before receiving atezolizumab • As monotherapy, for the first-line treatment of adult patients with advanced NSCLC who are ineligible for platinum-based therapy **For small cell lung cancer (SCLC):** • In combination with carboplatin and etoposide, for the first-line treatment of adult patients with extensive-stage small cell lung cancer (ES-SCLC)

	For urothelial carcinoma (UC): • As monotherapy, for the treatment of adult patients with locally advanced or metastatic UC after prior platinum-containing chemotherapy or for those who are considered cisplatin ineligible and whose tumours have a PD-L1 expression ≥ 5% **For hepatocellular carcinoma (HCC):** • In combination with bevacizumab, for the treatment of adult patients with advanced or unresectable HCC who have not received prior systemic therapy **For triple-negative breast cancer (TNBC):** • In combination with nab-paclitaxel, for the treatment of adult patients with unresectable locally advanced or metastatic TNBC whose tumours have PD-L1 expression ≥ 1% and who have not received prior chemotherapy for metastatic disease
Method of administration and dosage	The recommended dose of atezolizumab for NSCLC is: • **For IV infusion (9, 11)** o 840 mg administered intravenously every two weeks (Q2W), or o 1,200 mg administered intravenously every three weeks (Q3W), or o 1,680 mg administered intravenously every four weeks (Q4W) • **For SC injection (10)** o 1,875 mg every three weeks (Q3W) Treatment with atezolizumab will be given for one year, until disease recurrence or unmanageable toxicity (9-11)
Additional tests or investigations	Patients with early-stage NSCLC should be selected for treatment based on the tumour expression of PD-L1 as confirmed by a validated test (9)
List price and average cost of a course of treatment	1875 mg: £3,807.69 (list price) (subcutaneous injection price is used in the base case) [redacted] (PAS price) Average treatment cost per year with PAS: [redacted]
Patient access scheme	Yes ([redacted])

B.1.3 Health condition and position of the technology in the treatment pathway

B.1.3.1 Disease overview

B.1.3.1.1 Incidence and prevalence

In the UK, lung cancer is the third most common type of cancer, accounting for 13% of all new cancer diagnoses, with approximately 49,229 new cases every year between 2017 and 2019 (12). It is also the leading cause of cancer-related mortality, accounting for 21% of all cancer deaths from 2017 and 2019 (12). Primary malignant lung cancers are classified into two different categories: non-small cell lung cancer (NSCLC) and small-cell lung cancer (SCLC). According to the 2024 National Lung Cancer Audit (NLCA), 92% of all lung cancer cases in England were diagnosed as NSCLC (13).

B.1.3.1.2 Diagnosis, staging and screening

The diagnosis process for NSCLC involves a multifaceted approach that begins with patient history and physical examination, and extends to advanced imaging and histological examination. Current methods of detecting NSCLC include chest X-ray, computed tomography (CT) scan, magnetic resonance imaging (MRI), positron emission tomography (PET) scan, sputum analysis, and lung biopsy (14). These detection methods are also used to evaluate stage of disease, to determine the most appropriate form of treatment and provides an indication of prognosis.

For NSCLC, the staging system most frequently used is the Tumour, Node, Metastasis (TNM) system by the Union for International Cancer Control (UICC) and the American Joint Committee on Cancer (AJCC) (15, 16). The TNM system allows categorisation from Stage 0 to IV. Currently, the 8th edition of the UICC/AJCC TNM system reflects the latest standards in clinical practice (Appendix G). Approximately half of all NSCLC patients are diagnosed with early Stage I–III disease (hereafter referred to as early NSCLC, as per TNM 8th edition), with better prognosis seen in earlier stages of NSCLC (17).

Survival rates for NSCLC patients vary significantly depending on the disease stage at diagnosis. Following complete surgical resection, the 5-year survival for early

NSCLC patients is estimated at 68–92% for Stage I disease, 53–60% for Stage II disease, and 13–36% for Stage III disease (17). Although there are no publicly available survival data for early NSCLC patients in the UK, these figures are comparable with estimates by UK clinical experts (18, 19). Additionally, despite advancements in technology and extensive cancer research, 57% of lung cancer patients are diagnosed with advanced or metastatic disease (14). This is primarily due to the asymptomatic nature of early NSCLC, when diagnosis often occurs incidentally (18, 20), highlighting the need for effective screening programmes to identify patients at earlier stages of disease. Several trials have now established that early detection through low-dose CT screening could reduce mortality for high-risk individuals, as lung cancer is being diagnosed at early stages of disease (21, 22). Initial screening pilots in the UK have shown promising results, with one trial diagnosing 65% of lung cancer at Stage I and 12% at Stage IV, compared to 18% at Stage I and 48% at Stage IV prior to the trial (23). NHS England has started to roll out targeted lung cancer screening pilots, with potential for national implementation per the NHS Long Term Plan (23), which could increase early NSCLC diagnoses and improve survival outcomes. Currently, lung health checks are only available in some parts of England, and will be available everywhere by 2029 (24).

The diagnosis of NSCLC also includes assessing the tumour's molecular profile using immunohistochemistry (IHC) and genomic testing to identify biomarkers, such as programmed death-ligand 1 (PD-L1) expression, anaplastic lymphoma kinase (ALK) rearrangements, and epidermal growth factor receptor (EGFR) mutations (25). Identifying these biomarkers is essential for guiding personalised treatment strategies, as therapies are increasingly targeted based on the tumour's specific genetic and protein characteristics. In early NSCLC, PD-L1 testing is performed through a standardised reflex testing process that accelerates biomarker analysis, ensuring that more patients receive timely and accurate results. The integration of reflex testing, which includes both PD-L1 testing and next generation sequencing (NGS), has been fully implemented within the National Optimal Lung Cancer Pathway (NOLCP). This integration ensures that biopsies are quickly processed and sent for molecular analysis, facilitating comprehensive case discussions at multidisciplinary team (MDT) meetings and enabling effective management planning (26).

B.1.3.1.3 Quality of life

Patients with early NSCLC are generally asymptomatic, and their disease burden is relatively low when compared to patients in the metastatic setting. However, most disease-related symptoms for lung cancer increase in frequency and intensity with staging, in particular chest pain, back pain and dyspnoea (27, 28). The quality of life of early NSCLC patients is generally worse compared to the healthy population, due to the higher rate of co-morbidities, such as cardiovascular disease, former or current smokers and higher age at diagnosis within this patient population (29).

Although surgical intervention is a critical component of early NSCLC treatment, patients often experience a worsening of symptoms such as fatigue, pain, dyspnoea, insomnia, constipation, diarrhoea, and financial difficulties 30 days post-surgery (30). Adjuvant chemotherapy also has an immediate negative impact on a number of aspects of health-related quality of life (HRQoL) in patients who have undergone resection with curative intent, though these changes were relatively modest and acute (worsened fatigue, nausea, and vomiting, but a reduction in pain and no change in global HRQoL) (31). Whilst there is opposing information to the improvement of certain aspects of quality of life in the 12 months following surgery and/or adjuvant chemotherapy, it is clear that lung cancer survivors do not experience the same length of life and quality of life as other cancer survivors or, as their age-matched peers (32).

The IMpower010 study did not collect patient reported outcomes (PROs), as PROs were not widely used at the time of study design. Additionally, as these patients do not have a quality of life (QoL) similar to the general patient population (e.g. due to co-morbidities), it was thought to be difficult to demonstrate the impact of atezolizumab on QoL in a largely asymptomatic (concerning lung cancer symptoms) patient population that was not receiving an active control therapy.

B.1.3.2 Current clinical practice in the UK

The current management of early NSCLC in the UK is informed by NICE guidance and NLCA data collected in 2022 and published in 2024. Additionally, the Company conducted an advisory board on 4th November 2024 with UK clinical experts to gather further insights (1).

B.1.3.2.1 Surgery

For patients with early NSCLC, surgery is the primary treatment option with curative intent, though patients in the UK have historically been less likely to undergo surgery than patients in other countries. In 2022, NLCA reported that 18% of all NSCLC patients underwent surgery (13). For patients with Stage I–II NSCLC, who also had a good performance status (0–2), 76% of patients received treatment with curative intent, including surgery or radical radiotherapy, though regional variations were found (13). UK clinical experts provided various reasons as to why Stage II–III NSCLC patients would not undergo surgery; including poor performance status, co-morbidities, and/or patient preference; for Stage III patients, inoperability or unresectable tumours were additional factors (18).

B.1.3.2.2 Platinum-based chemotherapy

Following surgery, adjuvant cisplatin-based chemotherapy is one of the recommended options for patients with Stage IB (> 4cm) to Stage III patients, according to NICE guidelines (33). An international observational study comprising of 831 subjects found that less than half the patients with Stage IB–IIIA NSCLC (international, 48.4%; UK, 33.4%) received adjuvant systemic therapy (34). This was also observed in the United States with the use of adjuvant chemotherapy at 45%, with higher rates observed in Stage III NSCLC patients (35). Usage data of adjuvant chemotherapy in the UK is limited, though clinical experts reported that 30–60% of Stage II NSCLC patients received adjuvant chemotherapy, with a higher usage seen in Stage III patients at 60–80% (Data on File) (18, 19). In addition, the majority of patients (50–75%) who begun adjuvant chemotherapy completed 4 cycles (18). Reasons for patients not having adjuvant chemotherapy included perceived lack of clinical benefit, toxicity, patient fitness and patient preference.

A 2008 lung-adjuvant-cisplatin evaluation (LACE) analysis reported cisplatin-based adjuvant chemotherapy significantly improved survival in patients with NSCLC (36). The analysis demonstrated a 5% improvement in 5-year overall survival (OS) rates with adjuvant chemotherapy and an OS hazard ratio (HR) of 0.89. The OS benefit with adjuvant chemotherapy varied by stage, with a greater benefit in more advanced disease. Although these results show an improvement in OS with adjuvant chemotherapy, the absolute 5-year survival benefits are modest.

ESMO guidelines considers carboplatin an accepted alternative when cisplatin administration is not feasible (37). While the IMpower010 trial stipulated the use of cisplatin-based adjuvant chemotherapy to achieve optimal clinical outcomes, it also underscored the need for alternatives for those who cannot tolerate cisplatin. The updated licence (38) and NHS England guidance (39) have addressed these limitations by allowing the use of both cisplatin and carboplatin as part of platinum-based chemotherapy. This ensures broader access to effective adjuvant treatments for patients with co-morbidities or cisplatin intolerance. In a recent advisory board, 5 out of 6 clinical experts confirmed using carboplatin exclusively, with one centre still using cisplatin but planning to switch to carboplatin. This is due to due to carboplatin's more favourable tolerability profile (1).

B.1.3.2.3 Cancer immunotherapy (CIT)

The evolving landscape of CIT in early-stage NSCLC has seen some advancements, with both neoadjuvant and peri-operative approaches demonstrating benefits in reducing recurrence rate and extending survival. Nivolumab combined with chemotherapy is recommended as a neoadjuvant option for resectable NSCLC (tumours ≥ 4 cm or node positive) in adults, as supported by the Phase III CheckMate-816 trial (NICE TA876) (40), which showed improved event-free survival (EFS) (HR = 0.66; 95% confidence level [Cl], 0.49–0.90). Similarly, peri-operative pembrolizumab, assessed in the KEYNOTE-671 trial (NICE ID5094) (41), is recommended for neoadjuvant use with platinum-based chemotherapy followed by adjuvant monotherapy. Patients who received pembrolizumab had an improved EFS compared to those who received placebo (HR = 0.59; 95% CI, 0.48–0.72). OS data from the second interim analysis were still immature, nevertheless, they suggested a survival benefit (HR = 0.72; 95% CI, 0.56–0.93) (42).

However, there remains a critical and ongoing focus on adjuvant treatment options for patients who have undergone complete tumour resection. Not all patients are suitable candidates for neoadjuvant or peri-operative treatments, and for those who proceed directly to surgery, the risk of relapse remains significant. This underscores the crucial need for effective adjuvant therapies that can be administered post-surgery to help prevent disease recurrence and improve OS.

B.1.3.2.4 Novel adjuvant treatments

Although surgical resection is the cornerstone of curative treatment for early NSCLC, with adjuvant chemotherapy conferring further clinical benefits, recurrence rates in patients with Stage I–III disease remain high. The approximate rate of recurrence for patients with resectable, Stage I disease is 17–29%, Stage II 38–46%, and Stage III 47–64% (43-45), regardless of the use of adjuvant chemotherapy. This highlights the urgent need to reduce the incidence of recurrence following surgery and improve outcomes for these patients in this potentially curative setting.

The adjuvant treatment landscape is constantly evolving with the discovery of new treatment options for patients diagnosed with early-stage NSCLC. Progress in the identification of biomarkers such as PD-L1 expression, or oncogenic driver alterations such as the presence of ALK and EGFR alterations, have demonstrated benefit as potential targets for treatment in early NSCLC. Some of the key treatment options relevant to the present Cancer Drugs Fund (CDF) review are summarised below.

Tyrosine kinase inhibitors (TKIs)

Osimertinib

Osimertinib is an oral, third-generation EGFR-TKI that selectively targets EGFR mutations. In the ADAURA trial, osimertinib significantly improved outcomes in resected early-stage NSCLC patients with EGFR mutations. At 36 months, 84% of patients on osimertinib were disease-free, compared to 34% on placebo (HR = 0.23; 95% CI, 0.18–0.30) (46). The 5-year OS rates were 85% for patients on osimertinib patients, versus 73% for those on placebo (HR = 0.49; 95% CI, 0.33−0.73) (47). No new safety concerns were noted.

Although osimertinib for adjuvant treatment of EGFR-positive NSCLC is currently included in the CDF under NICE TA761 (48), draft guidance published in June 2024 does not recommend osimertinib within its marketing authorisation (49). Additionally, the current licensed indication for atezolizumab, aligned with the EMA license under the Windsor Framework, excludes patients with EGFR mutations. As a result, adjuvant osimertinib is not considered as a comparator for this CDF review.

Alectinib

Alectinib is a next-generation ALK-TKI with potent inhibitory activity against ALK mutations. In the phase III ALINA trial, alectinib demonstrated a statistically significant and clinically meaningful improvement in disease-free survival (DFS) compared to chemotherapy, with a 76% relative risk reduction of disease recurrence or death in both the Stage II–IIIA subpopulation and the overall ITT population (HR = 0.24; p<0.0001). OS data remain immature, with only a few recorded deaths, and no new safety concerns were identified.

In October 2024, alectinib was recommended for the adjuvant treatment of Stage IB–IIIA ALK-positive NSCLC within its marketing authorisation under NICE ID6368 (50). However, the current licensed indication for atezolizumab, aligned with the EMA license under the Windsor Framework, excludes patients with ALK mutations. As a result, adjuvant alectinib is not considered as a comparator for this CDF review.

Immunotherapy

Pembrolizumab

Pembrolizumab, a monoclonal antibody that binds to the PD-1 receptor, enhances the immune response against tumour cells. In the KEYNOTE-091/PEARLS trial, pembrolizumab demonstrated longer disease-free survival (DFS) and a potential survival benefit in patients with Stage IB–IIIA NSCLC, in the ITT population (HR = 0.81; 95% CI, 0.68 – 0.96) but not in the PD-L1 TPS ⩾ 50% population (HR = 0.83; 95% CI, 0.59 – 1.16; p=0.14) (51). Furthermore, in NICE ID3907, pembrolizumab was positioned for use in a narrower group than its licensed population - those with PD-L1 expression < 50% (HR = 0.72; 95% CI, 0.58–0.89), where active monitoring is standard (52). The effectiveness in this narrower population remains uncertain, impacting the reliability of cost-effectiveness estimates. Consequently, draft guidance published in August 2024 does not recommend pembrolizumab within its marketing authorisation (52). Therefore, adjuvant pembrolizumab is not considered as a comparator for this CDF review.

Atezolizumab

Atezolizumab is a humanised immunoglobin G1 monoclonal antibody immune checkpoint inhibitor that binds to PD-L1. By inhibiting the PD-L1 pathway,

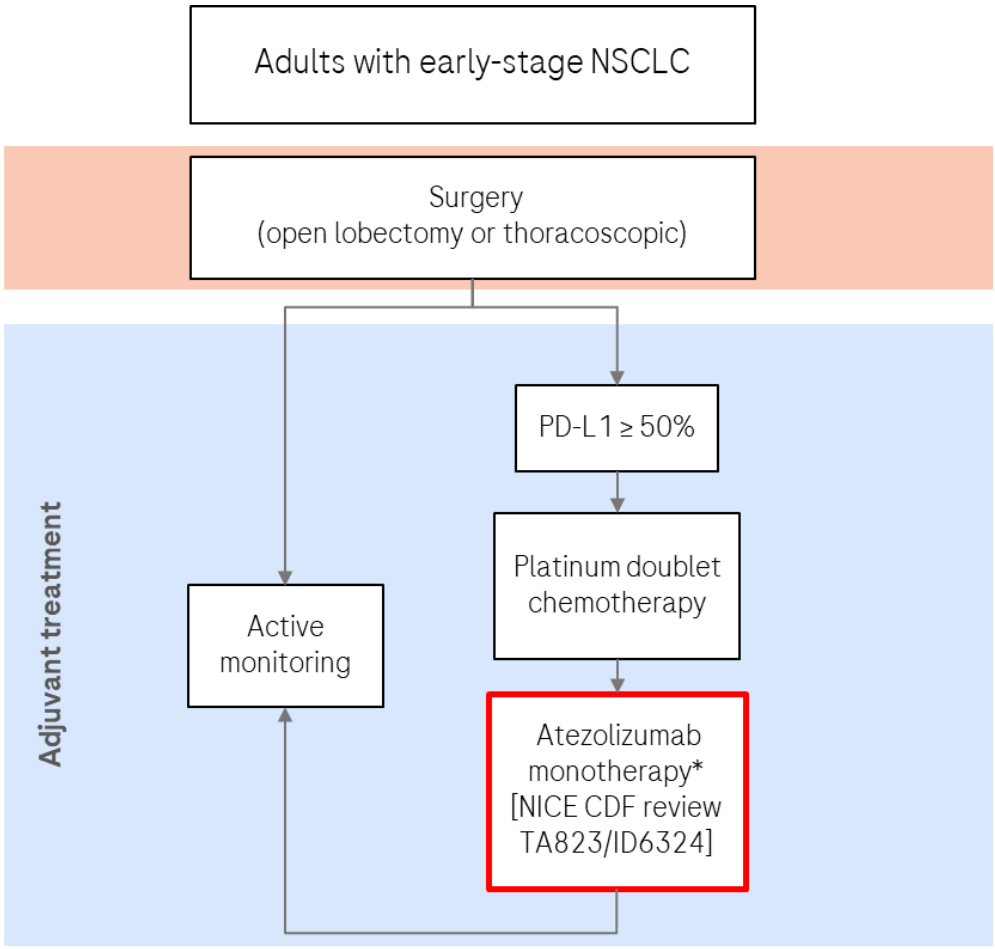
atezolizumab enhances the immune system's capacity to target residual disease, thus reducing the likelihood of recurrence in patients with resected, high-risk NSCLC. In the IMpower010 study, adjuvant atezolizumab demonstrated improved disease-free survival (DFS) compared to best supportive care (BSC), in the ITT population (HR = 0.81; 95% Cl, 0.67−0.99); PD-L1 ≥ 50% Stage II–IIIA population (HR = 0.48; 95% CI, 0.32–0.72); and PD-L1 ≥ 50% Stage II–IIIA population without known EGFR or ALK alterations (HR = 0.49; 95% CI, 0.32–0.75). The safety profile of atezolizumab was consistent with previous studies, with treatment-related Grade 3 and 4 AEs occurring in 11% of patients and Grade 5 events in 1% of patients (53). Given its demonstrated efficacy and manageable safety profile, atezolizumab is recommended by NICE NG122 (54), ESMO (55, 56) and NCCN (57) for patients with PD-L1 positive early-stage NSCLC.

The present CDF review is focused on atezolizumab as an adjuvant monotherapy for adults with completely resected NSCLC which expressed PD-L1 on 50% or more of tumour cells, who do not have EGFR mutant or ALK-positive NSCLC and has not progressed after platinum-based chemotherapy.

B.1.3.3 Disease management pathway

The information presented below is based on recent NICE decisions regarding adjuvant treatments, as well as data from the UKLCC report on active monitoring as the standard of care for certain patient groups (26).

Figure 1: Proposed positioning for adjuvant atezolizumab for early-stage NSCLC patients



The red box indicates the proposed positioning of adjuvant atezolizumab.
Abbreviations: NSCLC, non-small cell lung cancer; PD-L1, programmed death-ligand 1.

B.1.4 Equality considerations

The Company does not consider the introduction of atezolizumab into the adjuvant setting to cause any equity or equality issues.

B.2 Clinical effectiveness

B.2.1 Identification and selection of relevant studies

See Appendix D for full details of the process and methods used to identify and select the clinical evidence relevant to the technology being appraised.

B.2.2 List of relevant clinical effectiveness evidence

The randomised controlled trial (RCT) data used to assess the clinical effectiveness of atezolizumab in this appraisal is based on IMpower010: a Phase III, global, multi-centre, open-label, randomised study comparing the efficacy and safety of atezolizumab versus best supportive care (BSC) following resection and cisplatin-based adjuvant chemotherapy in Stage IB–IIIA NSCLC (7th edition of the UICC/AJCC-staging system) (58). Details are summarised below (Table 3).

In the original company submission (NICE TA823) (59), submitted in October 2021, data from the first interim DFS analysis from the IMpower010 trial was presented (clinical cutoff date [CCOD] 21st January 2021). OS was not formally tested, as statistical significance for DFS had not been reached in the intent-to-treat (ITT) population. This CDF exit submission presents updated IMpower010 trial results from the final DFS analysis and the second interim OS analysis, with data reflecting an additional 36 months of follow-up (CCOD 26th January 2024). The minimum duration of follow-up was 60 months.

Table 3: Clinical effectiveness evidence

Study	IMpower010
Study design	Global, randomised, Phase III, multi-centre, open-label study
Population	Adult patients with completely resected Stage IB (tumours greater ≥ 4cm)–Stage IIIA (T2-3 N0, T1-3 N1, T1-3 N2, T4 N0-1) NSCLC (per UICC/AJCC v7), with an ECOG performance status of 0 or 1
Intervention(s)	Atezolizumab
Comparator(s)	BSC following resection and cisplatin-based adjuvant chemotherapy

Study	IMpower010
Indicate if trial supports application for marketing authorisation	Yes
Indicate if trial used in the economic model	Yes
Rationale for use/non-use in the model	N/A
Reported outcomes specified in the decision problem	• Disease-free survival (DFS) • Overall survival (OS) • Adverse effects of treatment
All other reported outcomes	N/A

B.2.3 Summary of methodology of the relevant clinical effectiveness evidence

B.2.3.1 Study methodology

Unless otherwise stated, Sections B.2.3–B.2.7 and B.2.10 are based on the updated IMpower010 clinical study report (CSR) (CCOD 26th Jan 2024) (Data on File) (60).

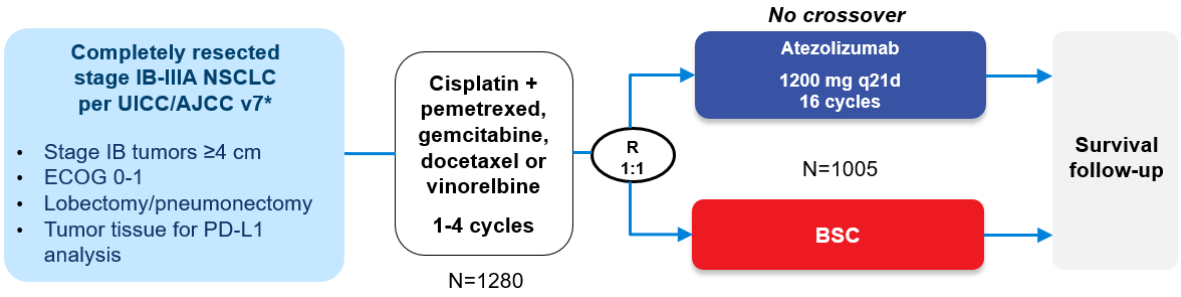
B.2.3.1.1 Study design

IMpower010 (NCT02486718) is a global, randomised, open-label, phase III trial, designed to compare the efficacy and safety of atezolizumab versus BSC. The BSC arm refers to the active monitoring of patients following adjuvant chemotherapy. Treatment with atezolizumab was investigated following adjuvant cisplatin-based chemotherapy in patients with completely resected Stage IB–IIIA NSCLC (TNM 7th edition).

The study consisted of two phases: an enrolment phase and randomised phase. In the enrolment phase, patients who had undergone complete resection of their NSCLC were screened, and eligible patients were enrolled to receive one of four regimens of cisplatin-based chemotherapy (cisplatin plus vinorelbine, docetaxel, gemcitabine, or pemetrexed; based on investigator choice). The patients received up to four cycles of cisplatin-based chemotherapy unless unacceptable toxicity, disease relapse, or

patient's decision to discontinue. The randomised phase started after patients had completed their cisplatin-based chemotherapy and were still considered eligible to proceed with randomisation. The study schema is presented below (Figure 2).

Figure 2: IMpower010 study schema for adult patients



** Stage II–IIIA in the AJCC 7th edition became IIB–IIIA and select IIIB in the AJCC 8th edition (Appendix G). Both arms included observation and regular scans for disease recurrence on the same schedule.*
Abbreviations: AJCC, American Joint Committee on Cancer; BSC, Best Supportive Care; DFS, Disease Free survival; ECOG, Eastern Cooperative Oncology Group; IC, tumour-infiltrating immune cells; ITT, intent to treat; OS, Overall Survival; PD-L1, Programmed death-ligand 1; TC, tumour cells; UICC, Union for International Cancer Control.

B.2.3.1.2 Enrolment

Patients were screened and deemed eligible if they were age ≥ 18 years with an Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1, who had a complete surgical resection of a histologically or cytologically confirmed Stage IB (tumours ≥ 4 cm) – Stage IIIA NSCLC (as per the UICC/AJCC staging system, 7th edition - see Appendix G for more information on staging). Patients were also tested for PD-L1 tumour expression by immunohistochemistry (IHC), but were enrolled in the study regardless of their PD-L1 status. Patients enrolled in the study included those with EGFR/ALK+ NSCLC since there was no clear rationale for their exclusion at the time of study design (2015). Such that, it was not standard practice to determine driver mutation status in early NSCLC, the efficacy of anti-PD-L1 immunotherapy in patients with EGFR/ALK+ NSCLC was unknown, and there was a lack of approved targeted treatment for these genetic alterations in the adjuvant setting (61-63).

B.2.3.1.3 Randomisation

The randomisation phase began 3–8 weeks after patients had completed their cisplatin-based chemotherapy. At the time of study design, there was no Phase II or III data of combining chemotherapy with cancer immunotherapy. Therefore, to avoid the adverse event profile of chemotherapy in combination with atezolizumab, the

treatments were administered sequentially, to minimise adverse effects in patients recovering from surgery whilst maximising benefit.

Patients were randomised in a 1:1 ratio to receive either atezolizumab (Arm A) or BSC (Arm B). Randomisation was stratified by gender (male vs. female), tumour histology (squamous vs. non-squamous), extent of disease (Stage IB vs. II vs. IIIA), and PD-L1 tumour expression by IHC (TC2/3 and any IC vs. TC0/1 and IC2/3 vs. TC0/1 and IC0/1 via SP142 IHC assay).

In Arm A, atezolizumab was administered intravenously on Day 1 of each 21-day cycle for a total of 16 cycles. Patients randomised to Arm B were continually followed starting on Day 1 of each 21-day cycle. To ensure the same frequency of study assessments between the treatment arms, including assessments for disease recurrence and safety, patients in Arm B were required to undergo medical contacts Q3W for assessments during the first year, which consisted of formal clinic visits alternating with clinical contacts (either via telephone call or formal outpatient clinic visit) for symptom and adverse event assessment. No crossover was allowed from Arm B to Arm A.

B.2.3.1.4 Assessments

All patients underwent scheduled tumour assessments at baseline, every 4 months starting at Cycle 1, Day 1 in the first year, and every 6 months in the second year by CT scan. Brain imaging was required for all patients at screening and during the study to rule out CNS metastasis.

Patients who did not experience recurrence of disease underwent tumour assessments every 6 months by CT and X-ray during Years 3–5 post-randomisation (starting with CT scan, alternating with X-ray), and annually thereafter by X-ray.

In the absence of disease recurrence, tumour assessments continued regardless of whether patients started new anti-cancer therapy, until disease recurrence, withdrawal of consent, death, loss to follow-up, or study termination by the Sponsor, whichever occurred first. Patients from both treatment arms underwent a mandatory tumour biopsy sample collection, at the first evidence of radiographic disease recurrence, unless assessed by investigators as not clinically feasible.

Safety assessments included the incidence, nature, and severity of adverse events (AEs), serious adverse events (SAEs), adverse events of special interest (AESIs), and laboratory abnormalities. AEs were reported per National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE) v4.0 and coded per Medical Dictionary for Regulatory Activities (MedDRA) v23.1.

B.2.3.1.5 Inclusion/exclusion criteria

To enrol in the study, patients must have had a complete surgical resection of Stage IB (tumours ≥ 4 cm) – IIIA (per the UICC/AJCC staging system, 7th edition) NSCLC, and an ECOG Performance Status of 0 or 1. Patients who had completed between 1 and 4 cycles of chemotherapy during the enrolment phase and continued to meet eligibility criteria were randomised to receive either atezolizumab or BSC.

See Appendix E for the full inclusion/exclusion criteria.

B.2.3.2 PD-L1 IHC assay comparison

The initial IMpower010 study protocol mandated the use of the SP142 (Ventana) assay for PD-L1 testing of tumour specimens and for patient stratification, which reflected knowledge at the time of study design (2014/2015). Although the SP142 assay, which measures PD-L1 expression in both tumour-infiltrating immune cells (IC) and tumour cells (TC), has shown predictive value for atezolizumab, it might be less sensitive compared to other PD-L1 assays (64). Based on external data, the PD-L1 diagnostic landscape in advanced NSCLC moved toward the routine use of TC-based PD-L1 assays. To harmonise with the changing PD-L1 testing landscape, the protocol was subsequently amended, so that the SP263 (Ventana) assay was used to define the primary efficacy endpoint (defined as TC ≥ 1%). See Appendix F for more details on IMpower010 protocol amendments.

While stratification remained by SP142 assay, baseline samples were re-analysed with the SP263 assay to define the primary analysis population of TC ≥ 1%. The proportion of baseline PD-L1 expression by SP263 were similar and well-balanced between study arms. In addition, within the Stage II–IIIA SP263 PD-L1 TC ≥ 50% group, baseline characteristics were generally well-balanced between the atezolizumab arm and the BSC arm. Therefore, analysis were adequately powered to

investigate the DFS benefit of atezolizumab vs BSC in the PD-L1 positive patient population defined by the SP263 assay.

B.2.3.3 Efficacy endpoint measures

The primary efficacy endpoint was duration of DFS as assessed by the investigator, tested hierarchically (see Section B.2.4 for more details):

- In the Stage II–IIIA population whose tumours expressed PD-L1 on 1% or more of tumour cells by the SP263 immunohistochemistry assay (hereafter referred to as PD-L1 ≥ 1% TC Stage II–IIIA population)
- In all randomised patients with Stage II–IIIA NSCLC
- In the ITT population (Stage IB–IIIA population, regardless of PD-L1 expression)

DFS was defined as the time from the date of randomisation to the date of occurrence of any of the following: first documented recurrence of disease, new primary NSCLC or death due to any cause, whichever occurred first.

Secondary efficacy endpoints included:

- OS analysis in the ITT population, from the date of randomisation to death due to any cause
- DFS 3- and 5-year landmark analysis for PD-L1 ≥ 1% TC Stage II–IIIA population, all-randomised Stage II–IIIA population, and the ITT population
- DFS analysis in additional PD-L1 subpopulation (defined by SP263 TC ≥ 50% in all randomised patients with Stage II–IIIA NSCLC)
- Safety analyses on all randomised patients who received any amount of the study drug, with patients allocated according to whether or not any amount of atezolizumab was received

Exploratory endpoints included:

- DFS and OS rate at landmark time points (in addition to DFS 3- and 5-year survival rates as secondary endpoints [every 1 year from randomisation])
- Subgroup analysis (the effects of demographics and baseline prognostic characteristics on duration of DFS and OS)
- Sensitivity analysis (impact of loss to follow-up on DFS)

- DFS analyses in other PD-L1 subpopulations
  - TC3 or IC3, TC2/3 or IC2/3, TC1/2/3 or IC1/2/3 subpopulations defined by SP142 IHC in both the Stage II–IIIA and the ITT populations;
  - PD-L1 subpopulations defined by 22C3 TPS ≥ 1% and TPS ≥ 50% in both the Stage II–IIIA and the ITT populations;
  - PD-L1 subpopulations defined by SP263 TPS ≥ 1% and TPS ≥ 50% in the ITT population)

B.2.3.4 Patient demographics and baseline characteristics

At the time of the first DFS interim analysis for IMpower010 (CCOD 21st January 2021), all patients had completed treatment and were either in follow-up, had withdrawn consent or had died (Table 4). As a result, baseline characteristics were not updated with the new CCOD.

Between 26th February 2016 and 16th January 2019, 1280 patients were recruited from 227 centres across 22 countries. A total of 1269 patients were enrolled and received up to 4 cycles of adjuvant chemotherapy (186 patients to the cisplatin + docetaxel regimen, 205 patients in the cisplatin + gemcitabine regimen, 472 patients in the cisplatin + pemetrexed regimen, and 406 patients in the cisplatin + vinorelbine regimen); and 1005 patients were subsequently randomised in a 1:1 ratio to receive atezolizumab or BSC.

Demographic data, baseline and disease characteristics, and stratification factors (see Section B.2.3.1.3) were generally well-balanced between treatment arms across various populations (Table 4). In the PD-L1 ≥ 50% Stage II – IIIA population, most patients were White (atezolizumab: 65.2%, BSC: 75.4%) or Asian (atezolizumab: 31.3%, BSC: 22.8%), with a median age of 62 years across both groups. The majority of patients were male (atezolizumab: 77.4%, BSC: 68.4%) and had non-squamous histology (atezolizumab: 59.1%, BSC: 60.5%). Disease stages included Stage II (atezolizumab: 53.9%, BSC: 50.0%) and Stage IIIA (atezolizumab: 46.1%, BSC: 50.0%) (65).

Table 4: Patient demographics and baseline characteristics by groups (PD-L1 TC ≥ 50%, PD-L1 TC ≥ 1%, and ITT populations) [CCOD 21 Jan 21]

Characteristics	All patients (N=1005)	PD-L1 TC ≥ 50% (SP263) (Stage II–IIIA)[e] (65)		PD-L1 TC ≥ 1% (SP263) (Stage II–IIIA)		ITT (Stage IB–IIIA)	
		Atezolizumab (n=115)	BSC (n=114)	Atezolizumab (n=248)	BSC (n=228)	Atezolizumab (n=507)	BSC (n=498)
Median age, y (range)	62 (26-84)	62 (34-77)	62 (36-84)	61 (34-82)	62 (26-84)	62 (33-83)	62 (26-84)
Age ≥ 65 y, n (%)	382 (38.0)	45 (39.1)	46 (40.4)	92 (37.1)	97 (42.5)	184 (36.3)	198 (39.8)
Sex, male, n (%)	672 (66.9)	89 (77.4)	78 (68.4)	171 (69.0)	147 (64.5)	337 (66.5)	335 (67.3)
Race, n (%)							
White	738 (73.4)	75 (65.2)	86 (75.4)	162 (65.3)	166 (72.8)	362 (71.4)	376 (75.5)
Asian	242 (24.1)	36 (31.3)	26 (22.8)	78 (31.5)	56 (24.6)	130 (25.6)	112 (22.5)
Other	25 (2.5)	4 (3.5)	2 (1.8)	8 (3.2)	6 (2 .6)	15 (3.0)	10 (2.0)
ECOG PS, n (%)							
0	556 (55.3)	71 (61.7)	60 (52.6)	140 (56.5)	125 (54.8)	273 (53.8)	283 (56.8)
1	446 (44.4)	44 (38.3)	53 (46.5)	107 (43.1)	102 (44.7)	232 (45.8)	214 (43.0)
Histology, non-squamous, n (%)	659 (65.6)	68 (59.1)	69 (60.5)	152 (61.3)	143 (62.7)	328 (64.7)	331 (66.5)
Stage, n (%)							
IB	123 (12.2)	NA	NA	NA	NA	65 (12.8)	58 (11.6)
IIA	295 (29.4)	62 (53.9)	57 (50.0)	85 (34.3)	76 (33.3)	147 (29.0)	148 (29.7)
IIB	174 (17.3)			46 (18.5)	37 (16.2)	90 (17.8)	84 (16.9)
IIIA	413 (41.1)	53 (46.1)	57 (50.0)	117 (47.2)	115 (50.4)	205 (40.4)	208 (41.8)
Type of surgery, n (%)[a]							
Lobectomy	785 (78.1)	87 (75.7)[f]	86 (75.4)[f]	-	-	394 (77.7)[f]	391 (78.5)[f]
Pneumonectomy	160 (15.9)	20 (17.4)	20 (17.5)	-	-	77 (15.2)	83 (16.7)
Bilobectomy	50 (5.0)	7 (6.1)	7 (6.1)	-	-	31 (6.1)	19 (3.8)

Median (range) time from surgery to first atezolizumab treatment or BSC, months	5.2 (2.3-8.0)	-	-	-	-	5.2 (2.4-7.7)	5.1 (2.3-8.0)
Chemotherapy treatment, n (%)							
Cisplatin-docetaxel	152 (15.1)	13 (11.3)	20 (17.5)	-	-	77 (15.2)	75 (15.1)
Cisplatin-gemcitabine	165 (16.4)	22 (19.1)	17 (14.9)	-	-	88 (17.4)	77 (15.5)
Cisplatin-vinorelbine	303 (30.1)	45 (39.1)	40 (35.1)	-	-	152 (30.0)	151 (30.3)
Cisplatin-pemetrexed	385 (38.3)	35 (30.4)	37 (32.5)	-	-	190 (37.5)	195 (39.2)
Tobacco use history, n (%)							
Never	222 (22.1)	16 (13.9)	15 (13.2)	51 (20.6)	41 (18.0)	114 (22.5)	108(21.7)
Current/previous	783 (77.9)	99 (86.1)	99 (86.8)	197 (79.4)	187 (82.0)	393 (77.5)	390 (78.3)
PD-L1 by SP263, TC ≥1%, n (%)[b]	535 (54.6)	-	-	248 (100)	228 (100)	283 (57.4)	252 (51.9)
EGFR mutation status , n (%)[c]							
Positive	117 (11.6)	6 (5.2)	8 (7.0)	23 (9.3)	20 (8.8)	53 (10.5)	64 (12.9)
Negative	527 (52.4)	60 (52.2)	64 (56.1)	123 (49.6)	125 (54.8)	261 (51.5)	266 (53.4)
Unknown	361 (35.9)	49 (42.6)	42 (36.8)	102 (41.1)	83 (36.4)	193 (38.1)	168 (33 .7)
ALK rearrangement status, n (%)[c]							
Positive	33 (3.3)	3 (2.6)	3 (2.6)	12 (4.8)	11 (4.8)	15 (3.0)	18 (3.6)
Negative	574 (57.1)	62 (53.9)	62 (54.4)	133 (53.6)	121 (53.1)	280 (55.2)	294 (59.0)
Unknown[d]	398 (39.6)	50 (43.5)	49 (43.0)	103 (41.5)	96 (42.1)	212 (41.8)	186 (37.3)

[a] Subgroups with ≤10 patients are not shown.

[b] 26 patients in the ITT population had unknown PD-L1 status as assessed by SP263.

[c] For patients with non-squamous NSCLC, EGFR/ALK status was assessed locally or centrally.

[d] 89.2% of patients with unknown EGFR status and 80.7% of patients with unknown ALK status in the ITT population had squamous NSCLC and were not required to undergo local or central testing.

[e] Baseline characteristics were similar in the PD-L1 ≥ 50% population excluding EGFR/ALK+ patients.

f Includes patients who had lobectomy and sleeve lobectomy.

Clinical data cut-off date (CCOD): 21 Jan 2021

At the updated CCOD of 26th January 2024, in the ITT population, the proportion of patients that had discontinued from the study remained balanced between treatment arms (BSC: 43% vs atezolizumab: 41%), with the most common reason being death (31% vs. 30%), followed by patient withdrawal (9% in each arm) (Table 5).

Table 5: Patient disposition (ITT population) [updated CCOD Jan 24]

	Atezolizumab (n=507)	BSC (n=498)	All patients (N=1005)
Received treatment	495 (97.6%)	495 (99.4%)	990 (98.5%)
On study status			
Ongoing	301 (59.4%)	282 (56.6%)	583 (58.0%)
Discontinued	206 (40.6%)	216 (43.4%)	422 (42.0%)
Discontinued study			
Death	154 (30.4%)	155 (31.1%)	309 (30.7%)
Disease relapse	1 (0.2%)	0	1 (<0.1%)
Lost to follow-up	5 (1.0%)	11 (2.2%)	16 (1.6%)
Physician decision	0	3 (0.6%)	3 (0.3%)
Protocol deviation	2 (0.4%)	0	2 (0.2%)
Withdrawal by subject	44 (8.7%)	47 (9.4%)	91 (9.1%)

Includes study disposition events occurring on or after the randomisation date.

B.2.4 Statistical analysis and definition of study groups in the relevant clinical effectiveness evidence

B.2.4.1 Statistical testing plan

The IMpower010 trial explored the efficacy of atezolizumab in the following populations:

Primary efficacy analysis of DFS in:

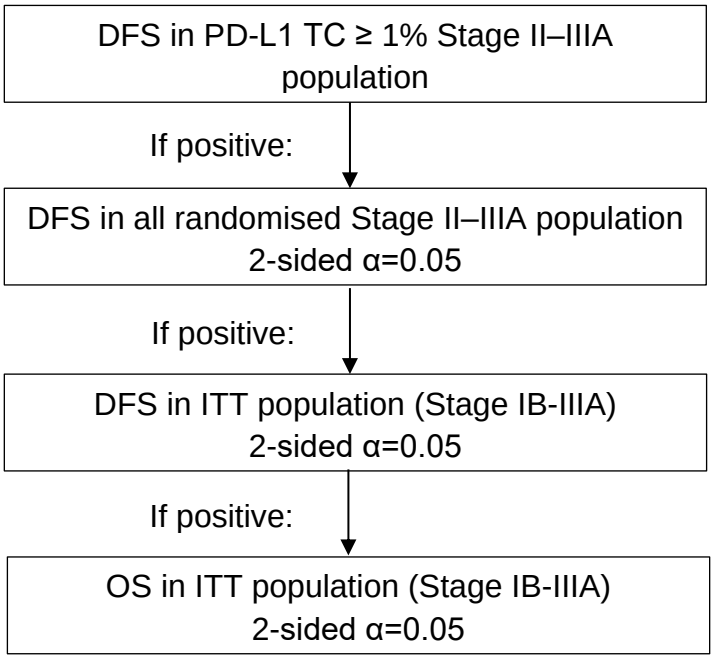
- PD-L1 TC ≥ 1% Stage II–IIIA population,
- All randomised Stage II–IIIA population,
- ITT Stage IB–IIIA population

Secondary efficacy analysis of:

- OS in ITT Stage IB–IIIA population

The IMpower010 statistical analysis plan is summarised below (Figure 3). DFS was tested hierarchically followed by OS. If the primary DFS endpoint was statistically positive in all three primary analysis populations, a two-sided significance level of 0.05 was passed down to compare OS in the ITT population.

Figure 3: IMpower010 statistical analysis plan



The hierarchical testing plan was designed to investigate the efficacy profile in patients most likely to benefit, taking into account PD-L1 expression level and disease stage (Table 6).

Table 6: Rationale for hierarchical testing in IMpower010

Population and endpoints	Rationale
DFS in PD-L1 TC ≥ 1% Stage II–IIIA population	• Data for chemotherapy in early NSCLC indicated a higher benefit in more advanced disease (36). Therefore, Stage IB patients were not included in the first population to be tested. • Data readouts for PD-L1/PD-1 therapies in advanced and metastatic NSCLC indicated a positive correlation between PD-L1 expression and clinical benefit (63, 66, 67).

	• Therefore, the first group to tested was based on PD-L1 expression of ≥ 1% for patients with higher stages of disease, i.e. Stage II–IIIA
DFS in all randomised Stage II–IIIA population	• All randomised patients regardless of PD-L1 expression, excluding Stage IB patients (see below)
DFS in ITT population (Stage IB–IIIA)	• Disease recurrence and survival in Stage I NSCLC is longer than Stage II-III disease (68), so it may take longer to demonstrate an improvement in this setting • Therefore, DFS in the ITT population, was the last population to be tested for DFS
OS in ITT population (Stage IB–IIIA)	• Overall survival data would take longer to read out in early NSCLC, therefore this was last to be tested in the statistical analysis testing hierarchy

B.2.5 Quality assessment of the relevant clinical effectiveness evidence

The quality assessment of the IMpower010 trial is shown below (Table 7). See Appendix D for the complete quality assessment of other relevant trials.

Table 7: Risk of bias assessment for IMpower010

Trial	Random sequence generation	Allocation concealment	Comparability of groups	Blinding	Imbalance in dropouts	Selective reporting	Complete reporting	Overall rating for risk of bias
IMpower010	Yes	Yes	Yes	No	No	No	Yes	Low

Blue text is used for answers that indicate a lack of bias; red text is used for answers that indicate potential bias.

B.2.6 Clinical effectiveness results from IMpower010

- **IMpower010 was the first Phase III study of adjuvant immunotherapy to demonstrate a DFS improvement in the fully resected early NSCLC patients following platinum-based chemotherapy.**
- **At the first DFS interim analysis (CCOD 21st January 2021), the study met its primary endpoint, demonstrating a statistically significant and clinically meaningful improvement in DFS as assessed by the investigator. A 34% reduction in risk of disease recurrence, new NSCLC or death (HR: 0.66; 95% CI: 0.50, 0.88; p=0.004) was observed with adjuvant atezolizumab as compared to BSC in the PD-L1 ≥ 1% TC Stage II–IIIA NSCLC population.**
    - **In the ITT population at the updated CCOD (26th January 2024), with a longer median duration of follow-up of 65.0 months (range, 0.0–94.4), the primary endpoint of DFS did not cross the statistical significance boundary (two-sided α = 0.0325). However, a trend of clinical benefit in the atezolizumab arm compared to the BSC arm was observed.**
- **The secondary endpoint of OS in the ITT population was not formally tested at the time of the DFS final analysis (CCOD 26th January 2024). It was considered immature with low event-to-patient ratios (31.4% atezolizumab vs. 31.5% BSC). As per pre-specified testing hierarchy, there will be no formal testing for subsequent OS analyses.**
- **The secondary endpoint of DFS in the PD-L1 ≥ 50% TC Stage II–IIIA population showed consistent results between the DFS final and interim analyses with a clinically meaningful improvement in the atezolizumab arm compared to the BSC arm (unstratified HR = 0.48; 95% CI: 0.32, 0.72).**
- **The exploratory endpoint of DFS in the PD-L1 ≥ 50% TC Stage II–IIIA population, without known EGRF or ALK alterations, showed consistent and robust benefits with atezolizumab excluding the 20 patients with these mutations (HR = 0.49; 95% CI: 0.32, 0.75).**
- **The exploratory endpoint of OS in the PD-L1 ≥ 50% TC Stage II–IIIA population, without known EGRF or ALK alterations, also showed consistent and robust survival benefit with atezolizumab excluding the 20 patients with these mutations (HR = 0.44; 95% CI: 0.26, 0.74).**

B.2.6.1 Overview of efficacy

At the first DFS interim analysis for IMpower010 (CCOD 21st January 2021), which occurred when 193 DFS events had occurred in the PD-L1 SP263 ≥ 1% TC Stage II–IIIA patient population, the study met its primary endpoint, showing a statistically significant and clinically meaningful DFS improvement for atezolizumab over BSC. While the results of DFS in the ITT population showed a trend in favour of atezolizumab, it did not cross the pre-specified alpha boundary (two-sided α = 0.0368), and OS was not formally tested due to immature data with low event-to-patient ratios.

By the time of the updated CCOD (26th January 2024), a total of 499 DFS events had been reported in the ITT population (239 [47.1%] in atezolizumab arm; 260 [52.2%] in the BSC arm). OS events in the ITT population were 159 (31.4%) in the atezolizumab arm and 157 (31.5%) in the BSC arm.

Table 8 provides an overview of key efficacy results for DFS and OS across various populations: PD-L1 SP263 ≥ 1% TC Stage II–IIIA population, all randomised Stage II–IIIA population, ITT (Stage IB-IIIA) population, PD-L1 SP263 ≥ 50% TC Stage II–IIIA population, and PD-L1 SP263 ≥ 50% TC Stage II–IIIA population excluding EGFR and ALK mutations.

Table 8: Overview of efficacy of IMpower010

	CCOD 26 Jan 2024		CCOD 21 Jan 2021	
	Atezolizumab	BSC	Atezolizumab	BSC
DFS in PD-L1 SP263 ≥ 1% TC Stage II-IIIA				
n	248	228	248	228
No. (%) of events	113 (45.6%)	127 (55.7%)	88 (35.5%)	105 (46.1%)
Median DFS (months, 95% CI)	68.5 (51.8, NE)	37.3 (30.1, 57.8)	NE (36.1, NE)	35.3 (29.0, NE)
Stratified HR (95% CI)	0.70 (0.55, 0.91)		0.66 (0.50, 0.88)	
3-year DFS rate (%, 95% CI)	62.7 (56.5, 68.9)	52.1 (45.4, 58.8)	60.0 (52.8, 67.1)	48.2 (40.7, 55.7)
5-year DFS rate (%, 95% CI)	53.2 (46.7, 59.6)	42.7 (36.0, 49.4)	NE	NE
DFS in all randomised Stage II-IIIA				
n	442	440	442	440
No. (%) of events	219 (49.5%)	240 (54.5%)	173 (39.1%)	198 (45.0%)
Median DFS (months, 95% CI)	57.4 (42.2, NE)	40.8 (31.4, 57.1)	42.3 (36.0, NE)	35.3 (30.4, 46.4)
Stratified HR (95% CI)	0.83 (0.69, 0.998)		0.79 (0.64, 0.96)	
3-year DFS rate (%, 95% CI)	59.3 (54.6, 64.0)	52.6 (47.8, 57.5)	55.7 (50.3, 61.2)	49.4 (44.0, 54.9)
5-year DFS rate (%, 95% CI)	49.3 (44.5, 54.1)	44.4 (39.6, 49.2)	NE	NE
DFS in ITT (Stage IB-IIIA)				
n	507	498	507	598
No. (%) of events	239 (47.1%)	260 (52.2%)	187 (36.9%)	212 (42.6%)
Median DFS (months, 95% CI)	65.6 (52.4, NE)	47.8 (37.0, 65.8)	NE (36.1, NE)	37.2 (31.6, NE)
Stratified HR (95% CI)	0.85 (0.71, 1.01)		0.81 (0.67, 0.99)	

p-value (Stratified log-rank)	0.0683		0.0395	
3-year DFS rate (%, 95% CI)	61.4 (57.1, 65.8)	55.5 (51.0, 60.0)	57.9 (52.9, 63.0)	52.6 (47.5, 57.6)
5-year DFS rate (%, 95% CI)	52.0 (47.5, 56.5)	46.5 (41.9, 51.1)	NE	NE
OS in ITT (Stage IB-IIIA)				
n	507	498	507	498
No. (%) of events	159 (31.4%)	157 (31.5%)	127 (25.0%)	124 (24.9%)
Median OS (months, 95% CI)	NE	NE (87.1, NE)	NE	NE
Stratified HR (95% CI)	0.97 (0.78, 1.22)		0.995 (0.78, 1.28)	
DFS in PD-L1 SP263 ≥ 50% TC Stage II-IIIA				
n	115	114	115	114
No. (%) of events	38 (33.0%)	62 (54.4%)	28 (24.3%)	52 (45.6%)
Median DFS (months, 95% CI)	NE	41.1 (29.7, NE)	NE (42.3, NE)	35.7 (29.7, NE)
Unstratified HR (95% CI)	0.48 (0.32, 0.72)		0.43 (0.27, 0.68)	
3-year DFS rate (%)	74.9	53.2	NA	
5-year DFS rate (%)	65.1	44.5		
OS in PD-L1 SP263 ≥ 50% TC Stage II-IIIA				
n	115	114	NA	
No. (%) of events	24 (20.9%)	43 (37.7%)		
Median OS (months, 95% CI)	NE	87.1 (72.6, NE)		
Stratified HR (95% CI)	0.47 (0.28, 0.77)			
3-year DFS rate (%)	89.1	77.8		
5-year DFS rate (%)	82.7	65.3		
DFS in PD-L1 SP263 ≥ 50% TC Stage II-IIIA, excluding EGFR and ALK				

n	106	103	NA
No. (%) of events	34 (32.1%)	55 (53.4%)	
Median DFS (months)	NE	42.9	
Unstratified HR (95% CI)	0.49 (0.32, 0.75)		
3-year DFS rate (%)	75.7	55.4	
5-year DFS rate (%)	66.1	45.8	
OS in PD-L1 SP263 ≥ 50% TC Stage II-IIIA, excluding EGFR and ALK			
n	106	103	NA
No. (%) of events	22 (20.8%)	41 (39.8%)	
Median OS (months, 95% CI)	NE	87.1	
Stratified HR (95% CI)	0.44 (95% CI: 0.26, 0.74)		
3-year OS rate (%)	89.1	77.5	
5-year OS rate (%)	82.1	63.7	

Abbreviations: BSC = best supportive care; CCOD = clinical cut-off date; DFS = disease-free survival; HR = hazard ration; IA = interim analysis; INV = investigator; ITT = intent-to-treat; NA = not available; NE = not estimable; OS = overall survival; PD-L1 = programmed death-ligand 1; TC = tumour cell.

B.2.6.2 Primary efficacy endpoint – disease-free survival (DFS)

DFS is a common endpoint for adjuvant studies in solid tumours. Both the FDA and EMA consider DFS as an acceptable endpoint for adjuvant treatment for solid tumours, and there is precedent for its utility in the approval of prior treatments within the adjuvant setting across different tumour types. For example, approval of adjuvant osimertinib in EGFR-positive, resected early NSCLC on the basis of DFS from the ADAURA study (69); as well as approval of adjuvant trastuzumab emtansine for early human epidermal growth factor receptor 2 (HER2)+ breast cancer based on invasive DFS from the KATHERINE study (70).

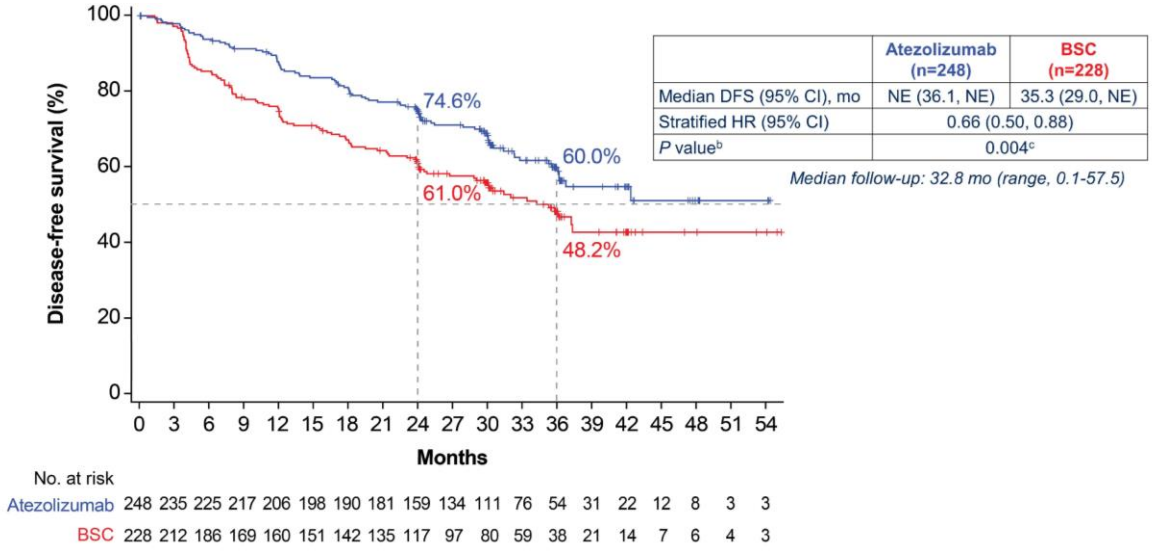
B.2.6.2.1 DFS in the PD-L1 ≥ 1% TC Stage II–IIIA population

At the CCOD on 21st January 2021, after a median follow up of 32.8 months, DFS showed a statistically significant and clinically meaningful improvement in the atezolizumab arm compared to the BSC arm in Stage II–IIIA patients with PD-L1 ≥ 1%. A higher proportion of patients in the BSC arm (46.1%) compared to the atezolizumab arm (35.5%) had experienced disease recurrence or death.

The primary endpoint was met as the pre-specified interim analysis alpha boundary (two-sided $\alpha = 0.0370$) was crossed for DFS in the PD-L1 ≥ 1% TC Stage II–IIIA population. The stratified HR was 0.66 (95% CI: 0.50, 0.88; $p = 0.0039$), which corresponds to a 34% reduction in the risk of recurrence, new NSCLC or death with atezolizumab compared to BSC.

The KM estimated median DFS was not reached in the atezolizumab arm and was 35.3 months in the BSC arm. The KM curves began to separate at approximately 4 months (corresponding to the first scheduled tumour assessment) after randomisation in favor of the atezolizumab arm and was maintained thereafter (Figure 4).

Figure 4: Kaplan-Meier plot of DFS (PD-L1 ≥ 1% TC Stage II–IIIA population) [CCOD 21 Jan 21]



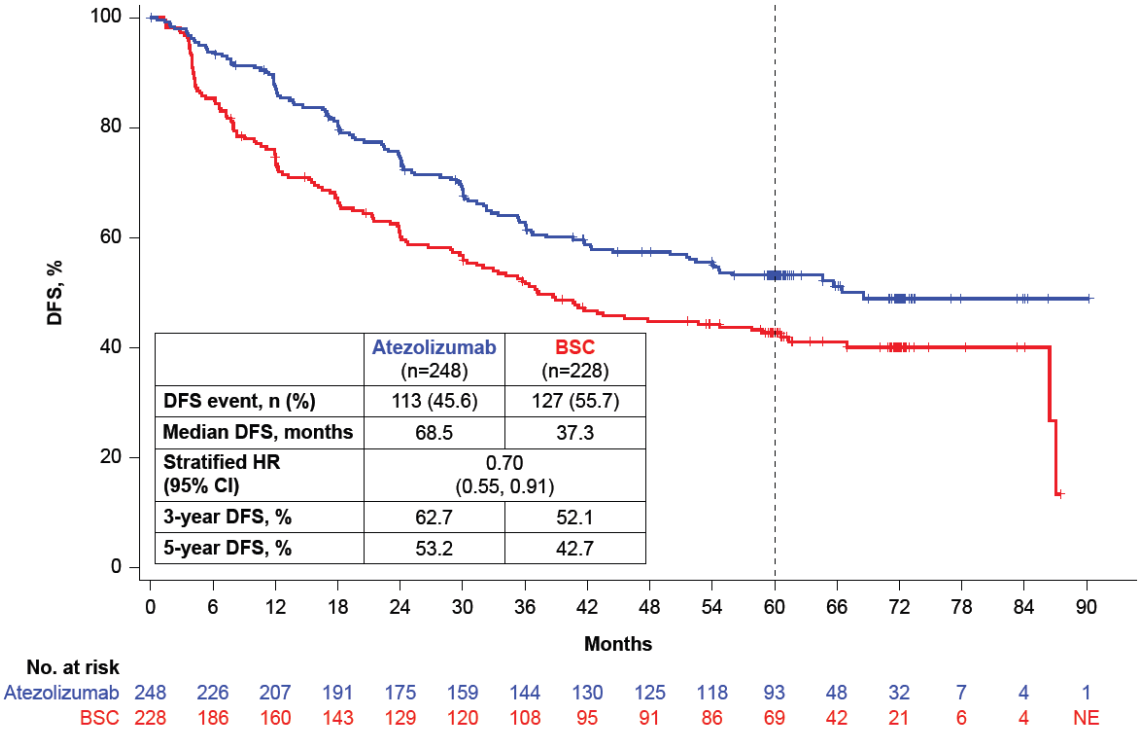
	Atezolizumab (n=248)	BSC (n=228)
Median DFS (95% CI), mo	NE (36.1, NE)	35.3 (29.0, NE)
Stratified HR (95% CI)	0.66 (0.50, 0.88)	
P value[b]	0.004[c]	

[a] *Per SP263 assay.* [b] *Stratified log-rank.* [c] *Crossed the significance boundary for DFS.*
Abbreviations: CI, confidence interval; HR, hazard ratio; NE, not evaluable
Clinical data cut-off date (CCOD): 21 Jan 2021

At the updated CCOD (26th January 2024), the DFS showed consistent results at the DFS final and interim analyses in the PD-L1 SP263 ≥1% TC Stage II–IIIA population. There was a clinically meaningful improvement in DFS in the atezolizumab arm compared to the BSC arm, where a higher proportion of patients in the BSC arm (55.7%) compared to the atezolizumab arm (45.6%) had experienced disease recurrence or death. The stratified HR was 0.70 (95% CI: 0.55, 0.91), which corresponds to a 30% relative risk reduction of a DFS event with atezolizumab compared to BSC (Table 8).

The KM estimated median DFS was 31.2 months longer in the atezolizumab arm (68.5 months) compared to the BSC arm (37.3 months). The KM curves began to separate in favour of the atezolizumab arm approximately 4 months after randomisation, which corresponds to the first scheduled tumour assessment. This separation of the curve was maintained thereafter (Figure 5).

Figure 5: Kaplan-Meier plot of DFS (PD-L1 ≥ 1% TC Stage II–IIIA population) [CCOD 26 Jan 24]

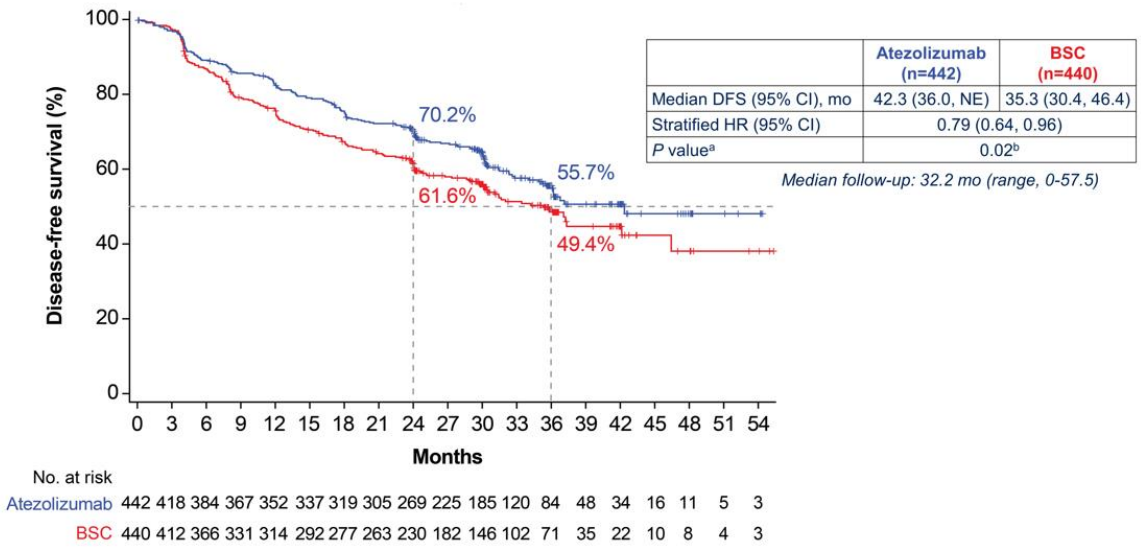


B.2.6.2.2 DFS in the all randomised Stage II–IIIA population

At the CCOD on 21st January 2021, DFS showed a statistically significant improvement in the atezolizumab arm compared to the BSC arm. A higher proportion of patients in the BSC arm (45%) compared to the atezolizumab arm (39%) had experienced disease recurrence or death. The primary endpoint was met as the pre-specified interim analysis alpha boundary (two-sided α=0.0366) was crossed for DFS in the Stage II–IIIA population. The stratified HR was 0.79 (95% CI: 0.64, 0.96; p-value = 0.0205), which corresponds to a 21% relative risk reduction of a DFS event with atezolizumab compared to BSC.

The KM estimated median DFS was 7.0 months longer in the atezolizumab arm (42.3 months) compared to the BSC arm (35.3 months). The KM curves began to separate in favour of the atezolizumab arm approximately 4 months after randomisation, which corresponds to the first scheduled tumour assessment. This separation of the curve was maintained thereafter (Figure 6).

Figure 6: Kaplan-Meier plot of DFS (all randomised Stage II–IIIA population) [CCOD 21 Jan 21]



	Atezolizumab (n=442)	BSC (n=440)
Median DFS (95% CI), mo	42.3 (36.0, NE)	35.3 (30.4, 46.4)
Stratified HR (95% CI)	0.79 (0.64, 0.96)	
P value[a]	0.02[b]	

Median follow-up: 32.2 mo (range, 0-57.5)

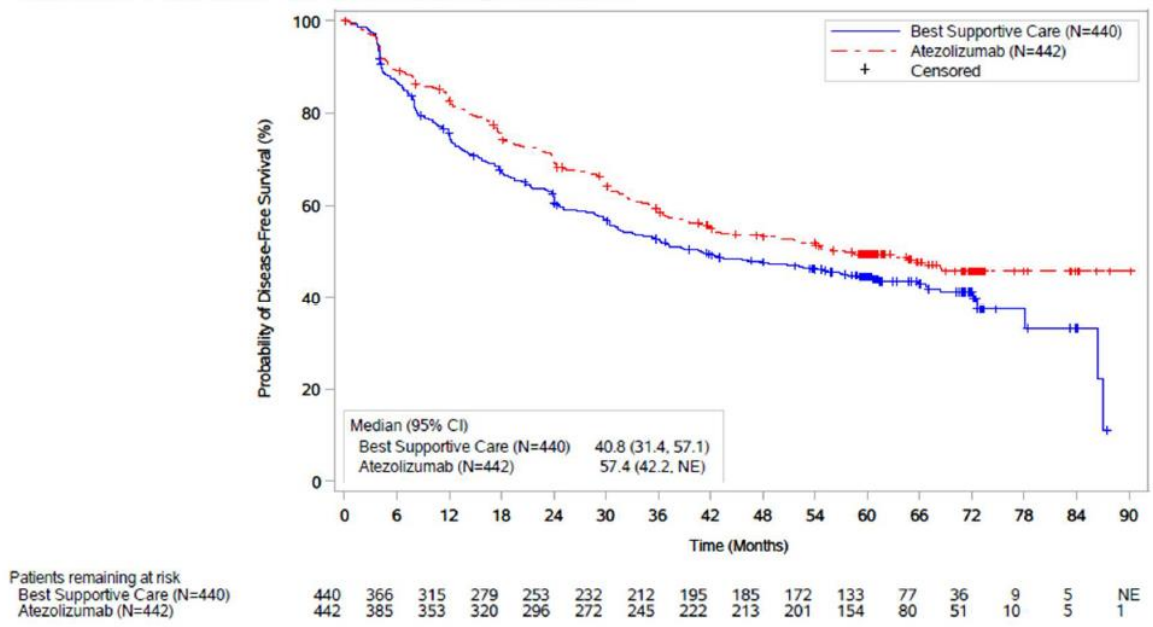
[a] Stratified log-rank. [b] Crossed the significance boundary for DFS.

Clinical data cut-off date (CCOD): 21 Jan 2021.

At the updated CCOD (26th January 2024), the DFS final analysis showed consistent results with the interim analysis of DFS with a clinically meaningful improvement of DFS in the atezolizumab arm compared to the BSC arm. A higher proportion of patients in the BSC arm (54.5%) compared to the atezolizumab arm (49.5%) had experienced disease recurrence or death (Table 8). The stratified HR was 0.83 (95% CI: 0.69, 1.00), which corresponds to a 17% relative risk reduction of a DFS event with atezolizumab compared to BSC.

The KM estimated median DFS was 16.6 months longer in the atezolizumab arm (57.4 months) compared to the BSC arm (40.8 months). The KM curves began to separate in favour of the atezolizumab arm approximately 4 months after randomisation, which corresponds to the first scheduled tumour assessment. This separation of the curve was maintained thereafter (Figure 7).

Figure 7: Kaplan-Meier plot of DFS (all randomised Stage II–IIIA population) [CCOD 26 Jan 24]

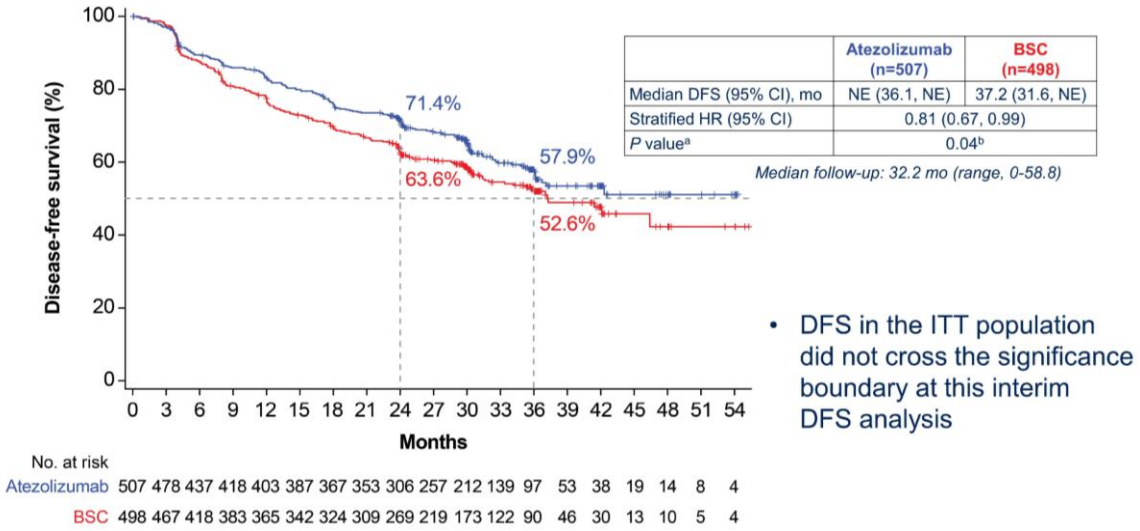


B.2.6.2.3 DFS in the ITT population

At the CCOD on 21st January 2021, although the pre-specified DFS interim analysis alpha boundary (two-sided α = 0.0368) was not crossed in the ITT population, DFS showed a trend in favour of atezolizumab over BSC. A higher proportion of patients in the BSC arm (42.6%) compared to the atezolizumab arm (36.9%) experienced disease recurrence or death. The stratified HR was 0.81 (95% CI: 0.67, 0.99; p-value=0.0395) which corresponds with a 19% relative risk reduction in a DFS event with atezolizumab compared to BSC.

The Kaplan-Meier (KM) estimated median DFS was not reached in the atezolizumab arm and was 37.2 months in the BSC arm. The KM curves began to separate in favour of the atezolizumab arm approximately 4 months after randomisation, which corresponds to the first scheduled tumour assessment. This separation of the curve was maintained thereafter (Figure 8).

Figure 8: Kaplan-Meier plot of DFS (ITT Population) [CCOD 21 Jan 21]



[a] *Stratified log-rank.* [b] *The statistical significance boundary for DFS was not crossed.*
Clinical data cut-off date (CCOD): 21 Jan 2021.

At the updated CCOD (26th January 2024), although DFS did not cross the statistical significance boundary (two-sided α=0.0325) in the ITT population, it showed a trend of clinical benefit in the atezolizumab arm compared with BSC. A higher proportion of patients in the BSC arm (52.2%) compared to the atezolizumab arm (47.1%) had experienced disease recurrence or death. The stratified HR was 0.85 (95% CI: 0.71, 1.01) (Table 8).

B.2.6.3 Secondary efficacy endpoints

B.2.6.3.1 OS in the ITT population

Overall survival (OS) is the gold standard for clinical trial endpoints; however, long-term follow up is required in early NSCLC. Therefore, surrogate endpoints are needed to bring effective treatments into the clinic more rapidly (71). DFS was adopted as the primary efficacy endpoint in IMpower010. Given the importance in understanding the role of a new therapy on prolonging patient survival, OS was included as a key secondary endpoint in IMpower010.

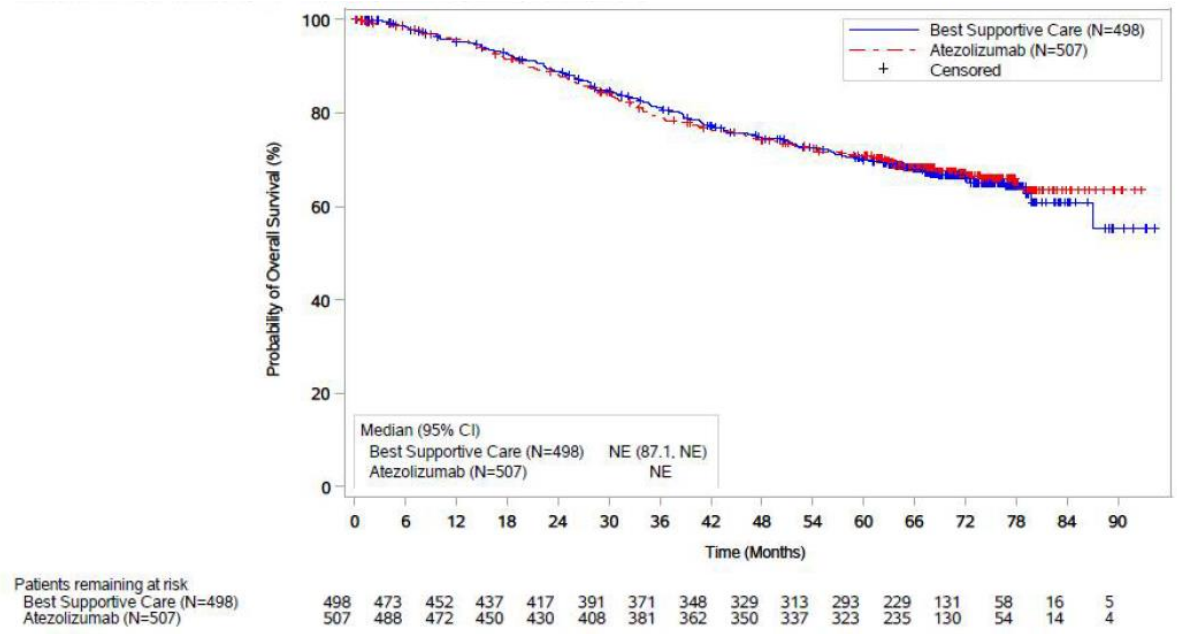
At the CCOD on 21st January 2021, the pre-specified interim analysis alpha boundary (two-sided α = 0.0368) for DFS was not crossed in the ITT population and OS data were immature with low event-to-patient ratios (19% atezolizumab vs. 18% BSC). As

a result, OS in the ITT population was not formally tested and the results presented are descriptive only.

At the updated CCOD (26th January 2024), a similar proportion of patients had died in the atezolizumab (159 [31.4%]) and BSC (157 [31.5%]) arms (Table 8). OS was not formally tested at this second OS interim analysis because DFS in the ITT population did not cross the statistical significance boundary. The stratified HR for OS was 0.97 (95% CI: 0.78, 1.21). The median OS could not be estimated in either arm at the time of the OS second interim analysis.

The KM curve is provided in Figure 9.

Figure 9: Kaplan-Meier plot of OS (ITT population) [CCOD 26 Jan 24]



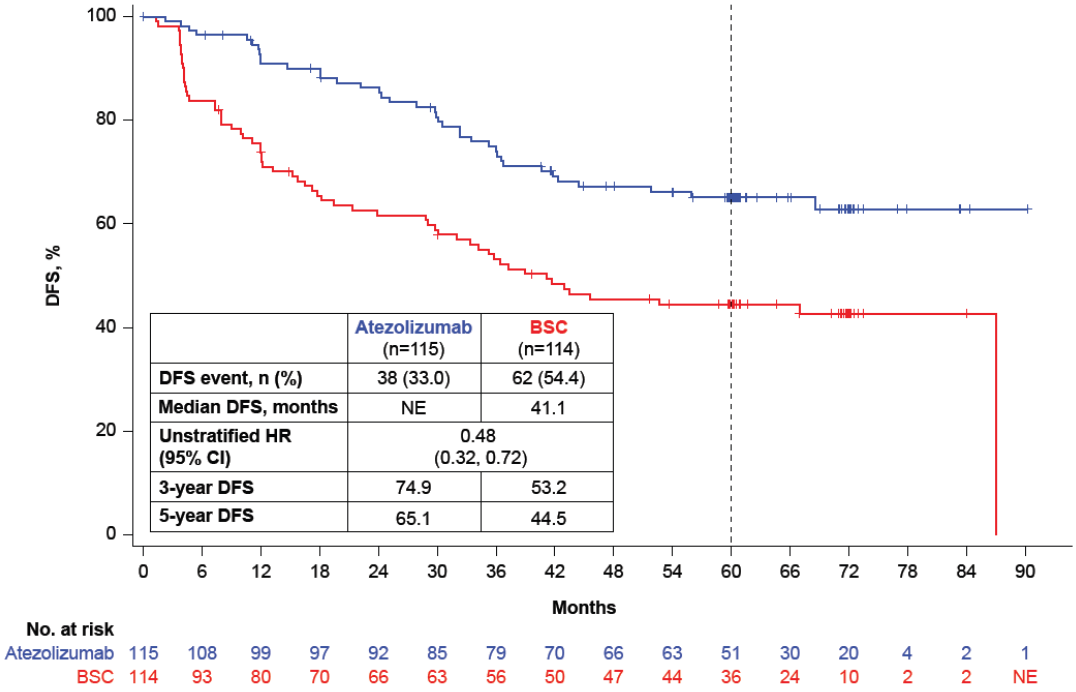
Clinical data cut-off date (CCOD): 26 Jan 2024.

B.2.6.3.2 DFS in the PD-L1 ≥ 50% TC Stage II–IIIA population

At the updated CCOD (26th January 2024), the DFS results were consistent between the DFS final and interim analyses with a clinically meaningful improvement in DFS in the atezolizumab arm compared to the BSC arm. A higher proportion of patients in the BSC arm (54.4%) compared to the atezolizumab arm (33.0%) experienced disease recurrence or death. The unstratified HR was 0.48 (95% CI: 0.32, 0.72), which corresponds to a 52% relative risk reduction of a DFS event with atezolizumab compared to BSC.

The KM estimated median DFS could not be estimated in the atezolizumab arm and was 41.1 months in the BSC arm. The KM curves began to separate in favour of the atezolizumab arm approximately 4 months after randomisation, which corresponds to the first scheduled tumour assessment. This separation of the curve was maintained thereafter (Figure 10).

Figure 10: Kaplan-Meier plot of DFS (PD-L1 ≥ 50% TC Stage II–IIIA population) [CCOD 26 Jan 24]



B.2.6.4 Exploratory endpoints

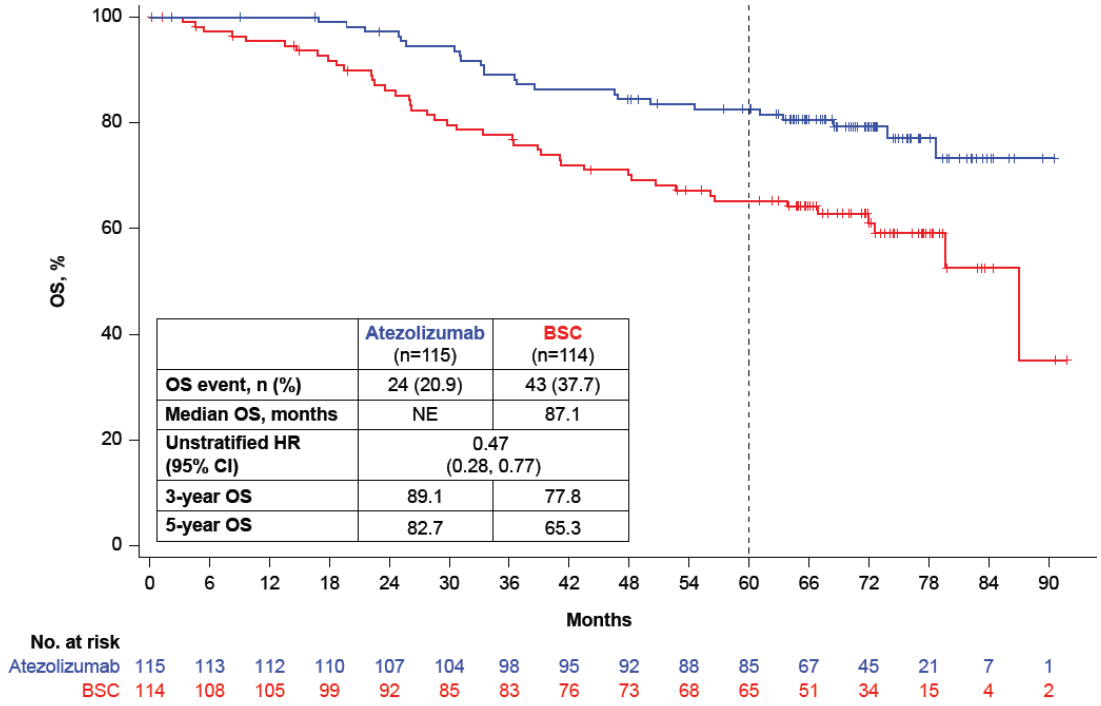
B.2.6.4.1 OS in the PD-L1 ≥ 50% TC Stage II–IIIA population

At the updated CCOD (26th January 2024), the exploratory analysis of OS showed a clinically meaningful improvement in the atezolizumab arm compared to the BSC arm in the PD-L1 SP263 ≥ 50% TC Stage II-IIIA population. The proportion of deaths observed was 20.9% in the atezolizumab arm and 37.7% in the BSC arm.

The unstratified HR for OS was 0.47 (95% CI: 0.28, 0.77) which corresponds to a 53% relative risk reduction of an OS event with atezolizumab compared to BSC. The median OS could not be estimated in the atezolizumab arm at the time of the OS second interim analysis.

There was an early separation in the OS KM curves in favour of the atezolizumab, which was maintained over time (Figure 11).

Figure 11: Kaplan-Meier plot of OS (PD-L1 ≥ 50% TC Stage II–IIIA population) [CCOD 26 Jan 24]



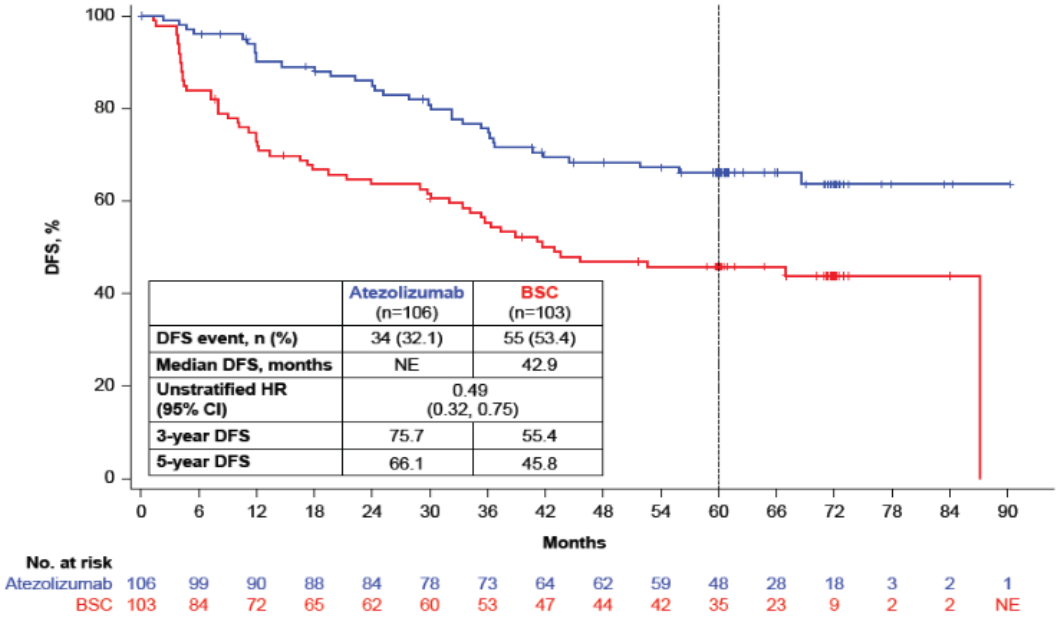
B.2.6.4.2 DFS in the PD-L1 ≥ 50% TC Stage II–IIIA population, without known EGRF or ALK alterations (72)

When the 20 patients with known EGFR mutations or ALK rearrangements were excluded from the analysis, the DFS results remained similar to Section B.2.6.3.2. At the updated CCOD (26th January 2024), the DFS results showed a clinically meaningful improvement in DFS in the atezolizumab arm compared to the BSC arm. A higher proportion of patients in the BSC group (53.4%) experienced disease recurrence or death compared to those in the atezolizumab group (32.1%). The unstratified HR was 0.49 (95% CI: 0.32, 0.75), indicating a 51% reduction in the risk of a DFS event (recurrence or death) with atezolizumab compared to BSC.

The KM estimated median DFS was not reached for the atezolizumab arm, while the median DFS in the BSC arm was 42.9 months. The DFS curves begin to separate early in the study and continue to diverge, favoring atezolizumab over time. At the 3-year and 5-year marks, DFS rates are notably higher in the atezolizumab group (75.7%

and 66.1%, respectively) compared to the BSC group (55.4% and 45.8%), highlighting the long-term benefit of atezolizumab in reducing the risk of disease recurrence in this high-risk population (Figure 12).

Figure 12: Kaplan-Meier plot of DFS (PD-L1 ≥ 50% TC Stage II–IIIA population, without known EGFR or ALK alterations) [CCOD 26 Jan 24]

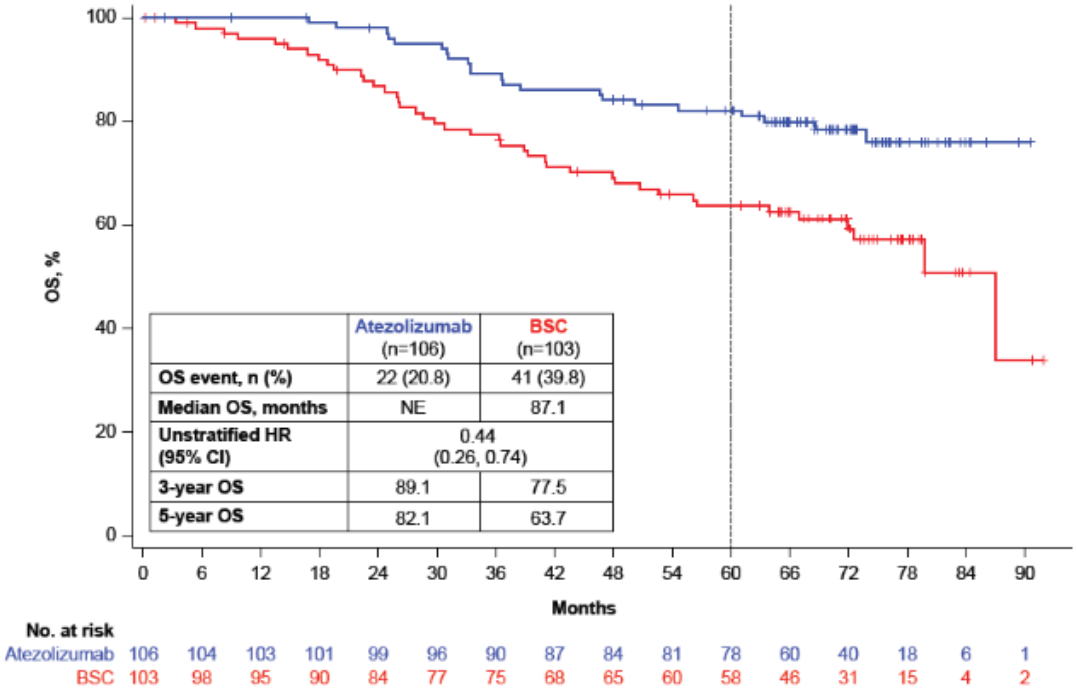


B.2.6.4.3 OS in the PD-L1 ≥ 50% TC Stage II–IIIA population, without known EGRF or ALK alterations (72)

When the 20 patients with known EGFR mutations or *ALK* rearrangements were excluded from the analysis, the OS data remained consistent to Section B.2.6.4.1, highlighting the robustness of the observed survival benefit with atezolizumab. At the updated CCOD (26th January 2024), the OS results revealed a clinically significant improvement in the atezolizumab arm compared to the BSC arm. A higher proportion of patients in the BSC group (39.8%) experienced an OS event (death) compared to those in the atezolizumab group (20.8%). The unstratified HR was 0.44 (95% CI: 0.26, 0.74), indicating a 56% reduction in the risk of death with atezolizumab compared to BSC. Clinicians consulted at a recent advisory board noted that removal of patients with ALK and EGFR alterations did not affect the outcomes of the subgroup analyses, and that there was no significant difference in OS outcomes compared to those observed in the total population (1).

The KM estimated median OS was not reached for the atezolizumab arm, while the median OS in the BSC arm was 87.1 months. The OS curves began to separate early and maintained this separation, favouring atezolizumab over time. At the 3-year and 5-year marks, OS rates were significantly higher in the atezolizumab group (89.1% and 82.1%, respectively) compared to the BSC group (77.5% and 63.7%). These findings underscore the long-term survival benefit of atezolizumab in reducing the risk of death for patients in this high-risk population (Figure 13).

Figure 13: Kaplan-Meier plot of OS (PD-L1 ≥ 50% TC Stage II–IIIA population, without known EGFR or ALK alterations) [CCOD 26 Jan 24]

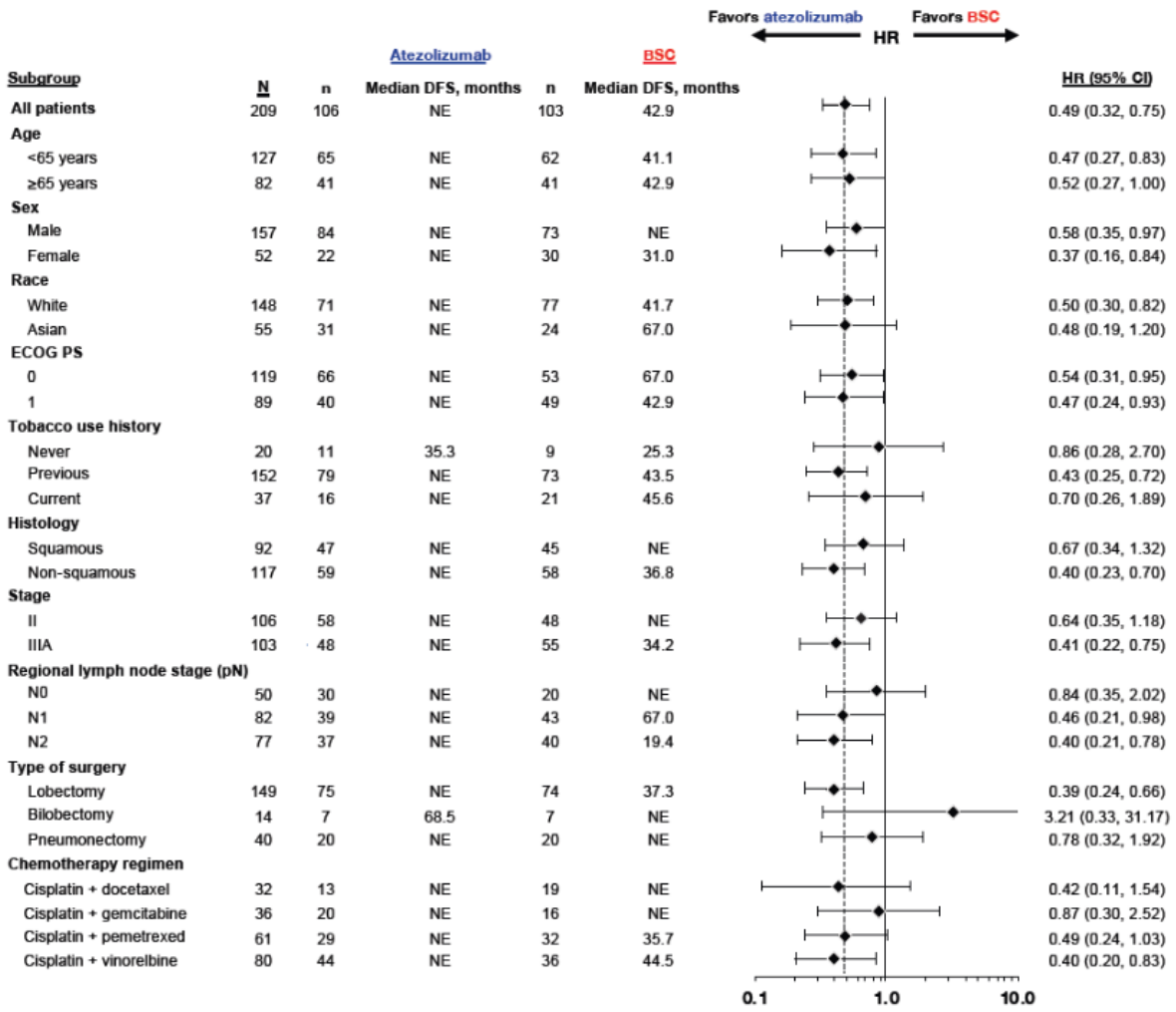


B.2.7 Subgroup analysis

B.2.7.1 DFS in the PD-L1 ≥ 50% TC Stage II–IIIA population, without known EGFR or ALK alterations (72)

At the updated CCOD (26th January 2024), the DFS benefit of atezolizumab was consistent across most pre-defined subgroups, even after excluding patients with known EGFR or ALK alterations. This analysis further reinforces the efficacy of atezolizumab in a population without these mutations, targeting those at high risk who do not typically benefit from targeted therapies for EGFR or ALK (Figure 14).

Figure 14: Subgroup analysis of DFS in the PD-L1 ≥ 50% TC Stage II–IIIA population, without known EGFR or ALK alterations [CCOD 26 Jan 24]

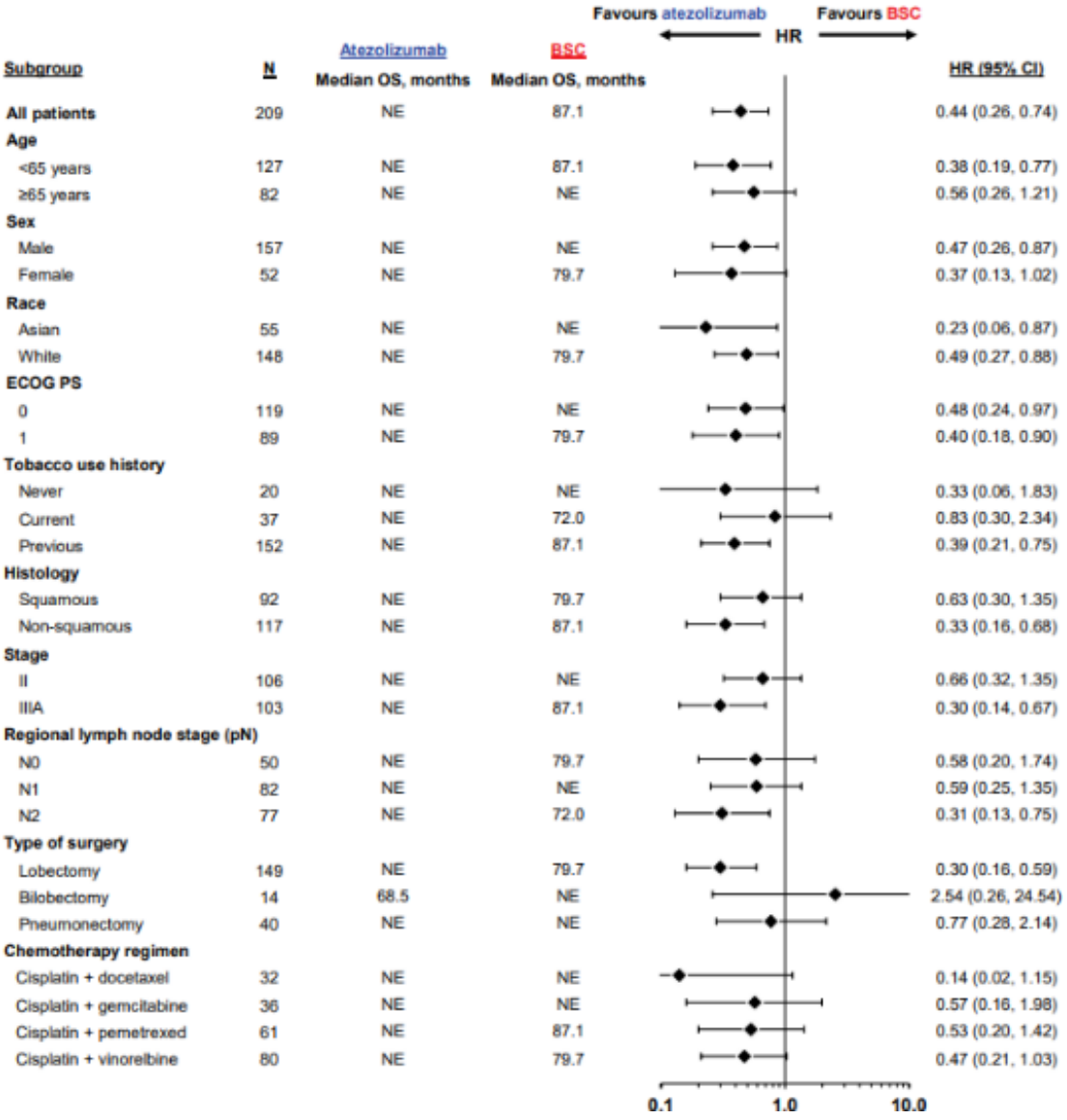


Subgroup	N	Atezolizumab n	Atezolizumab Median DFS, months	BSC n	BSC Median DFS, months	HR (95% CI)
All patients	209	106	NE	103	42.9	0.49 (0.32, 0.75)
Age						
<65 years	127	65	NE	62	41.1	0.47 (0.27, 0.83)
≥65 years	82	41	NE	41	42.9	0.52 (0.27, 1.00)
Sex						
Male	157	84	NE	73	NE	0.58 (0.35, 0.97)
Female	52	22	NE	30	31.0	0.37 (0.16, 0.84)
Race						
White	148	71	NE	77	41.7	0.50 (0.30, 0.82)
Asian	55	31	NE	24	67.0	0.48 (0.19, 1.20)
ECOG PS						
0	119	66	NE	53	67.0	0.54 (0.31, 0.95)
1	89	40	NE	49	42.9	0.47 (0.24, 0.93)
Tobacco use history						
Never	20	11	35.3	9	25.3	0.86 (0.28, 2.70)
Previous	152	79	NE	73	43.5	0.43 (0.25, 0.72)
Current	37	16	NE	21	45.6	0.70 (0.26, 1.89)
Histology						
Squamous	92	47	NE	45	NE	0.67 (0.34, 1.32)
Non-squamous	117	59	NE	58	36.8	0.40 (0.23, 0.70)
Stage						
II	106	58	NE	48	NE	0.64 (0.35, 1.18)
IIIA	103	48	NE	55	34.2	0.41 (0.22, 0.75)
Regional lymph node stage (pN)						
N0	50	30	NE	20	NE	0.84 (0.35, 2.02)
N1	82	39	NE	43	67.0	0.46 (0.21, 0.98)
N2	77	37	NE	40	19.4	0.40 (0.21, 0.78)
Type of surgery						
Lobectomy	149	75	NE	74	37.3	0.39 (0.24, 0.66)
Bilobectomy	14	7	68.5	7	NE	3.21 (0.33, 31.17)
Pneumonectomy	40	20	NE	20	NE	0.78 (0.32, 1.92)
Chemotherapy regimen						
Cisplatin + docetaxel	32	13	NE	19	NE	0.42 (0.11, 1.54)
Cisplatin + gemcitabine	36	20	NE	16	NE	0.87 (0.30, 2.52)
Cisplatin + pemetrexed	61	29	NE	32	35.7	0.49 (0.24, 1.03)
Cisplatin + vinorelbine	80	44	NE	36	44.5	0.40 (0.20, 0.83)

B.2.7.2 OS in the PD-L1 ≥ 50% TC Stage II–IIIA population, without known EGFR or ALK alterations (72)

At the updated CCOD (26th January 2024), the OS benefit of atezolizumab was consistent across most pre-defined subgroups, even after excluding patients with known EGFR or ALK alterations. This analysis further reinforces the efficacy of atezolizumab in a population without these mutations, targeting those at high risk who do not typically benefit from targeted therapies for EGFR or ALK (Figure 15).

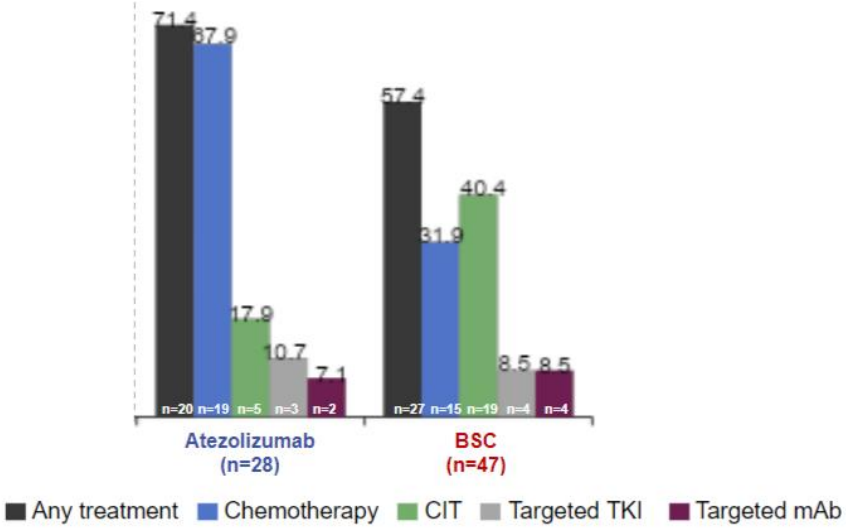
Figure 15: Subgroup analysis of OS in the PD-L1 ≥ 50% TC Stage II–IIIA population, without known EGFR or ALK alterations [CCOD 26 Jan 24]



B.2.7.3 Post-relapse non-protocol anticancer therapy

In the PD-L1 ≥ 50% TC Stage II–IIIA population without known EGFR or ALK alterations, patients in both the atezolizumab and BSC arms required post-relapse interventions. A higher proportion of patients in the BSC arm received cancer immunotherapy (CIT) (40.4%) compared to the atezolizumab arm (17.9%), while chemotherapy was more frequently administered in the atezolizumab arm (67.9% vs 31.9%) (Figure 16). Surgery was more frequent in the BSC arm compared to the atezolizumab arm (19.1% vs 10.7%); and radiation therapy was used similarly in both groups (Table 9).

Figure 16: Post-relapse systemic non-protocol anticancer therapy in PD-L1 ≥ 50% TC Stage II–IIIA population, without known EGFR or ALK alterations [CCOD 26 Jan 24] (73)



CIT, cancer immunotherapy; mAb, monoclonal antibody; TKI, tyrosine kinase inhibitor.
The denominators for post-relapse treatments are based on number of patients with relapse.
CCOD: 26 January 2024.

Table 9: Radiation therapy and surgery in PD-L1 ≥ 50% TC Stage II–IIIA population, without known EGFR or ALK alterations [CCOD 26 Jan 24] (73)

Patients, n (%)	PD-L1 ≥ 50% TC Stage II – IIIA population, without known EGFR or ALK alterations	
	Atezolizumab (n = 28)	BSC (n = 47)
Radiation therapy	13 (46.4)	23 (48.9)
Surgery	3 (10.7)	9 (19.1)

B.2.8 Meta-analysis

As no further Phase III RCTs studying the efficacy and safety of atezolizumab for adjuvant treatment of resected NSCLC were found, no meta-analysis was conducted.

B.2.9 Indirect and mixed treatment comparisons

No indirect or mixed treatment comparisons were conducted for this appraisal.

B.2.10 Adverse reactions

Safety analyses were performed on the randomised safety-evaluable population, which included 495 patients who received at least one dose of atezolizumab treatment, and 495 patients in the BSC arm who had at least one post-baseline safety measurement.

It should be noted that as of the CCOD of the initial DFS analysis on 21st January 2021, all patients had either completed study treatment/observation or had withdrawn from treatment/observation and were all beyond the protocol defined AE reporting period. Between 21st January 2021 and 26th January 2024 (updated CCOD presented in this submission), per protocol, only treatment related SAEs and treatment related AESIs were to be reported. The safety data are generally consistent with the previous analyses.

B.2.10.1 Overview of safety

At the updated CCOD (26th January 2024), atezolizumab continued to be well tolerated and the safety profile remained consistent with the safety profile observed at the time of the DFS interim analysis (CCOD 21st January 2021) and the first OS interim analysis (CCOD 18th April 2022). No new or unexpected clinically significant safety concerns were identified. An overview of the key safety results for the entire safety-evaluable population, based on the updated CCOD, presented side-by-side with the results from the previous analyses, is provided in Table 10. The key findings are as follows:

- **As expected and observed at the DFS interim analysis, AEs were more frequent across all categories (including all grade AEs, Grade 3-4 AEs, and SAEs) in the atezolizumab arm compared to the BSC arm.**

- **Since the DFS interim analysis/first OS interim analysis, no additional Grade 5 AEs were reported in either arm, the overall incidence remains the same with 1.8% (9 patients) in the atezolizumab arm and 0.6% (3 patients) in the BSC arm. Grade 5 events reported previously were all single cases reported across multiple System Organ Classes (SOCs). Four of the events in the atezolizumab arm were considered by the investigator to be treatment-related.**

  AESIs were more frequent in the atezolizumab arm compared to the BSC arm, with the most common being hepatitis (diagnosis and lab abnormalities), rash and hypothyroidism as observed at the DFS interim analysis. The majority of the AESIs were of Grade 1-2 severity and were generally manageable by withholding atezolizumab and/or appropriate treatment. The majority of the AESIs were resolved by the CCOD (26th January 2024).

Table 10: Safety summary (safety-evaluable population)

	Final DFS and OS IA2 CCOD 26 Jan 2024		OS IA1 CCOD 18 Apr 2022		DFS IA CCOD 21 Jan 2021	
	Atezolizumab (n=495)	BSC (n=495)	Atezolizumab (n=495)	BSC (n=495)	Atezolizumab (n=495)	BSC (n=495)
Total number of patients with at least one AE	458 (92.5%)	351 (70.9%)	458 [b] (92.5%)	351 (70.9%)	459 [b] (92.7%)	350 (70.7%)
Total number of events	2776	1258 [a]	2776	1260 [a]	2742	1253
Total number of patients with at least one:						
AE with fatal outcome	9 [c] (1.8%)	3 (0.6%)	9 [c] (1.8%)	3 (0.6%)	8 (1.6%)	3 (0.6%)
Related AE with fatal outcome	4 (0.8%)	0	4 (0.8%)	0	4 (0.8%)	0
Serious AE	88 (17.8%)	42 (8.5%)	88 (17.8%)	42 (8.5%)	87 (17.6%)	42 (8.5%)
Related Serious AE	37 (7.5%)	0	37 (7.5%)	0	37 (7.5%)	0
Grade 3-4 AE	109 (22.0%)	57 (11.5%)	109 (22.0%)	57 (11.5%)	108 (21.8%)	57 (11.5%)
Related Grade 3-4 AE	53 (10.7%)	0	53 (10.7%)	0	53 (10.7%)	0
Related AE	336 (67.9%)	0	336 (67.9%)	0	335 (67.7%)	0
AE leading to dose interruption of atezolizumab	143 (28.9%)	0	142 (28.7%)	0	142 (28.7%)	0
AE leading to atezolizumab discontinuation	90 (18.2%)	0	90 (18.2%)	0	90 (18.2%)	0
Total number of patients with at least one AESI	258 (52.1%)	48 (9.7%)	258 (52.1%)	47 (9.5%)	256 (51.7%)	47 (9.5%)
Total number of events	520	71	516	70	510	70
Total number of patients with at least one:						
AESI with fatal outcome	2 (0.4%)	1 (0.2%) [d]	2 (0.4%)	0	2 (0.4%)	0
Related AESI with fatal outcome	2 (0.4%)	0	2 (0.4%)	0	2 (0.4%)	0
Serious AESI	21 (4.2%)	4 (0.8%)	21 (4.2%)	2 (0.4%)	21 (4.2%)	2 (0.4%)
Related Serious AESI	20 (4.0%)	0	20 (4.0%)	0	20 (4.0%)	0

Grade 3–4 AESI	39 (7.9%)	4 (0.8%)	39 (7.9%)	3 (0.6%)	39 (7.9%)	3 (0.6%)
Related Grade 3–4 AESI	31 (6.3%)	0	31 (6.3%)	0	31 (6.3%)	0
Related AESI	227 (45.9%)	0	227 (45.9%)	0	223 (45.1%)	0
AESI leading to dose interruption of atezolizumab	59 (11.9%)	0	58 (11.7%)	0	58 (11.7%)	0
AESI leading to atezolizumab discontinuation	52 (10.5%)	0	52 (10.5%)	0	52 (10.5%)	0

AE = adverse event; AESI = adverse event of special interest; BSC = best supportive care; CCOD = clinical cut-off date; CSR = clinical study report; DFS = disease-free survival; IA = interim analysis; OS = overall survival.

[a] *The change in the number of patients with total AEs between the two CCODs (18th April 2022 to 26th January 2024) is due to 4 patients for whom three AEs (seasonal allergy, intestinal metastasis and forearm fracture) were reported during the interval. The AEs of Gilbert's disease, "Colon cancer metastatic" and "Colonoscopy", and "Radius fracture" and "Ulna fracture" were removed from and subsequently being updated in the database after confirmation by the sites that its entry was erroneous.*

[b] *The change in the number of patients with at least one AE between the two CCODs (21st January 2021 to 18th April 2022) is due to one patient for whom only one AE ‘’weight gain’’ was reported during the interval. The AE was subsequently removed from the database after confirmation by the site that its entry was erroneous.*

[c] *No new Grade 5 AEs has occurred since the previous analyses (DFS interim analysis and first OS interim analysis). This death was previously reported as "other", and not as a Grade 5 AE in the Primary CSR. The death was obtained from public records and a corresponding fatal adverse event was entered after the last analysis and is therefore categorised as an 'Adverse Event'.*

[d] *This was previously classified as a Grade 5 AE and has been recategorised under immune-mediated pericardial disorders (a newly identified AESI since the previous analyses) as Grade 5 AESI.*

B.2.10.2 Adverse events (AEs)

At the initial DFS analysis on 21st January 2021, the proportion of patients with at least one AE was higher in the atezolizumab arm (92.7%) than the BSC arm (70.7%) (Table 10). The most common (≥ 20% of patients in either arm) SOC in which AEs were reported (atezolizumab vs BSC, respectively) were:

- Infections and infestations (37.0% vs 27.1%)
- Respiratory, thoracic and mediastinal disorders (29.5% vs 20.8%)
- General disorders and administration site conditions (32.7% vs 15.2%)
- Investigations (34.3% vs 12.1%)
- Gastrointestinal disorders (28.1% vs 16.4%)
- Musculoskeletal and connective tissue disorders (25.5% 16.0%)
- Nervous system disorders (22.8% vs 15.8%)
- Skin and subcutaneous tissue disorders (29.9% vs 6.1%)

The AEs by preferred term (PT) with a notable difference (≥ 5%) between the arms are shown in Table 11. While there were differences between arms, all events presented are consistent with the known safety profile for atezolizumab.

Table 11: AEs with a difference of at least 5% between treatment arms by preferred term (safety-evaluable population) [CCOD 21 Jan 21]

MedDRA Preferred Terms	Atezolizumab (n=495)	BSC (n=495)
Number of occurrences, n (%)		
Arthralgia	52 (10.5)	26 (5.3)
Pyrexia	65 (13.1)	11 (2.2)
Alanine aminotransferase (ALT) increased	53 (10.7)	16 (3.2)
Aspartate aminotransferase (AST) increased	53 (10.7)	16 (3.2)
Hypothyroidism	55 (11.1)	3 (0.6)
Pruritus	51 (10.3)	3 (0.6)
Rash	48 (9.7)	5 (1.0)
Diarrhoea	37 (7.5)	9 (1.8)
Hyperthyroidism	32 (6.5)	3 (0.6)

Investigator text for AEs encoded using MedDRA version 23.1.
Includes adverse events occurring on or after the start of treatment in randomisation period.
For frequency counts by preferred term, multiple occurrences of the same AE in an individual were counted only once.

Since the first OS interim analysis (CCOD 18th April 2022), there were minor changes in the total number of AEs reported in the BSC arm due to data correction of reported terms. The proportion of patients with at least one AE remains the same (92.5% in the atezolizumab arm vs 70.9% in the BSC arm). There were no AEs associated with COVID-19.

The most common (≥ 20% of patients in either arm) SOC in which AEs were reported did not change. There was one minor update to the frequency of the following SOC (< 1% change): Investigations (34.5% atezolizumab vs. 12.1% BSC).

The AEs by PT with a notable difference (> 5%) between the arms are shown in Table 12. These are generally consistent with the first OS interim analysis with all events occurring more frequently in the atezolizumab arm. Notably, upper respiratory tract infections (URTIs) were reported at a higher rate on the atezolizumab arm (7.5% vs. 2.4%). All of the URTI events were Grade 1–2 and non-serious, with most (36/37) of the patients recovered. The majority of the patients recovered without interrupting atezolizumab ([29/37], 78.4%).

Table 12: AEs with a difference of at least 5% between treatment arms by preferred term (safety-evaluable population) [CCOD 26 Jan 24]

MedDRA Preferred Terms	Atezolizumab (n=495)	BSC (n=495)
Number of occurrences, n (%)		
Arthralgia	52 (10.5)	26 (5.3)
Pyrexia	65 (13.1)	11 (2.2)
Alanine aminotransferase (ALT) increased	54 (10.9)	16 (3.2)
Aspartate aminotransferase (AST) increased	54 (10.9)	16 (3.2)
Hypothyroidism	54 (10.9)	3 (0.6)
Pruritus	51 (10.3)	3 (0.6)
Rash	48 (9.7)	5 (1.0)
Upper respiratory tract infection	37 (7.5)	12 (2.4)
Diarrhoea	37 (7.5)	9 (1.8)
Hyperthyroidism	33 (6.7)	3 (0.6)

Investigator text for AEs encoded using MedDRA version 26.1.
Includes adverse events occurring on or after the start of treatment in randomisation period.
For frequency counts by preferred term, multiple occurrences of the same AE in an individual are counted only once.

B.2.10.2.1 Serious adverse events (SAEs)

At the initial CCOD of 21st January 2021, the proportion of patients with at least one SAE was higher in the atezolizumab arm (17.6%) than in the BSC arm (8.5%) (Table 10). The most common SAEs (≥ 1% of patients in either atezolizumab arm or BSC arm) were pneumonia (1.6% and 1.0%) and pyrexia (1.2% and 0.2%). All other SAEs occurred in ≤ 1% of patients in each treatment arm. The majority of SAEs were Grade 3 or less in severity and had resolved or were resolving by the CCOD.

The proportion of patients with at least one SAE assessed by the investigator as related to atezolizumab was 7.5%. All SAEs assessed by the investigator as related to atezolizumab occurred in ≤ 1% of patients in the atezolizumab arm. Treatment-related SAEs that were reported in two or more patients included pneumonitis, interstitial lung disease (ILD), meningitis, peripheral neuropathy, pyrexia, drug-induced liver injury, hepatitis, and sarcoidosis.

Since the first OS interim analysis (CCOD 18th April 2022), there was no change in the reported number of SAEs. The proportion of patients with at least one SAE remains the same (17.8% in the atezolizumab arm vs 8.5% in the BSC arm). The most common SAEs by PT (≥ 1% of patients in either BSC arm or atezolizumab arm) were pneumonia (1.0% vs. 1.6%) and pyrexia (0.2% vs. 1.2%). All other SAEs occurred in < 1% of patients in each treatment arm. The majority of SAEs were Grade 3 or less in severity and had resolved or were resolved by the CCOD.

There were no SAEs with a difference of ≥ 2% between treatment arms.

The proportion of patients with at least one SAE assessed by the investigator as related to atezolizumab remains the same at 7.5%. All SAEs assessed by the investigator as related to atezolizumab occurred in <1% of patients in the atezolizumab arm. Treatment-related SAEs that were reported in 2 or more patients included: pneumonitis, interstitial lung disease (ILD), meningitis, peripheral neuropathy, pyrexia, drug-induced liver injury, hepatitis, and sarcoidosis.

B.2.10.2.2 Treatment-related AEs

At the initial CCOD of 21st January 2021, the proportion of patients with atezolizumab-related AEs was 67.7% (Table 10). The most common atezolizumab-related AEs were hypothyroidism (10.7%), pruritus (8.7%), rash (8.1%), increased AST (7.5%), increased ALT (7.3%), hyperthyroidism (5.9%), pyrexia (5.5%), and arthralgia (5.3%).

Since the first OS interim analysis (CCOD 18th April 2022), there was no change in the reported number of atezolizumab-related AEs (Table 10). The proportion of patients with atezolizumab-related AEs remains the same at 67.9% with the most common atezolizumab-related AEs were hypothyroidism (10.5%), pruritus (8.7%), rash (8.3%), increased AST (7.7%), increased ALT (7.5%), hyperthyroidism (6.1%), pyrexia (5.5%), and arthralgia (5.3%).

B.2.10.2.3 AEs that led to withdrawal of treatment

At the initial CCOD of 21st January 2021, the proportion of patients who discontinued atezolizumab due to AEs was 18.2%. The most common AEs by preferred term (PT) (≥ 1% of patients in the atezolizumab arm) that led to discontinuation of atezolizumab were pneumonitis, hypothyroidism, increased AST (1.4% each), and increased ALT (1.0%). All patients had completed study treatment/observation at the time of the DFS interim analysis and there are no changes to the data on AEs leading to treatment withdrawal beyond those reported above.

B.2.10.2.4 AEs that led to dose interruption

At the initial CCOD of 21st January 2021, dose modifications to atezolizumab were not permitted but interruptions or delays to the infusion were allowed. The proportion of patients who experienced AEs leading to atezolizumab dose interruptions was 28.7%. The most common (≥ 1%) AEs by PT leading to atezolizumab dose interruption were hyperthyroidism (2.8%), increased AST, pyrexia (1.6% each), increased ALT, rash, upper respiratory tract infection (1.4% each), hypothyroidism, headache (1.2% each), and pneumonia (1.0%).

Since the first OS interim analysis (CCOD 18th April 2022), due to data correction at a study site, there was one previously reported patient with an AE of alanine aminotransferase increased, for which the action taken was changed from “dose not

changed" to "drug interrupted". The proportion of patients who experienced AEs leading to atezolizumab dose interruptions was 28.9%.

The most common SOCs (≥ 2%) in which AEs led to dose interruptions of atezolizumab were Infections and infestations (6.7%), Investigations (5.9%), General disorders and administration site conditions (4.6%), Endocrine disorders (4.4%), Skin and subcutaneous tissue disorders (3.6%), Nervous system disorders (2.8%), and Respiratory, thoracic, and mediastinal disorders (2%).

The most common (≥ 1%) AEs by PT leading to atezolizumab dose interruption were hyperthyroidism (2.8%), pyrexia (1.6%), increased AST (1.6%), increased ALT (1.4%), upper respiratory tract infection (1.4%), rash (1.4%), hypothyroidism (1.2%), headache (1.2%), and pneumonia (1%).

B.2.10.2.5 Adverse events of special interest (AESIs)

The AESIs represent risks with an established or potential causal association of atezolizumab use and are grouped by medical concepts.

At the initial CCOD of 21st January 2021, the overall proportion of patients who experienced AESIs was 51.7% in the atezolizumab arm and 9.5% in the BSC arm (Table 13). The majority of AESIs were of Grade 1–2 severity. Grade 3–4 AESIs were reported in 7.9% (39 patients) in the atezolizumab arm and 0.6% (3 patients) in the BSC arm. There were two patients with Grade 5 AESIs reported in the atezolizumab arm (myocarditis and ILD). The proportion of patients who experienced AESIs reported as serious was 4.2% (21 patients) in the atezolizumab arm and 0.4% (2 patients) in the BSC arm. The proportion of patients in the atezolizumab arm who experienced AESIs leading to treatment discontinuation and dose interruption was 10.5% and 11.7%, respectively. The proportion of patients who experienced AESIs that required systemic corticosteroid treatment was 12.1% (60 patients) in the atezolizumab arm and 0.8% (4 patients) in the BSC arm.

By the first OS interim analysis (CCOD 18th April 2022), the proportion of patients who experienced AESIs was 52.1% in the atezolizumab arm and 9.7% in the BSC arm (Table 13). The majority of AESIs were of Grade 1–2 severity (43.8% atezolizumab vs. 8.7% BSC arm). Grade 3–4 AESIs were reported in 7.9% (39 patients) in the

atezolizumab arm and 0.8% (4 patients) in the BSC arm. There were 0.4% (2 patients) in the atezolizumab arm (myocarditis and ILD) and 0.2% (1 patient) with Grade 5 AESIs reported in the BSC arm (cardiac tamponade). The proportion of patients who experienced AESIs reported as serious was 4.2% and 0.8%, in the atezolizumab and BSC arms, respectively. AESIs leading to atezolizumab discontinuation and interruption was 10.5% and 11.9%, respectively. The proportion of patients who experienced AESIs that required systemic corticosteroid treatment was 12.3% (61 patients) in the atezolizumab arm and 1% (5 patients) in the BSC arm.

Table 13: Overview of AESIs (safety-evaluable population)

	Final DFS and OS IA2 CCOD: 26 Jan 2024		OS IA1 CCOD: 18 Apr 2022		DFS IA CCOD: 21 Jan 2021	
	Atezolizumab (N=495)	BSC (N=495)	Atezolizumab (N=495)	BSC (N=495)	Atezolizumab (N=495)	BSC (N=495)
Total number of patients with at least one AESI	258 (52.1%)	48 (9.7%)	258 (52.1%)	47 (9.5%)	256 (51.7%)	47 (9.5%)
Total number of events	520	71	516	70	510	70
Total number of patients with at least one:						
AESI with fatal outcome	2 (0.4%)	1 (0.2%)	2 (0.4%)	0	2 (0.4%)	0
Related AESI with fatal outcome	2 (0.4%)	0	2 (0.4%)	0	2 (0.4%)	0
Serious AESI	21 (4.2%)	4 (0.8%)	21 (4.2%)	2 (0.4%)	21 (4.2%)	2 (0.4%)
Related Serious AESI	20 (4.0%)	0	20 (4.0%)	0	20 (4.0%)	0
Grade 3-4 AESI	39 (7.9%)	4 (0.8%)	39 (7.9%)	3 (0.6%)	39 (7.9%)	3 (0.6%)
Related Grade 3-4 AESI	31 (6.3%)	0	31 (6.3%)	0	31 (6.3%)	0
Related AESI	227 (45.9%)	0	227 (45.9%)	0	223 (45.1%)	0
AESI leading to dose interruption of atezolizumab	59 (11.9%)	0	58 (11.7%)	0	58 (11.7%)	0
AESI leading to atezolizumab discontinuation	52 (10.5%)	0	52 (10.5%)	0	52 (10.5%)	0
Medical concepts: patients with identified risks for atezolizumab						
Immune-mediated hepatitis (diagnosis and lab abnormalities)	87 (17.6%)	22 (4.4%)	87 (17.6%)	22 (4.4%)	86 (17.4%)	22 (4.4%)
Immune-mediated hepatitis (lab abnormalities)	82 (16.6%)	21 (4.2%)	82 (16.6%)	21 (4.2%)	81 (16.4%)	21 (4.2%)
Immune-mediated rash	91 (18.4%)	10 (2.0%)	91 (18.4%)	11 (2.2%)	91 (18.4%)	11 (2.2%)

Immune-mediated hypothyroidism	84 (17.0%)	3 (0.6%)	84 (17.0%)	3 (0.6%)	86 (17.4%)	3 (0.6%)
Immune-mediated hyperthyroidism	33 (6.7%)	4 (0.8%)	33 (6.7%)	4 (0.8%)	32 (6.5%)	4 (0.8%)
Immune-mediated pneumonitis	19 (3.8%)	3 (0.6%)	19 (3.8%)	3 (0.6%)	19 (3.8%)	3 (0.6%)
Immune-mediated hepatitis (diagnosis)	7 (1.4%)	1 (0.2%)	7 (1.4%)	1 (0.2%)	7 (1.4%)	1 (0.2%)
Infusion-related reactions	8 (1.6%)	0	8 (1.6%)	0	7 (1.4%)	0
Immune-mediated adrenal insufficiency	5 (1.0%)	0	5 (1.0%)	0	6 (1.2%)	0
Immune-mediated colitis	4 (0.8%)	1 (0.2%)	4 (0.8%)	1 (0.2%)	4 (0.8%)	1 (0.2%)
Immune-mediated diabetes mellitus	4 (0.8%)	1 (0.2%)	4 (0.8%)	1 (0.2%)	4 (0.8%)	1 (0.2%)
Immune-mediated myositis	4 (0.8%)	1 (0.2%)	4 (0.8%)	1 (0.2%)	4 (0.8%)	1 (0.2%)
Immune-mediated myositis (myositis + rhabdomyolysis)	4 (0.8%)	1 (0.2%)	4 (0.8%)	1 (0.2%)	4 (0.8%)	1 (0.2%)
Immune-mediated meningoencephalitis	4 (0.8%)	0	4 (0.8%)	0	4 (0.8%)	0
Immune-mediated pancreatitis	2 (0.4%)	1 (0.2%)	2 (0.4%)	1 (0.2%)	2 (0.4%)	1 (0.2%)
Immune-mediated pericardial disorders	1 (0.2%)	2 (0.4%)	0	0	0	0
Immune-mediated encephalitis	2 (0.4%)	0	2 (0.4%)	0	2 (0.4%)	0
Immune-mediated meningitis	2 (0.4%)	0	2 (0.4%)	0	2 (0.4%)	0
Immune-mediated myocarditis	2 (0.4%)	0	2 (0.4%)	0	2 (0.4%)	0
Immune-mediated severe cutaneous reactions	2 (0.4%)	0	2 (0.4%)	0	2 (0.4%)	0
Immune-mediated Guillain-Barre syndrome	1 (0.2%)	0	1 (0.2%)	0	1 (0.2%)	0
Immune-mediated hypophysitis	2 (0.4%)	0	1 (0.2%)	0	1 (0.2%)	0
Immune-mediated nephritis	1 (0.2%)	0	1 (0.2%)	0	1 (0.2%)	0

Medical concepts: patients with potential risks for atezolizumab						
Autoimmune haemolytic anaemia	2 (0.4%)	0	2 (0.4%)	0	2 (0.4%)	0
Immune-mediated ocular inflammatory toxicity	1 (0.2%)	1 (0.2%)	1 (0.2%)	1 (0.2%)	1 (0.2%)	1 (0.2%)
Immune-mediated vasculitis	0	1 (0.2%)	0	1 (0.2%)	0	1 (0.2%)

AE = adverse event; AESI = adverse event of special interest; BSC = best supportive care; CCOD = clinical cut-off date; DFS = disease-free survival; IA = interim analysis; OS = overall survival.

Includes adverse events occurring on or after the start of treatment in randomisation period.

Immune-mediated adverse events are those adverse events of special interest that were ongoing upon the initiation of systemic corticosteroid therapy and where the systemic corticosteroid therapy was administered no later than 30 days from the start of the adverse event.

B.2.10.3 Deaths

At the CCOD on 21st January 2021, the frequency of deaths were comparable between the arms (19.2% atezolizumab vs 18.2% BSC) with the most common cause of death being disease relapse (12.7% atezolizumab vs 15.6% BSC) (Table 14). In both treatment arms, the majority of deaths occurred more than 30 days after the last dose of study drug.

A total of 11 deaths (8 in atezolizumab arm vs. 3 in BSC arm) in the overall safety-evaluable population were due to fatal Grade 5 AEs (1.8% atezolizumab vs. 0.6% BSC). All fatal AEs in both arms were single occurrences reported across several SOCs. Of the eight Grade 5 events observed in the atezolizumab arm, four (0.8%) were considered treatment related. These events were myocarditis, interstitial lung disease, multiple organ dysfunction syndrome and acute myeloid leukaemia. Other non-related grade 5 events in the atezolizumab arm were pneumothorax, cerebrovascular accident, arrhythmia and acute cardiac failure. One patient in the BSC arm experienced two Grade 5 AEs reported as PTs of cardiac tamponade and septic shock when coded by MedDRA. See Appendix I for the list of fatal AEs.

Table 14: Deaths and causes of death (safety-evaluable patients) [CCOD 21 Jan 21]

	Atezolizumab (n=495)	BSC (n=495)	All patients (N=990)
All deaths, n (%)	95 (19.2)	90 (18.2)	185 (18.7)
≤ 30 days from last study treatment/safety visit, n (%)	4 (0.8)	5 (1.0)	9 (0.9)
> 30 days from last study treatment/safety visit, n (%)	91 (18.4)	85 (17.2)	176 (17.8)
Primary cause of death, n (%)			
Adverse event	8 (1.6)	3 (0.6)	11 (1.1)
Disease relapse	63 (12.7)	77 (15.6)	140 (14.1)
Other	24 (4.8)	10 (2.0)	34 (3.4)

Includes deaths occurring on or after the start of treatment in randomisation period.

Since the first OS interim analysis (CCOD 18th April 2022), there was no change in the reported number of Grade 5 AEs. As of the current CCOD (26th January 2024), the frequency of deaths was comparable between arms (31.5% atezolizumab vs. 31.7% BSC) with the most common cause of death being disease relapse (58.3% vs. 75.2%,

respectively) (Table 15). In both study arms, the majority of deaths occurred more than 30 days after the last dose of study drug / safety visit.

Table 15: Deaths and causes of death (safety-evaluable patients) [CCOD 26 Jan 24]

	Atezolizumab (n=495)	BSC (n=495)	All patients (N=990)
All deaths, n (%)			
n	156 (31.5)	157 (31.7)	313 (31.6)
≤30 days from last study treatment/safety visit	4 (0.8)	6 (1.2)	10 (1.0)
>30 days from last study treatment/safety visit	152 (30.7)	151 (30.5)	303 (30.6)
Primary cause of death, n (%)			
n	156	157	313
Adverse event	9 (5.8)	3 (1.9)	12 (3.8)
Disease relapse	91 (58.3)	118 (75.2)	209 (66.8)
Other	56 (35.9)	36 (22.9)	92 (29.4)
Other cause of death, n (%)			
n	56	36	92
COVID-19	6 (10.7)	3 (8.3)	9 (9.8)
Medical	26 (46.4)	17 (47.2)	43 (46.7)
Public record	5 (8.9)	2 (5.6)	7 (7.6)
Second primary cancer	7 (12.5)	6 (16.7)	13 (14.1)
Unknown	12 (21.4)	8 (22.2)	20 (21.7)

Includes deaths occurring on or after the start of treatment in randomisation period.

The date of death for one patient is not able to be determined or imputed and the patient is excluded.

B.2.11 Ongoing studies

Atezolizumab is currently being tested in multiple Phase I, II, and III studies, both as monotherapy and in combination with several anti-cancer therapies. Relevant ongoing NSCLC studies are listed below:

- IMpower010: A Phase III, multicentre, randomised study evaluating the efficacy and safety of atezolizumab as adjuvant therapy in patients with completely resected Stage IB–IIIA NSCLC following platinum-based chemotherapy. The study demonstrated a significant improvement in DFS in patients receiving atezolizumab compared to BSC, particularly in those with PD-L1 expression on tumour cells.

[redacted]

- IMpower030: A Phase III, randomised, open-label study assessing the safety and efficacy of neoadjuvant atezolizumab combined with platinum-based chemotherapy in patients with resectable early-stage NSCLC. The study aims to determine whether this combination improves surgical outcomes and long-term survival rates.

- IMscin002: A Phase III, randomised study investigating the non-inferiority of subcutaneous atezolizumab in two patient cohorts: those with resected Stage IIB-IIIB (T3-N2) early-stage NSCLC and chemotherapy-naïve Stage IV NSCLC. The study assesses whether subcutaneous administration is as effective and safe as intravenous administration in managing disease progression in these populations.

B.2.12 Interpretation of clinical effectiveness and safety evidence

B.2.12.1 Adjuvant atezolizumab in early NSCLC

Lung cancer is the leading cause of cancer-related deaths worldwide. Half of all patients with NSCLC are diagnosed with Stage I–III disease, with a better prognosis for patients at earlier stages of disease (17).

For patients with Stage I and II NSCLC and select Stage III patients, surgery represents the primary treatment option and the best chance of cure (74). While adjuvant chemotherapy can provide additional benefit, its impact on survival is modest, improving OS by approximately 5% at 5 years (HR = 0.89). Recently, immunotherapy has been introduced in the neoadjuvant and peri-operative settings, expanding the range of options beyond traditional chemotherapy. However, for patients who undergo surgery as the first step in their treatment, adjuvant choices remain limited. These include targeted therapies, such as osimertinib for EGFR-positive early NSCLC (currently in the CDF, pending NICE appraisal) (49), and alectinib for ALK-positive patients (50). Additionally, adjuvant atezolizumab is available in the CDF for patients with PD-L1 high early-stage NSCLC (54), and adjuvant pembrolizumab is currently undergoing NICE appraisal (52). While these advances provide new options for the

treatment of early NSCLC, only alectinib is routinely funded for a specific subgroup of patients.

Atezolizumab is a step change in the management of early NSCLC. In more than 15 years, atezolizumab is the first cancer immunotherapy to bring about an improvement in adjuvant treatment, for PD-L1 high early NSCLC patients. In a potentially curative setting, adjuvant atezolizumab has significant benefits for both patients and society in preventing or delaying early lung cancer recurrence, or progression to metastatic disease.

In a recent advisory board, [redacted] In line with these considerations, the current CDF review focuses specifically on atezolizumab as an adjuvant monotherapy for adults with completely resected NSCLC expressing PD-L1 on 50% or more of tumour cells, without EGFR mutations or ALK-positive alterations, provided their disease has not progressed following platinum-based chemotherapy.

B.2.12.2 Efficacy and safety profile of IMpower010

The IMpower010 study is the first Phase III study of adjuvant immunotherapy to demonstrate a DFS improvement in fully resected early NSCLC patients, following platinum base chemotherapy. At the first DFS interim analysis in January 2021, the study met its primary endpoint, showing a 34% reduction in risk of disease recurrence, new NSCLC, or death with adjuvant atezolizumab compared to BSC in the PD-L1 ≥ 1% TC Stage II–IIIA population (HR = 0.66; 95% CrI: 0.50, 0.88) (Table 8) (60). By the time of the updated CCOD in January 2024, with a median follow-up duration of 65 months in the ITT population, a favourable trend continued in the atezolizumab arm

compared to the BSC arm, although the DFS did not reach the statistical significance boundary (two-sided α = 0.0325) (60). This trend, despite not meeting statistical significance, points to a sustained DFS benefit and highlights the potential long-term clinical value of atezolizumab in early NSCLC.

The secondary endpoint of overall survival (OS) in the ITT population was not formally tested at the time of the DFS final analysis due to pre-specified testing requirements, with low event-to-patient ratios observed (31.4% in the atezolizumab group versus 31.5% in the BSC group). In accordance with the study's testing hierarchy, there will be no formal OS testing in subsequent analyses, though exploratory analyses may continue to observe OS trends.

For patients with PD-L1 ≥ 50% TC Stage II–IIIA, both the interim and final DFS analyses indicated a clinically meaningful benefit for atezolizumab (HR = 0.48; 95% CrI: 0.32, 0.72). Exploratory analyses also showed robust DFS and OS benefits in patients with high PD-L1 expression without known EGFR or ALK mutations (DFS HR = 0.49; OS HR = 0.44) (Table 8). These DFS and OS benefits were also consistently observed across most pre-defined subgroups (Figure 14 and Figure 15).

The current CCOD in Jan 2024 represents the final DFS analysis and second OS interim analysis, with the IMpower010 trial ongoing and a final OS analysis planned. With 65 months of follow-up, additional events were recorded in the licensed population, showing a DFS event rate of 32.1% for the atezolizumab arm vs. 53.4% for the BSC arm. This low event rate should be interpreted taking into consideration the treatment setting. Firstly, in this adjuvant setting, not all patients will experience disease recurrence or a new malignancy. Furthermore, the risk of recurrence following radical treatment in early stage NSCLC is understood to be higher in the first 3 years post resection (75, 76). In IMpower010, the DFS rates at 2, 3, and 5 years were 87%, 74%, and 65% for the atezolizumab arm, respectively, compared to 63.6%, 53.2%, and 44.5% for the BSC arm, consistent with a slower event rate as expected. [redacted] For OS, with an event rate of 20% in the atezolizumab arm versus 39.8% in the BSC arm, longer follow-up is needed

to address data immaturity, particularly for patients potentially achieving long-term survival.

[redacted]

Among patients who experienced disease relapse, it is important to understand the impact of how adjuvant treatment with atezolizumab may affect subsequent treatment paradigms. For patients in the PD-L1 ≥ 50% TC Stage II–IIIA group without EGFR or ALK mutations, those treated with adjuvant atezolizumab required less follow-up CIT upon relapse compared to those who received BSC (17.9% vs. 40.4%) (Figure 16). Additionally, surgery was less commonly required among patients initially treated with atezolizumab (10.7% vs. 19.1%) (Table 9), suggesting that adjuvant atezolizumab may delay progression to a point where surgical intervention is necessary. These findings reflect different relapse patterns between patients treated with adjuvant atezolizumab versus chemotherapy alone, and demonstrate how the use of CIT in the earlier NSCLC stages is likely to impact the treatment landscape of advanced NSCLC.

The safety profile for atezolizumab monotherapy demonstrated in IMpower010 was consistent with previous clinical studies (63, 66, 67, 77). At the updated CCOD on in January 2024, atezolizumab continued to show a favourable safety profile, consistent with previous analyses (Table 10). While AEs occurred more frequently in patients treated with atezolizumab, they were consistent with safety profile observed when used in other indications. No additional Grade 5 AEs have been reported since the previous DFS and OS analyses (1.8% atezolizumab vs. 0.6% BSC). The previously noted Grade 5 events were isolated and distributed across different organ systems, with a small subset considered treatment-related. Common AESIs in the atezolizumab group, such as mild-to-moderate hepatitis, rash, and hypothyroidism, were effectively managed by temporarily discontinuing treatment or through standard supportive therapies. Most of these AESIs resolved by the time of the updated analysis, suggesting that side effects of atezolizumab are typically reversible and do not lead to long-term issues for most patients.

Overall, more toxicity was observed in atezolizumab compared with BSC, as expected since the latter was comprised only of active monitoring. However, these risks should be weighed against the degree of treatment benefit, and within this context, the overall benefit-risk ratio with atezolizumab in the licensed population appeared to be favourable. Clinicians in a recent advisory board agreed that atezolizumab's safety profile is manageable and consistent with their previous experience (1). In a potentially curative setting, where limited treatment options exist, the addition of adjuvant atezolizumab to the treatment paradigm has the potential to prevent early lung cancer recurrence or progression to metastatic disease, providing a significant benefit for both patients and society.

B.3 Cost effectiveness

B.3.1 Published cost effectiveness studies

- **An SLR was conducted to identify early NSCLC cost-effectiveness studies**
- **The studies identified in the SLR showed that there is limited data available on cost-effectiveness analyses.**
- **No published studies were found that assessed the cost effectiveness of adjuvant treatment with atezolizumab in patients with Stage II–IIIA NSCLC.**

B.3.1.1 Summary of identified studies and results

A total of 35 publications from the original review (March 2021), 11 publications from the July 2022 update, 15 publications from the July 2023 update, 3 publications from the September 2023 update, and 17 publications from the August 24 update were identified, which met the eligibility criteria of the economic evaluation SLR (full publications, n=41; conference abstracts, n=33; HTA submissions, n=7; NICE guidelines, n=1). Due to limited reporting and the difficulties associated with meaningful quality assessment, studies presented as conference abstracts only were isolated and tagged. These were not considered further in the current report.

The review identified a total of 41 published economic evaluations (original review, n=24; July 2022 update n=4; July 2023 update, n=5; September 2023 update, n=3; August 2024 update, n=5) presented as full publications considering interventions for early-stage NSCLC (78-118). A range of different treatment comparisons were considered, covering first-line treatment options (surgery and/or radiotherapy), adjuvant or neoadjuvant therapy, and supportive care. The analyses were primarily based across the US, Canada, China, and Europe. The majority of studies were cost-utility analyses reporting the cost per quality-adjusted life year (QALY) gained for the interventions of interest (n=31)(78-81, 84-87, 89, 91, 92, 95-98, 101-103, 105, 106, 108-118). The most commonly cited published sources of utility values across these studies was Chouaid et al (2013) (119); however, this study reported utilities for health states associated with advanced stages of NSCLC. This indicates a lack of suitable utility values specifically for patients with early-stage NSCLC for use in economic evaluations.

A total of 30 of the published economic evaluations reported use of a model (78-82, 84-87, 91, 95-98, 101-106, 108-118). A high level of variation was observed across the studies, with regard to the selected disease states and pathways used in the models (see Appendix I for all available model structures). The traditional three-state model typically utilised in oncology indications was not generally used; model structures were more complex and included a variety of alternative health states, including those for local/regional recurrence (91, 97, 101, 102, 105, 106, 110, 112-115, 118, 120-125), metastasis/distant recurrence/advanced disease (91, 97, 101, 105, 106, 112-115, 118, 120), no evidence of disease (NED) (97, 108, 109), progression-free survival (81, 101, 111, 116), progression (78, 80, 85-87, 108, 111, 116), treatment with radiotherapy (91, 110), treatment with robotic-assisted thoracoscopic surgery (RATS)/open thoracotomy/video-assisted thoracoscopic surgery (VATS) (116), and treatment-related adverse events (AEs) (including dysphagia, dyspnoea, pneumonitis, and oesophagitis) (91, 96, 101, 103).

Further details and results for the identified cost effectiveness studies and abstracts can be found in Appendix I. Overall, no published studies were found that assessed the cost effectiveness of adjuvant treatment with atezolizumab in patients with Stage II–IIIA NSCLC.

B.3.2 Economic analysis

- **An economic model was built which reflects the disease pathway for early NSCLC**
- **The population of interest is adult patients with completely resected NSCLC which expressed PD-L1 on 50% or more of tumour cells, who do not have EGFR-positive or ALK-positive NSCLC and has not progressed after platinum based chemotherapy**
- **A Markov model consisting of five health states was developed: "disease-free survival"; "non-metastatic recurrence"; "first-line metastatic recurrence"; "second-line metastatic recurrence"; "death"**
- **The economic base case used a lifetime time horizon of 40 years and a cycle length of one month**
- **Discounting was set to 3.5% for costs and health benefits**

The cost effectiveness studies identified in Section B.3.1.1 were intended to inform the structure for the model used in the economic analysis. A number of studies were identified in the SLR, which further validated the approach taken in this model. See Section J.5.3 in the Appendices to get an overview of the different economic submission. Furthermore, Table 16 shows a comparison between previous submission and ID6324. Therefore, an economic model was built to inform decision making, which reflects the disease pathway in this therapeutic area.

B.3.2.1 Patient population

ID6324 is a CDF review of TA823, which was recommended (via the CDF) in 2022. Since 2022 the company has updated its target population to align with the Windsor Framework. The Windsor Framework is a government agreement, which comes into effect on the 1st of January 2025, which ensures medicines supplied to Northern Ireland can be approved and licensed on a UK-wide basis by the Medicines and Healthcare products Regulatory Agency (MHRA). The updated target population and indication states "atezolizumab as monotherapy as adjuvant treatment following complete resection and platinum-based chemotherapy for adult patients with NSCLC with a high risk of recurrence whose tumours have PD-L1 expression on ≥ 50% of

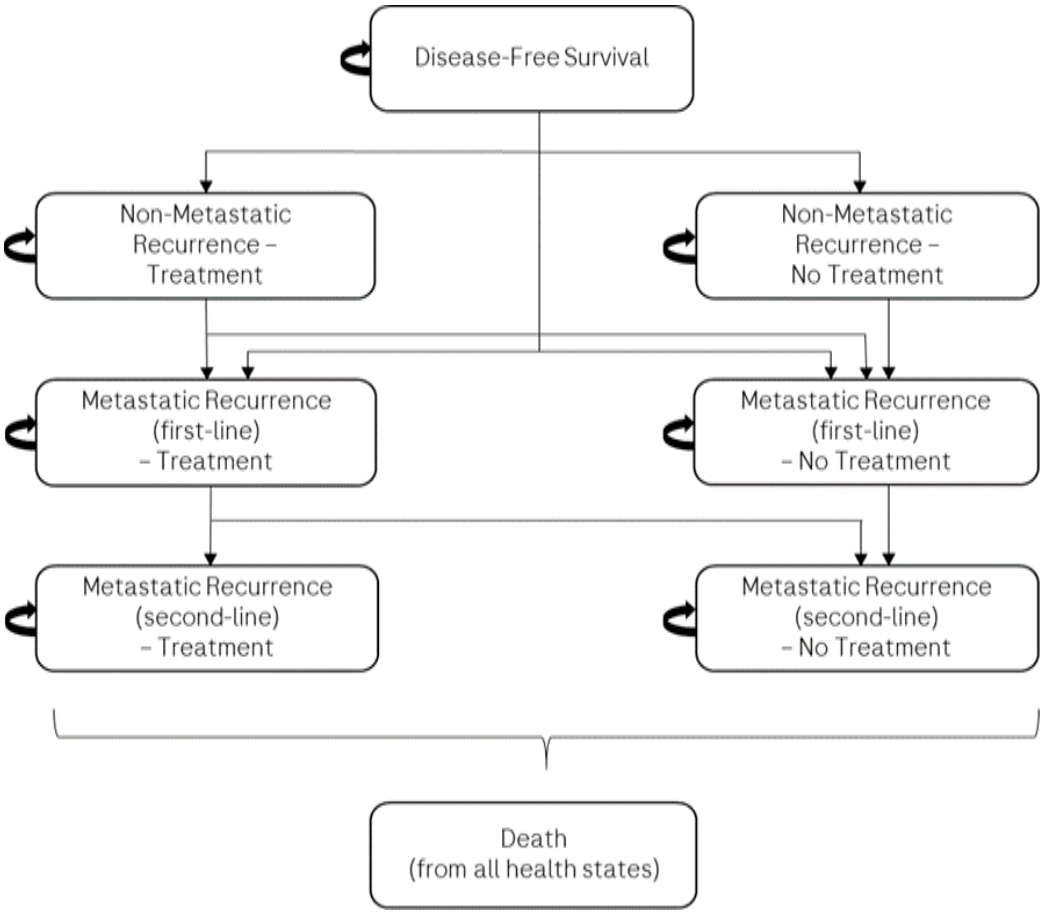
tumour cells (TC) and who do not have EGFR mutant or ALK-positive NSCLC", narrowing the patient population slightly in 2024 compared to 2022. It is critical to highlight that a change in license will not have an impact on the ALK-positive and EGFR-positive mutation patients for a number of reasons. First, SAC-T data collected between 23 August 2022 and 31 December 2023 confirms that patients with these mutations would not be treated with atezolizumab or any other immunotherapy. Secondly, this assumption has been extensively validated by clinicians, who confirmed that they would treat ALK-positive and EGFR-positive NSCLC patients in the adjuvant setting with alectinib and osimtertinib. Therefore, Roche will use the following target population in this appraisal; adults with completely resected NSCLC which expressed PD-L1 on 50% or more of tumour cells, who do not have EGFR mutant or ALK-positive NSCLC and have not progressed after platinum based chemotherapy. This change in license will not affect outcomes in early NSCLC.

B.3.2.2 Model structure

A Markov model was developed in Microsoft Excel® as this model structure allows for consideration of the long-term clinical and economic outcomes associated with early NSCLC. Early 1:1 discussions with UK oncologists and Health Economists provided valuable insights on the model's validity (i.e. model structure, assumptions, and inputs values) during model conceptualisation and post-model build (18, 19). Their feedback confirmed that the structure of the model accurately represents the disease and treatment pathways of NSCLC. In addition, the SLR carried out to identify relevant economic evaluations (see Section 3.1.1) noted that the traditional three-state model was not generally used and tended to use more complex structures consisting of a variety of alternative health states.

The five health states in the economic model are "disease-free survival"; "non-metastatic recurrence"; "first-line metastatic recurrence"; "second-line metastatic recurrence"; "death". Figure 17 presents the model's structure and its five health states.

Figure 17: Model structure and health states



B.3.2.2.1 Health states

Disease-free survival

Patients entered the model in the DFS health state, in the post-DFS health states, patients are further stratified according to whether or not they receive active treatment. Patients in the intervention arm received atezolizumab for a maximum of 16 cycles (treatment duration 11 months) and simultaneously received follow-up care for a maximum length of 5 years, which is the time point at which they are considered to be cured i.e. no risk of recurrence, while those in the BSC arm received follow-up care only. Each treatment cycle lasts 3 weeks. Patients who had a recurrence (either non-metastatic or metastatic), or died, transitioned to the non-metastatic recurrence, metastatic recurrence or death health states, respectively.

Non-metastatic or locoregional recurrence

Patients transitioned to this health state from DFS if they had non-metastatic recurrence and could either receive treatment or no treatment. Hence, the model

accounted for patients who could not or might not choose to be treated, as this choice would affect the clinical and economic outcomes. Patients on treatment for non-metastatic recurrence, who then developed metastatic recurrence or died, transitioned to the first line metastatic recurrence or death health states, respectively. Those who received no active treatment would eventually progress to the metastatic health state or death health state.

1L metastatic recurrence

Patients transitioned to this health state from DFS and non-metastatic recurrence if they had a metastatic recurrence, and were then split by whether they were treated and not treated. The model used this separation to account for patients who could not or might not choose to be treated, as this choice would affect the clinical and economic outcomes. Patients on treatment who progressed or died, transitioned to metastatic recurrence (second-line treatment) or death health states, while those not on treatment could only transition to the death health state.

2L metastatic recurrence

Patients transitioned to this health state from metastatic recurrence (first-line treatment) if they had disease progression and were split by whether they were treated and not treated. The model used this separation to account for patients who could not or might not choose to be treated, as this choice would affect the clinical and economic outcomes. Furthermore, patients from the 2L metastatic recurrence health state could only transition to the death health state. The model did not include subsequent lines of metastatic treatment beyond second-line; when validating the model with UK clinical oncologists (18, 19), they agreed the proportion of patients treated were lower at later lines and excluding further lines of metastatic treatment would have a minimal impact on the results from the model.

Death

Death is an absorbing health state where all patients transitioned by the end of the model's (lifetime) time horizon.

B.3.2.3 Time horizon

The economic base case used a (lifetime) time horizon of 40 years, which was considered sufficiently long enough to capture all clinical and economic outcomes of the disease and full treatment pathway for the modelled cohort. This takes into account:

1. Prognosis of patients treated in this setting
2. Expected survival times following present NHS treatment in this setting
3. The maximum plausible impact of improved outcomes following treatment with atezolizumab in the adjuvant setting

B.3.2.4 Cycle length

A limitation with Markov models is that time is discrete. Thus, they allow patients to transition across health states only once per model cycle which may not be consistent with reality as they may transition continuously. The model used a cycle length of 1 month to address this issue as it was expected that any differences in the timing of transitions between the model and reality would be less significant with shorter cycle lengths. This aligns with the expected speed of progression in people with early NSCLC. The alectinib for untreated ALK-positive advanced NSCLC (TA1014) submission (recommended) and ongoing osimertinib for adjuvant treatment of EGFR mutation-positive NSCLC after complete tumour resection (ID5120) also used a cycle length of approximately 4 weeks.

Half cycle corrections were not applied in the model, given that it is expected to have a minimal impact on the results.

B.3.2.5 Discounting and perspective

Discounting was set to 3.5% with the perspective of the NHS and personal social services (PSS) adopted, as per the NICE reference case (126). The model discounted the costs and health benefits on a yearly basis after the first year.

B.3.2.6 Utilities and costs

For each health state, a specific cost (Section B.5.2) and utility (Section B.3.4.2) was assigned for each time period (represented by a model cycle). Costs and utilities were multiplied by state occupancy to calculate the weighted costs and quality-adjusted life

years (QALYs) per cycle. These were then added across all cycles in the model time horizon to find the total costs and QALYs, which in turn were used to calculate incremental cost per life years gained (LYG) and the incremental cost per QALY gained. This appropriately reflects the decision problem.

B.3.2.7 Features of the economic analysis

There is currently one approved and two ongoing appraisals in the adjuvant setting; alectinib for untreated ALK-positive advanced non-small-cell lung cancer [TA1014] (recommended) (50), osimertinib for adjuvant treatment of EGFR mutation-positive NSCLC after complete tumour resection [ID5120] (49) and pembrolizumab for adjuvant treatment of resected non-small-cell lung cancer [ID3907] (52). Although TA1014 focused on ALK-positive NSCLC and ID5120 focused EGFR-positive NSCLC, there are a few similarities that can be drawn between these appraisals and atezolizumab for adjuvant treatment of resected non-small-cell lung cancer (MA review of TA823) [ID6324].

In the table below we provide an overview of how the economic analysis of atezolizumab compared to the alectinib, osimertinib and pembrolizumab for adjuvant treatment following early NSCLC (Table 16). In addition to the 3 appraisals listed above, Table 16 also shows a comparison between TA823 (IMpower010) (59) and our current approach for ID6324. When comparing the two submissions, it becomes evident that TA823 took a robust approach to modelling the costs and benefits of adjuvant atezolizumab due to the similarities between all appraisals. Therefore, ID6324 will only include a small number of changes in the base case to model the cost-effectiveness of adjuvant atezolizumab.

Table 16: Features of the economic analysis

Factor	Ongoing appraisal		Recommended	CDF entry	Current appraisal ID6324	
	Osimertinib [ID5120] (49)	Pembrolizumab [ID3907] (52)	Alectinib [TA1014] (50)	Atezolizumab [TA823] (59)	Chosen values	Justification
Model structure	Markov with five health states	Markov with four health states	Markov with five health states	Markov with five health states	Markov with five health states	Allowed consideration of the long-term clinical and economic outcomes associated with early NSCLC
Time horizon	37 years	35.7 years	30 years	40 years	40 years	Aligned with NICE reference case. Time horizon sufficiently long to reflect any differences in costs or outcomes between the technologies being compared.
Cycle length	4.35 weeks	1 week	1 month	1 month	1 month	Aligned with previous NSCLC appraisals

Half-cycle correction	Yes	Yes	No	Yes	No	Minimal impact on the results and complicates the model.
Were health effects measured in QALYs; if not, what was used?	Mapped EQ-5D-3L utilities were used from ADAURA (SF-36) and FLAURA (EORTC-QLQC30)	EQ-5D-3L from KEYNOTE-091	EQ-5D-3L data from ALEX Peters et al., 2016 Roughley et al., 2014	No PROs measured in the IMpower010 trial. QALYs from literature are used.	No PROs measured in the IMpower010 trial. QALYs from literature are used.	Not aligned with reference case as no PRO data from the IMpower010 data were collected.
Discount of 3.5% for utilities and costs	Yes	Yes	Yes	Yes	Yes	Aligned with NICE reference case.
Perspective (NHS/PSS)	Yes	Yes	Yes	Yes	Yes	Aligned with NICE reference case.
Treatment waning effect	Uncertain from the available committee papers	Not included. Cure point instead.	No	Yes	Yes	Company took a more conservative approach and applied a treatment waning effect.
Source of utilities	EQ-5D-3L estimates from ADAURA37 (mapped from the SF-36), EQ-5D-3L	EQ-5D-3L from KEYNOTE-091	EQ-5D-3L data from ALEX Peters et al., 2016 Roughley et al., 2014	Jang et al. 2010 for DFS health state, Chouaid et al. (2013) for the non-metastatic	Grutters et al. (2010) for DFS health state Chouaid et al. (2013) for the	Aligned with NICE reference case.

	estimates from FLAURA63 (mapped from the EORTC QLQ-C30) and published EQ-5D3L estimates from the literature (Labbé et al (127).			and metastatic setting.	non-metastatic and metastatic setting.	
Source of costs	NHS Reference costs (2021/2022), BNF, eMIT	NHS Reference costs (2021/2022), BNF, eMIT	NHS Reference costs (2021/2022), BNF, eMIT	NHS Reference costs (2021/2022), BNF, eMIT	NHS reference costs 2022/23, BNF, eMIT	Widely used and accepted sources of cost and resource use data in UK HTAs.

B.3.2.8 Intervention technology and comparators

The intervention technology, atezolizumab (1825 mg every 21 days; 74% of patients completed 16 cycles). Note that for the atezolizumab treatment cost only the subcutaneous (subcut) injection cost is presented as the subcut formulation is used in the base case.

The comparator best supportive care (BSC) (as per the trial protocol, patients will undergo randomised CT scans (assuming no recurrence at each timepoint [Year 1: every 4 months, Year 2: every 6 months, Year 3-5: every 6 months, after 5 years: once a year by X-ray]) is consistent with what is included in the decision problem as outlined in Section B.1.1. The intervention and comparator is listed in Table 17.

Table 17: Adjuvant treatment regimens and comparator

Intervention	Intervention arm	Control arm
	Atezolizumab	**Best supportive care**
Administration	Fixed dose, subcutaneous injection	-
Dose size	1825 mg	-
Frequency	3 weeks	-
Duration	74% of patients completed 16 cycles	Until recurrence

B.3.3 Clinical parameters and variables

- **The primary data source for the economic model was the IMpower010 trial**
- **Additional evidence came from published literature, clinical expert advice, and clinically validated assumptions**
- **DFS data was extrapolated over a lifetime time horizon of 40 years and the curves were adjusted to avoid overestimating patients who have recurrences in the longer term. This involved:**
  - **Fitted parametric curves to the IMpower010 patient-level data as per NICE Decision Support Unit methodology**

  - **Referred to literature identified on longer term survival and "cure" proportions, gathered in Section B.3.3.4**
  - **Adjusted curves with five-year "cure" assumption**
  - **Validated cure assumption survival outputs with identified literature and UK clinical expert opinion**
- **The model did not allow the estimates for the proportion of patients who transitioned to death to be greater than the probabilities from the literature or trial data, instead, it would switch to the use of age-adjusted probabilities of death from the general population**
- **To determine the treatments that patients received in the non-metastatic and metastatic health states, an Advisory board of 6 UK clinical oncologists (4th of November 2024) was undertaken.**
- **Transition probabilities for non-metastatic and metastatic disease recurrences were extrapolated from published literature and NSCLC NICE appraisals**
- **Grade ≥ 3 treatment-related, AEs. 2% incidence in the IMpower010 trial were included in the economic model**
- **For the remaining health states, the following sources were used:**
  - **Non-metastatic recurrence – Antonia et al. 2017**
  - **First-line metastatic recurrence – Reck et al. 2014, Herbst et al. 2020, Ghandi et al. 2018**
  - **Second-line metastatic recurrence – OAK trial (TA520), Reck et al. 2014**

B.3.3.1 Incorporation of clinical data into the economic model

The primary data source for the economic model are data from the IMpower010 trial (CCOD 26th January 2024). IMpower010 is a Phase III, randomised, open-label study evaluating adjuvant atezolizumab (1200 mg every 21 days; for 16 cycles or 1 year) versus BSC (observation and regular scans for disease recurrence) after adjuvant platinum-based chemotherapy (one to four cycles) in adult patients with completely resected Stage IB (≥ 4 cm) – IIIA NSCLC. The final analysis data (CCOD 26th January

2024) used in this economic model are for patients with completely resected NSCLC which expressed PD-L1 on 50% or more of tumour cells, who do not have EGFR-positive or ALK-positive NSCLC and have not progressed after platinum based chemotherapy. For health states not captured by the IMpower010 data (i.e. non-metastatic recurrence, first-line metastatic recurrence, second-line metastatic recurrence, death), additional evidence from various sources were used, including published literature, UK clinical expert advice and assumptions.

Adjuvant chemotherapy (cisplatin plus vinorelbine, docetaxel, gemcitabine, or pemetrexed; based on investigator choice) administered in the IMpower010 trial as a prerequisite to treating patients with adjuvant atezolizumab is reflective of current UK clinical practice, therefore the responses and outcomes seen in the IMpower010 trial are expected to be reflective of UK clinical practice.

B.3.3.2 Modelling of DFS

Patients remain in the DFS health state while they are disease-free and alive. The probability of remaining in the DFS health state is derived from patient-level data in the IMpower010 trial. Given the relatively short median follow-up [65 months follow-up] period in the IMpower010 trial, and the fact that a sizable proportion of DFS events in the PD-L1 high population (atezolizumab (32.1%) and BSC (53.4%)) had not occurred by the end of the available follow-up period, extrapolation techniques were essential to model DFS over a (lifetime) time horizon of 40 years.

Guidance from the NICE Decision Support Unit Technical Support 14 was followed to identify parametric survival models for DFS in the base-case of the model (128). The following steps were followed to identify the base-case model:

- Testing the proportional hazard (PH) assumption, to assess whether joint or separate statistical models were more appropriate for atezolizumab and best supportive care arms in the study. The log-cumulative hazard plot was used to assess the proportional hazard assumption.
- The Akaike Information Criterion (AIC) and the Bayesian Information Criterion (BIC) goodness-of-fit statistics were calculated to assess the goodness of fit to the observed data.

- Within the various parametric survival models explored, visual inspection was used to assess the fit of the curves to the observed clinical trial data.
- Parametric functions were adjusted to produce more clinically realistic curves and long term DFS estimations and the following sources used to inform these adjustments:
    - Published literature
    - Clinical expert opinion

B.3.3.3 DFS extrapolation

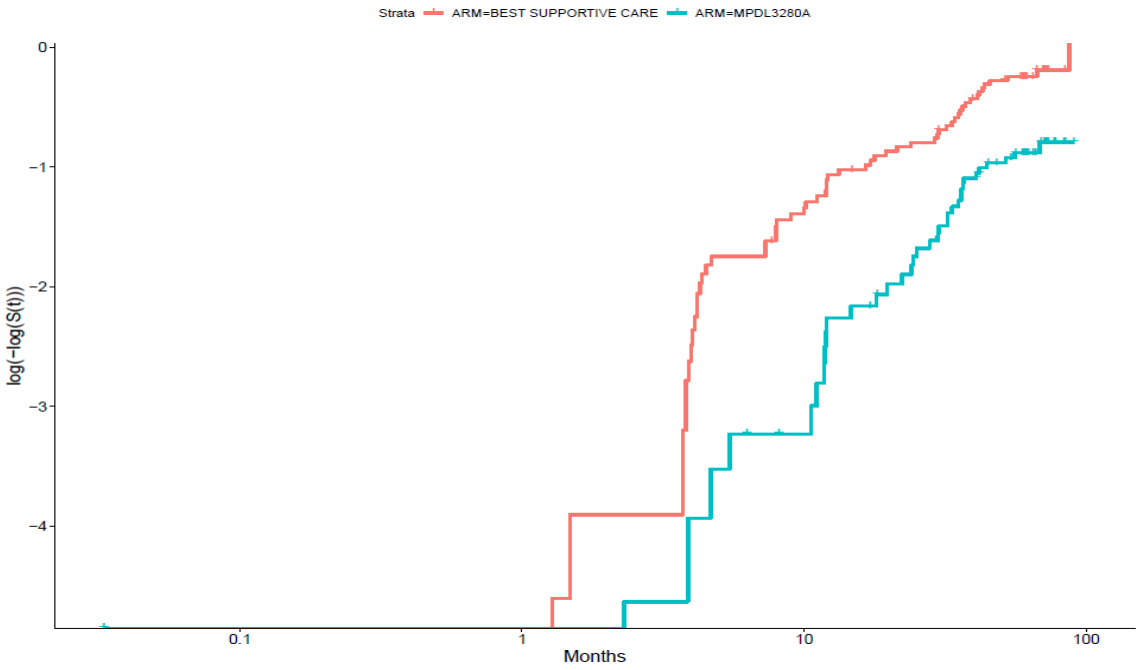
B.3.3.3.1 DFS as a surrogate for OS

Whilst there is limited evidence on the correlation between DFS and OS in the specific population of this appraisal, UK Clinical oncologists note that in the adjuvant setting, DFS is a suitable surrogate for OS. Meta-analyses by Mauguen et al. 2013 (129) found that for trials of adjuvant chemotherapy, there was correlation between DFS and OS and concluded that the evidence showed that DFS is a valid surrogate endpoint for OS.

B.3.3.3.2 Proportional hazards assumption

The analysis fitted seven parametric distributions to the data to extrapolate DFS beyond the observed time-period (Exponential, Weibull, Log-Logistic, Log-Normal, Gompertz, Generalised Gamma and Gamma). It separately fitted the parametric distributions to the intervention and comparator arms of the trial as the proportional hazards assumption did not hold. The proportional hazards assumption requires that the hazards of a DFS event are proportional over time across the atezolizumab and BSC arms (Collett, 2015) (130). However, Figure 18 shows that the curves separate then converge, and for this reason, the proportion hazards assumption does not hold.

Figure 18: Log-cumulative hazard plot – Investigator-assessed DFS (IMpower010; Stage II–IIIA, PD-L1 ≥ 50% (excluding EGFR-positive and ALK-positive) [CCOD 26 Jan 24]



B.3.3.3.3 Assessing the statistical fit of the trial data to the parametric functions

An analysis was carried out to assess the goodness of fit of the various parametric distributions using the Akaike and Bayesian Information Criteria (AIC and BIC). A limitation with these criteria is that they can only assist in determining the accuracy of the different parametric models in representing the observed data on DFS. They do not provide any information on how plausible the extrapolation of an outcome is across the models.

Table 18 shows that the performance of the different distributions depends on whether you prioritise the AIC or BIC, and the ranking differs across the different arms.

Table 18: AIC and BIC across parametric models (Investigator-assessed DFS (IMpower010; Stage II–IIIA, PD-L1 ≥ 50% (excluding EGFR-positive and ALK-positive) [CCOD 26 Jan 24])

Distribution	Atezolizumab arm				BSC arm			
	AIC (Rank)		BIC (Rank)		AIC (Rank)		BIC (Rank)	
Exponential	410.2	2	412.9	1	581.2	7	583.9	6
Weibull	412.2	6	417.5	5	577.7	5	583.0	5
Log-logistic	411.2	5	416.5	4	572.2	3	577.5	3
Log-normal	409.1	1	414.5	2	569.7	2	575.0	2
Gompertz	410.8	4	416.1	3	573.7	4	578.9	4
Generalised Gamma	410.5	3	418.5	7	566.3	1	574.2	1
Gamma	412.2	7	417.5	6	579.1	6	584.4	7

Note: this table reports the AIC and BIC values from the analysis run in R as the Gamma model was not able to be run in SAS. AIC, Akaike Information Criterion; BIC, the Bayesian Information Criterion; DFS, disease-free survival; PD-L1, Programmed Death-Ligand 1; EGFR, epidermal growth factor receptor; ALK, naplastic lymphoma kinase.

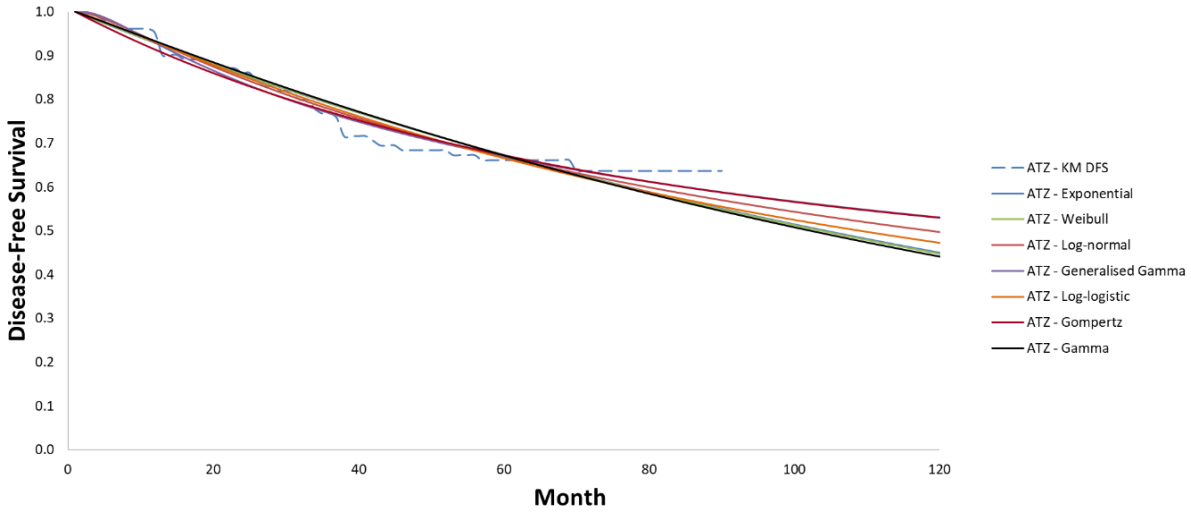
Table 18 shows that for the atezolizumab arm, Log-normal, Exponential and Generalised Gamma are the highest ranked extrapolations with the overall best statistical fit. For the BSC arm, Generalised Gamma, Log-normal and Log-logistic are the highest ranked extrapolations with the best overall statistical fit.

Statistical fit is one of a few criteria, which will be considered when selecting the best fitting extrapolation for each arm.

B.3.3.3.4 Visual fit

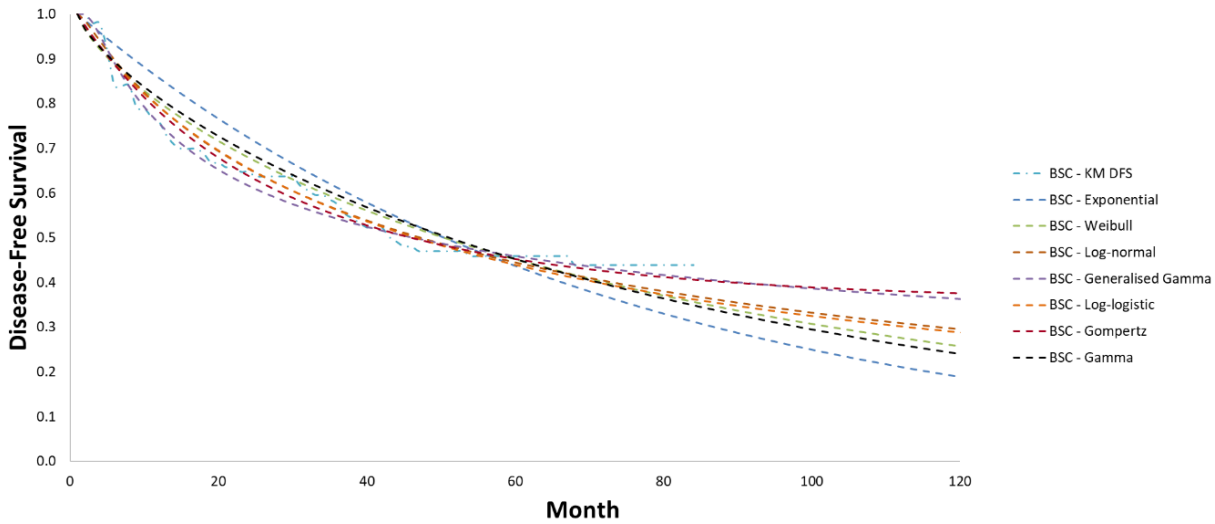
Visual fit was also tested, and Figure 19 and Figure 20 also appear to show that the accuracy of the different parametric distributions in representing the observed data was comparable. The good visual fit was expected based on the shape of the KM and follow-up time, as the KM curves in this short follow-up time are standard and dispersion of data would not be expected until later.

Figure 19: Fit of estimated DFS to Kaplan-Meier plot across parametric models (Investigator-assessed DFS (IMpower010; Stage II–IIIA, PD-L1 ≥ 50% (excluding EGFR-positive and ALK-positive) [CCOD 26 Jan 24], <u>atezolizumab arm</u>



DFS, disease-free survival; PD-L1, Programmed Death-Ligand 1; EGFR, epidermal growth factor receptor; ALK, naplastic lymphoma kinase; CCOD, clinical cut-off date.

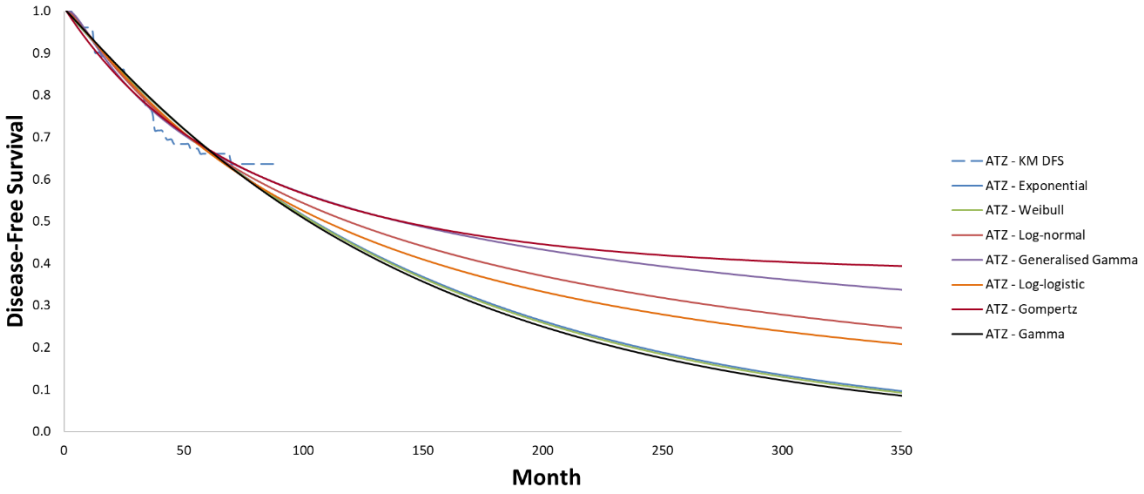
Figure 20: Fit of estimated DFS to Kaplan-Meier plot across parametric models (Investigator-assessed DFS (IMpower010; Stage II–IIIA, PD-L1 ≥ 50% (excluding EGFR-positive and ALK-positive) [CCOD 26 Jan 24], <u>BSC arm</u>



DFS, disease-free survival; PD-L1, Programmed Death-Ligand 1; EGFR, epidermal growth factor receptor; ALK, naplastic lymphoma kinase, CCOD, clinical cut-off date.

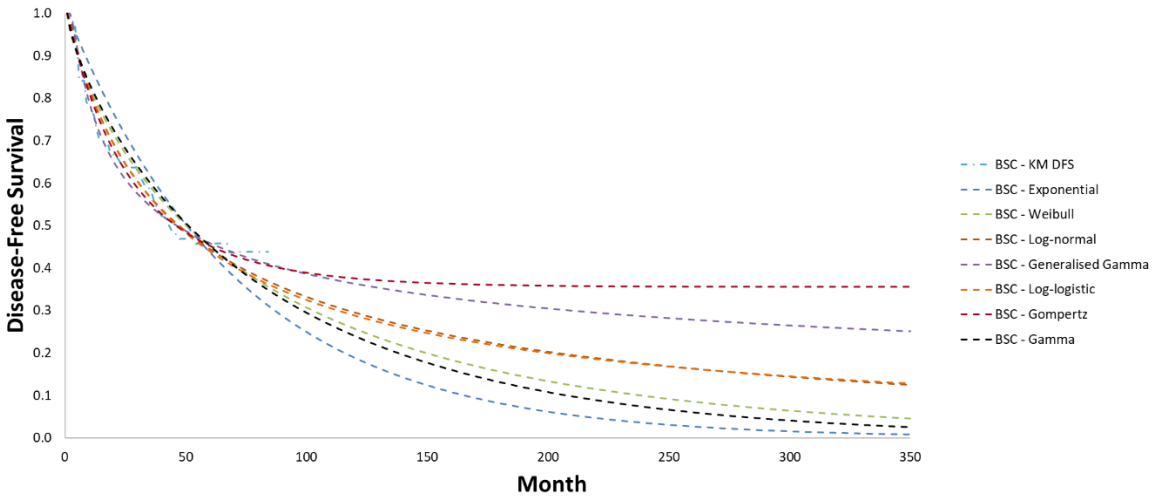
Figure 21 and Figure 22 present a comparison of the extrapolation of DFS across the different parametric models beyond the follow-up of the trial (trial median follow-up: 65 months).

Figure 21: Long-term extrapolation of DFS across Parametric Models Fit of estimated DFS to Kaplan-Meier plot across parametric models (Investigator-assessed DFS (IMpower010; Stage II–IIIA, PD-L1 ≥ 50% (excluding EGFR-positive and ALK-positive) [CCOD 26 Jan 24], <u>atezolizumab arm</u>



DFS, disease-free survival; PD-L1, Programmed Death-Ligand 1; EGFR, epidermal growth factor receptor; ALK, naplastic lymphoma kinase, CCOD, clinical cut-off date.

Figure 22: Long-term extrapolation of DFS across parametric models Fit of estimated DFS to Kaplan-Meier plot across parametric models (Investigator-assessed DFS (IMpower010; Stage II–IIIA, PD-L1 ≥ 50% (excluding EGFR-positive and ALK-positive) [CCOD 26 Jan 24], <u>BSC arm</u>



DFS, disease-free survival; PD-L1, Programmed Death-Ligand 1; EGFR, epidermal growth factor receptor; ALK, naplastic lymphoma kinase, CCOD, clinical cut-off date.

A comparison of the DFS events at different time points was carried out. Table 19 and Table 20 presents the proportion of patients who are disease free at 1, 5, 10 and 20 years according to the parametric extrapolations of the Kaplan-Meier data. When

observing the curves in Figure 19 and Figure 20 and the proportions in Table 19 and Table 20, no meaningful difference can be seen between year 1 and year 5. However, when looking at 10 to 20 years, a meaningful difference in the number of patients who are disease-free can be observed.

Table 19: Expected proportion (%) patients who are event-free at 1, 5, 10 and 20 after treatment initiation – atezolizumab arm

Distribution	Proportion (%) patients event-free after treatment initiation			
	1 year	5 years	10 years	20 years
Exponential	92.3	66.8	44.7	19.9
Weibull	92.4	66.8	44.4	19.5
Log-logistic	92.4	66.1	47.0	28.7
Log-normal	92.5	66.4	49.5	32.6
Gompertz	90.7	66.9	52.9	42.4
Generalised-Gamma	92.1	66.7	52.9	40.0
Gamma	92.7	66.7	43.8	18.6

Table 20: Expected proportion (%) patients who are event-free at 1, 5, 10 and 20 years after treatment initiation – BSC arm

Distribution	Proportion (%) patients event-free after treatment initiation			
	1 year	5 years	10 years	20 years
Exponential	84.5	43.1	18.5	3.4
Weibull	79.1	44.7	25.4	9.8
Log-logistic	77.8	43.5	28.6	17.3
Log-normal	77.9	44.1	29.4	17.4
Gompertz	76.7	45.0	37.5	35.6
Generalised-Gamma	73.9	45.6	36.2	28.6
Gamma	80.1	44.8	23.8	7.3

B.3.3.3.5 Literature and expert clinical opinion

Given the need to clinically validate the DFS projections, a SLR was conducted on the efficacy and safety of treatment for early-stage NSCLC in an attempt to identify evidence to clinically validate the projections. However, no evidence was found in the literature which presents estimates for patients who are Stage II and IIIa and disease-free and alive at any given time point. As a result, the DFS extrapolations were validated by 6 clinicians during an advisory board held on 4th November 2024. During

that advisory board, clinicians acknowledged the uncertainty in the tail of the original DFS curve due to censoring. Nevertheless, in their opinion the most likely extrapolations for the atezolizumab arm were Generalised Gamma and Gompertz, and for the BSC arm it was Log-Logistic or Log-Normal (1). Clinicians ruled out the Weibull model as they felt it was too pessimistic (1). The conclusions of the clinicians in terms of extrapolation choice broadly align with the findings when analysing statistical and visual fit in Section B.3.3.3.4.

B.3.3.5.6 Base case DFS extrapolation

During the advisory board on 4th November 2024, clinicians stated that there is an inherent uncertainty in determining which are the most appropriate extrapolations to select for the treatment arms. This uncertainty primarily stems from the limited data available in the adjuvant NSCLC setting.

When observing the statistical fit, it can be observed that for the first few years the extrapolations don't show a meaningful difference, however, as time progresses, post 5 years, a meaningful difference can be observed between the different extrapolations. Statistical fit estimates show that for the atezolizumab arm, Log-normal, Exponential and Generalised Gamma are the highest ranked extrapolations with the best statistical fit. For the BSC arm, Generalised Gamma, Log-normal and Log-logistic are the highest ranked extrapolations with the best statistical fit.

Visually for the atezolizumab arm, almost all extrapolations are very similar therefore it is difficult to determine which one provides the best visual fit. However, visually for the BSC log-normal seems to provide the best fit.

No clinical evidence was available to evaluate the proportion of patients that are disease free at any given time point. Therefore, clinical input was sought to validate the curves. 6 clinicians during an Advisory board held on the 4th of November 2024 concluded that the Generalised Gamma and Gompertz models as well as the Log-Logistic and Log-Normal models provide the most appropriate DFS projections for the adjuvant atezolizumab and best supportive care arm.

Based on the different steps taken above, the following curves were selected as the most plausible extrapolations to inform the base case. For the atezolizumab case, due

to clinical expert opinion and statistical fit, the Generalized Gamma curve was initially selected as the base case. As the Generalized Gamma curve did not converage, no PSA could be run thus resulting in unreliable extrapolations. As the next best fit statistically, and the only other extrapolation clinicians felt was plausible, the Gompertz extrapolation was selected. In addition, when looking at the two extrapolations and the proportion of patients who are alive and disease-free at any given timepoint, both curves provide very similar estimates. For the BSC arm, log-normal was chosen as the base case since it provided the best statistical AIC fit, visual fit and clinicians confirmed that the only two extrapolations that appropriate to extrapolate BSC are log-logistic and log-normal. As a result, the distribution selected for the base case for the atezolizumab arm is Gompertz whilst the distribution for the BSC arm is Log-Normal.

B.3.3.4 Adjusting the DFS curves

DFS curve adjustment and validation process:

1. **Fitted parametric curves to the IMpower010 patient-level data as per NICE Decision Support Unit methodology**
2. **Referred to literature identified on longer term survival and "cure" proportions, gathered in Section B.3.3.3.5**
3. **Adjusted curves with five-year "cure" assumption at 79% cure rate**
4. **A mortality rate of 1.25 of "cure" patients is assumed**
5. **Treatment waning after 60 months is assumed.**
6. **Validated cure assumption survival outputs with identified literature and UK clinical expert opinion**

A real world evidence (RWE) structured review was carried out to identify evidence on clinical burden and treatment patterns for early NSCLC in August 2023 and was re-run in September 2023, and September 2024, which were used to inform the inputs of the model. The full report is provided in Appendix L.

The model made three adjustments to the extrapolated DFS to ensure that it predicted proportions of patients in this health state over time that were realistic:

Cure adjustment: The median duration of follow-up in IMpower010 is 65 months. Evidence shows that most patients with completely resected NSCLC relapse within 5 years (131). As a result, the model assumes that a certain proportion of patients may be considered cured if disease-free for 5 years after resection, an assumption, which was validated by clinicians during the November 2024 advisory board (1).

An SLR on the conditional DFS of patients who underwent surgical resection for early-stage NSCLC was conducted in an attempt to identify evidence that could estimate the proportion of patients that could be considered cured at 5 years. The SLR identified two studies that show that being in DFS for 3 years, conditional on already being DFS for 3-5 years, is 83% to 91% depending on disease stage (132, 133). This is in contrast to the input provided by clinical experts during the 4th of November 2024 Advisory Board who stated that they expect around 95% and 94% of patients to be considered cured if disease-free at years 5 and 10. Given that the ERG during the IMpower010 2022 NICE appraisal of adjuvant atezolizumab considered it optimistic to assume that more than 90% of patients could be considered cured if disease-free at Year 5, the cost-effectiveness analysis uses literature to inform the cure assumption.

Table 21 presents the literature used in the model to inform the proportion of patients that are cured after 5 years. Chaudhry T et al. (2023) was used in the base case (Stage I–IIIA (5-years): 79% to take a more conservative approach and use a patient population, which is broadly representative of the UK patient population compared to the Shin et al paper (2023) which reported on the cure proportion of NSCLC patients in South Korea, which is not representative of the UK patient population. A scenario will be conducted in Section 3.8.3 using the clinician validated proportion of patients cured at 5 years.

Table 21: Conditional disease-free survival (real-world evidence SLR; search: 09.2024)

Study	Country	Disease stage	Results
(133)	US	Stage I: 70% Stage II: 19% Stage III: 11%	Conditional DFS – 2 and 5 years without recurrence conditional on 3 years disease-free after surgery Stage I-IIIA (2-years): 89% Stage I-IIIA (5-years): 79%

			Stage IIIA (2-years): 90% Stage IB (2-years): 90%

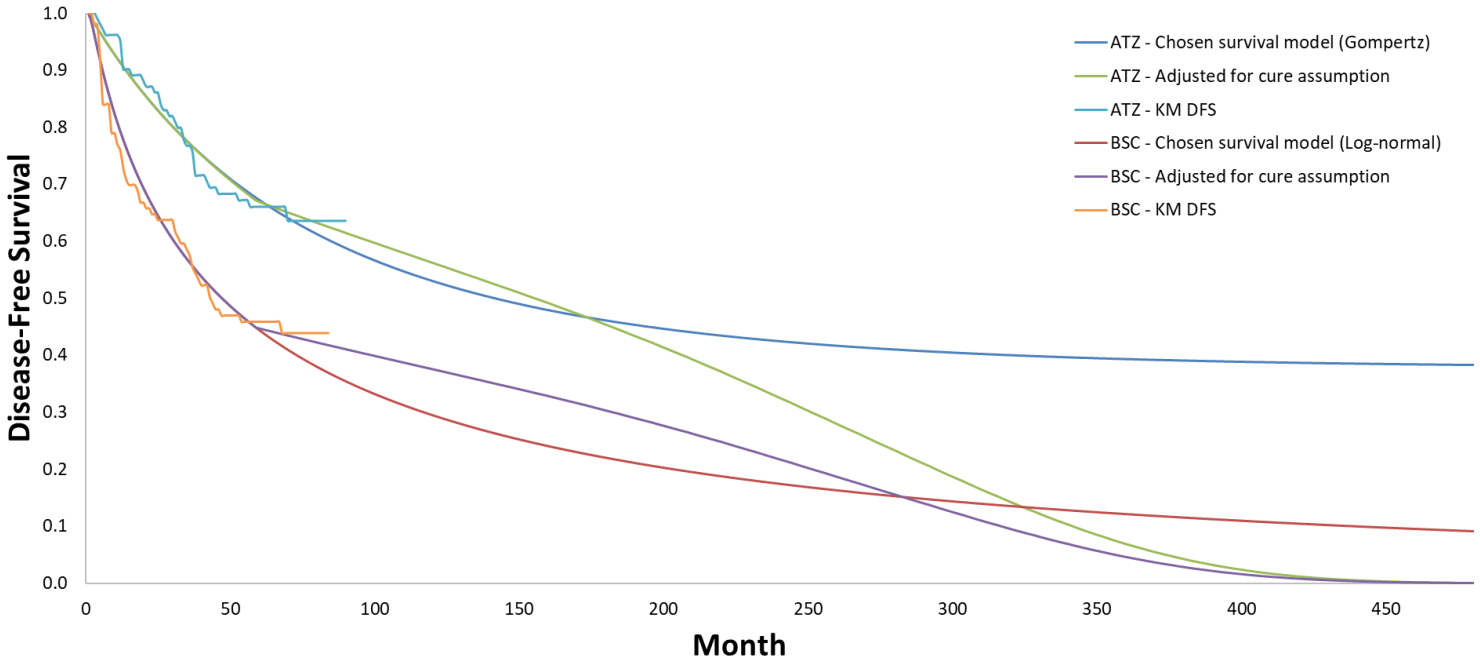
Mortality adjustment: The study uses lifetable statistics from the UK to inform the probability of death of cured patients (134). As lung cancer survivors are likely to have comorbidities, these probabilities can be adjusted upwards. The model adjusts the probability of death of these patients with a standardised mortality ratio of 1.25 (25% more cases of death than the general population) to account for excess mortality faced by these lung cancer survivors. This estimate was based on Janssen-Heijnen et al. (2012)[1] , who reported a 10-year conditional relative survival of 69–82% with a sample of Stage I–III patients (dependent on stage and age at diagnosis) (135). During the advisory board on 4th November 2024, clinical experts validated this evidence from which it was concluded that it would be appropriate to assume that lung cancer survivors face a higher probability of death than age and sex adjusted individuals from the general population. Note that this paper was accepted in TA823 (59).

Treatment effect: the model allows the treatment effect of atezolizumab to decrease over time. There is currently a lack of data from IMpower010 and external evidence to inform at which time point the treatment effect of atezolizumab ceases. Thus, the model assumes that it ceases at Year 5 or the same year at which the proportion of cured patients reaches its maximum. This is aligned with assumptions in previous NSCLC appraisals (TA531 (136), TA428 (137), TA557 (138), TA600 (139)).

Figure 23 shows that without these adjustments, the proportion of patients in DFS is lower.

[1] A structured review was carried out in June 2021 to identify evidence on clinical burden and treatment patterns for patients with early NSCLC in the DFS and locoregional recurrence health state (see Appendix L)

Figure 23: DFS curve extrapolations for BSC and atezolizumab) – unadjusted and adjusted

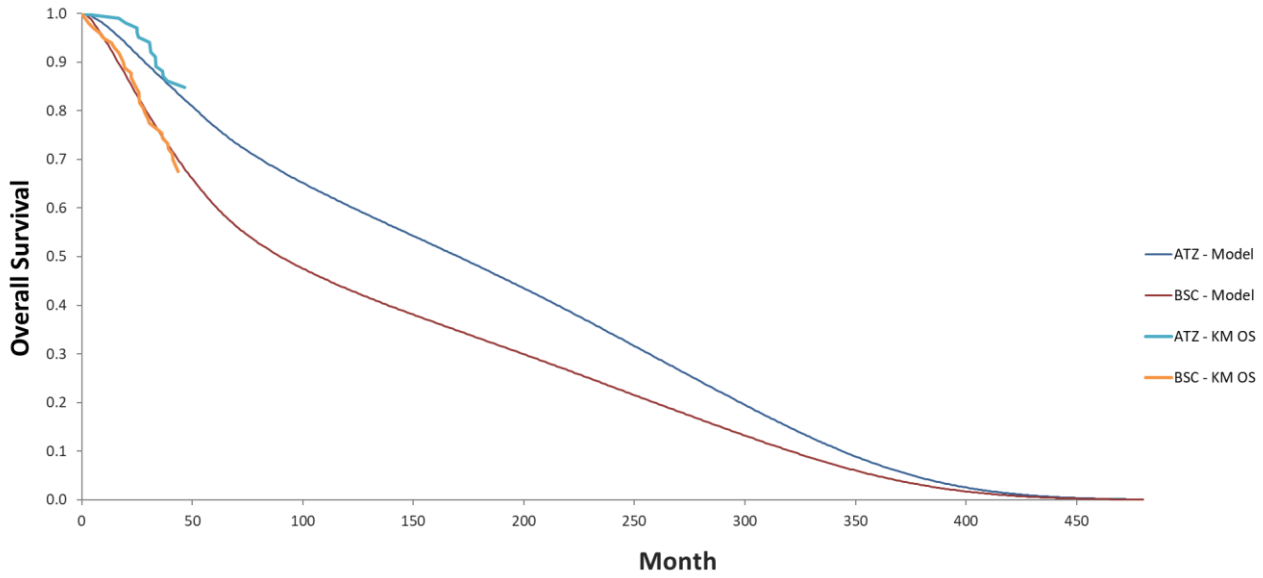


DFS, disease-free survival; BSC, best supportive care

B.3.3.5 Overall survival

OS was not captured as a primary endpoint in the IMpower010 and was analysed post-hoc in an exploratory analysis. As a result, OS was modelled and derived using DFS as a surrogate and literature was used to derive patients and their progression across different health states. OS was used to visually match the derived OS to the OS KM data. In addition, the curves were validated in the UK clinical Advisory Board on the 4th of November 2024 and were deemed appropriate. Clinicians validated the assumptions that significant improvements in DFS observed with atezolizumab are likely to translate into corresponding OS benefits (1). This perspective is informed by historical precedents in oncology where enhanced DFS has been shown to predict improved OS, particularly in treatments targeting specific cancer mechanisms, like NSCLC. Figure 24 shows the OS of atezolizumab vs. BSC. Note that in Figure 24 the atezolizumab extrapolations are most likely underestimating OS, which can be observed when looking at the atezolizumab KM data. This is most likely due to the curve adjustments and taking a more conservative approach such as the 79% of cure proportion, treatment waning and 1.25 SMR.

Figure 24: Modelled and observed overall survival (IMpower010; Stage II–IIIA, PD-L1 ≥ 50% (excluding EGFR-positive and ALK-positive) [CCOD 18 Apr 2022] – atezolizumab and BSC



PD-L1, Programmed Death-Ligand 1; EGFR, epidermal growth factor receptor; ALK, naplastic lymphoma kinase, CCOD, clinical cut-off date; BSC, best supportive care.

B.3.3.6 Treatment after recurrence

The following section will lay out the treatment patterns for patients after they progress from DFS to non-metastatic, metastatic or death. The model allows patients who experience non-metastatic recurrence and/or metastatic recurrence (separately for first- and second line) to either be treated or not. For those patients who are treated, four of the most common treatment options in the UK are included. The model also accounts for treatment choices whether patients have been treated with adjuvant immunotherapy within or after 18 months (1 year of treatment with atezolizumab plus the 6 month rechallenge period according to the Blueteq form) or with best supportive care. Clincians at the advisory board on 4th November 2024 confirmed that patients who were treated with adjuvant immunotherapy and relapsed within 18 months of treatment initiation would be treated differently to patients who were treated with adjuvant immunotherapy and relapsed after 18 months of treatment initiation or had only received best supportive care after adjuvant chemotherapy (1).

The same advisory board on 4th November 2024 informed what treatments patients within each of the different health states would receive and their respective proportions

(1). In addition, the treatment patterns were supplemented by NICE guidelines as described in Section B.3.3.7 (140).

B.3.3.7 Types of disease recurrences in the DFS setting

To inform the relative split in disease-free events, the model uses evidence from IMpower010 as seen in Table 22. It can leverage two sets of estimates to inform the proportions. The first set was derived separately for each study arm while the second set was derived from the pooled sample of patients from both study arms. The base case uses the pooled sample estimates in the base case, which differs to the original approach that was in the IMpower010 2022 submission. While this approach restricts the type of events that patients experience across all treatment arms, the ERG stated during the NICE technical appraisal of NICE that using separate estimates is not appropriate. This is because it was not clinically plausible to assume that there would be difference in the split of these events (141).

Table 22: Type of disease-free survival events (IMpower010; Stage II–IIIA, PD-L1 ≥ 50% (excluding EGFR-positive and ALK-positive) [CCOD 26 Jan 24]

DFS event	Adjuvant atezolizumab	Best supportive care	Adjuvant atezolizumab and best supportive care
Total events	**33**	**52**	**85**
Death	6 (18.2%)	8 (15.4%)	14 (16.5%)
Non-Metastatic recurrence	16 (48.5%)	16 (30.8%)	32 (37.6%)
Metastatic recurrence	11 (33.3%)	28 (53.8%)	39 (45.9%)

In the adjuvant atezolizumab and best supportive care arms of IMpower010, 1 and 3 patients experienced a new primary lung cancer in this population.

Types of disease-free events

The model uses the results from external sources to inform the progression-free survival (PFS) and OS of patients who are treated and not treated after experiencing recurrence. This is because IMpower010 does not systematically collect data on disease progression after a patient's earliest disease progression. Regarding sources for which the study does not have access to the data, it digitises the Kaplan-Meier estimates of PFS and/or OS and uses the Guyot, Ades, Ouwens and Welton (2012) algorithm to transform the data to approximated individual patient-level datasets (IPD). To take a more conservative approach, the transition probabilities use the results

produced by the exponential model to inform death or further disease progression rather than the best fitting model. This is because the exponential model tends to overestimate patients who are progression free up to a point in time (this point in time might slightly vary depending on the treatment) when most patients would have progressed or died when reviewing the KM data. The impact of this overestimation benefits the best supportive care arm, as a larger proportion of patients tend to progress on best supportive care and across each line of treatment the exponential extrapolation estimates that patients are progression free for longer. Appendix M shows the different extrapolations and their estimates. One limitation of using exponential means that the probabilities of experiencing these events are time-invariant.

B.3.3.7.1 Non-metastatic recurrence

Patients who have non-metastatic recurrence could either be treated or not treated. The model included this separation to account for the fact that some patients cannot or choose not to be treated. The split between treatment and no treatment was informed by UK clinical expert opinion (1):

- Treatment: 70%
- No treatment: 30%

Treatment

Table 23 presents 4 treatment options and their respective market shares, which was provided by clinicians. The model assumes the following 4 treatment options for patients who experience non-metastatic recurrence; chemoradiotherapy plus durvalumab, chemoradiotherapy, radiotherapy or pembrolizumab monotherapy, applying market share data, which was informed by clinicians during the 4th of November 2024 Advisory board, so that the total market share of these treatments add up to 100%, as seen in the table below. Note that the market share has been adapted to account for patients who have a recurrence within 6 months or after 6 months of receiving adjuvant atezolizumab. If patients have a recurrence within 6 months of receiving atezolizumab, then patients can only be treated with Option 2 and 3. This is because patients cannot be retreated within 6 months with an immunotherapy (pembrolizumab and durvalumab) after receiving atezolizumab in the

adjuvant setting. If patients have a recurrence after 6 months of receiving atezolizumab then they can be treated with Option 1, 3 and 4. The 6 month treatment rule also applies to the 1st line and 2nd line metastatic second.

Table 23: Cost-effectiveness analysis – treatment after non-metastatic recurrence

	Option 1	Option 2	Option 3	Option 4
Drug 1	Cisplatin	Cisplatin	-	Pembrolizumab
Dose Size	80 mg/m2	80 mg/m2	-	200 mg/fixed
Treatment Intervals	3 weeks	3 weeks	-	3 weeks
Treatment Duration	4 cycles	4 cycles	-	7 cycles
Drug 2	Vinorelbine	Vinorelbine	-	-
Dose Size	60 mg/m2	60 mg/m2	-	-
Treatment Intervals	3 weeks	3 weeks	-	-
Treatment Duration	4 cycles	4 cycles	-	-
Drug 3	Durvalumab	-	-	-
Dose Size	10 mg/kg	-	-	-
Treatment Intervals	2 weeks	-	-	-
Treatment Duration	24 cycles	-	-	-
Radiotherapy		-	-	-
Total Dose Size	66 Gy	66 Gy	66 Gy	-
Dose per Fraction	2 Gy	2 Gy	2 Gy	-
Fractions per Week	5	5	5	-
Market Shares				
Adjuvant Immunotherapy (Early-Relapse)	[redacted]	[redacted]	[redacted]	[redacted]
Adjuvant Immunotherapy (Late-Relapse)	[redacted]	[redacted]	[redacted]	[redacted]
Best Supportive Care	[redacted]	[redacted]	[redacted]	[redacted]
Reference	(142)	(142)	(142)	(143)

Mg = milligrams; m2 = body surface area; Kg = kilograms; Gy = Grays.

1 & 2. Chemoradiotherapy with and without durvalumab

To inform the PFS of chemoradiotherapy with or without the combination of maintenance durvalumab, the study conducted a pragmatic search of the literature to identify the most recent evidence from PACIFIC. Attention was placed on this study as it appears to be the only study presenting evidence on durvalumab. The review identified three sources (142, 144, 145). The study proceeds with the use of Spigel et al. (2022) to inform PFS because it presents Kaplan-Meier estimates and uses the most recent clinical cut-off for the analysis. A limitation inherent with the use of this source is that the PACIFIC study enrolled patients into the trial after they had already completed chemoradiotherapy. The PFS estimates derived from this source may not, thus, account for the higher risk patients who would have progressed or died while on chemoradiotherapy.

3. Radiotherapy

To inform the PFS of radiotherapy, the model also uses evidence from Spigel et al. (2022). A limitation with the use of this approach is that the study may overestimate the PFS of radiotherapy. Nevertheless, this limitation will likely favour the comparator as a higher proportion of patients experience non-metastatic recurrence in the BSC arm.

4. Pembrolizumab

To inform the PFS of pembrolizumab monotherapy, a SLR was conducted on the efficacy and safety of first-line interventions for advanced-stage NSCLC. The SLR did not identify any studies that only focussed on the efficacy and safety on the use of pembrolizumab to treat non-metastatic recurrence after initial diagnosis of early-stage NSCLC or de novo locally advanced NSCLC. However, it did identify four studies that focussed on the efficacy and safety on the use of this intervention to treat a mix of patients with locally advanced and metastatic NSCLC (143, 146-148). Due to the identified studies mixing patients with locally advanced and metastatic NSCLC and to prevent bias, PFS of pembrolizumab is informed by the PFS of chemoradiotherapy and durvalumab.

No treatment

To inform the OS of patients with non-metastatic recurrence but who did not receive treatment, the study conducted a targeted literature review (TLR) on the clinical outcomes of patients with non-metastatic recurrence after being diagnosed with resected early-stage NSCLC and who did not receive treatment.

The TLR identified three studies (149-151). Wong et al. (2016) was chosen to inform OS. This study used a much larger sample size compared to the other papers, and included much less stage I patients. 9,001 patients were randomly selected from the US National Cancer Data Base. Patients were followed for 5 years or until first NSCLC recurrence, new primary cancer, or death, whichever came first. Patient characteristics were broadly aligned with the UK patient population. Appendix M presents the OS projections from the exponential and log-normal model (best-fitting model).

B.3.3.7.2 First-line metastatic recurrence

Patients with metastatic recurrence could be treated with first-line treatment or not be treated. The model used this separation to account for the fact that some patients cannot or choose not to be treated. The proportion of patients treated or not treated were informed by UK clinical oncologists.

- Treatment: 60%
- No treatment: 40%

Treatment

As mentioned in the previous section, Table 24 presents 4 treatment options and respective market shares for patients treated with immunotherapy (early-relapse), immunotherapy (late-relapsed), and chemotherapy. The treatment options were informed by clinicians and further informed by NICE guidance. The treatment options were adjusted to use the 4 most common treatment options in the first-line metastatic setting, applying market share data, which was informed by clinicians during the November 2024 Advisory board so that the total market shares of these treatments add up to 100%, as seen in the table below.

Table 24: Cost-effectiveness analysis – treatment after metastatic recurrence (first-line)

	Option 1	Option 2	Option 3	Option 4
Drug 1	Pembrolizumab	Atezolizumab	Pembrolizumab	Pemetrexed
Dose Size	200mg/fixed	1, 200 mg/fixed	200mg/fixed	500mg/m2
Treatment Intervals	3 weeks	3 weeks	3 weeks	3 weeks
Doses per cycle	1	1	1	1
Drug 2	-	-	Pemetrexed	Carboplatin
Dose Size	-	-	500mg/m2	150mg AUC
Treatment Intervals	-	-	3 weeks	3 weeks
Doses per cycle	-	-	1	1
Drug 3	-	-	Carboplatin	-
Dose Size	-	-	150mg AUC	-
Treatment Intervals	-	-	3 weeks	-
Doses per cycle	-	-	1	-
Market Shares				
Adjuvant Immunotherapy (Early-Relapse)	[redacted]	[redacted]	[redacted]	[redacted]
Adjuvant Immunotherapy (Late-Relapse)	[redacted]	[redacted]	[redacted]	[redacted]
Best Supportive Care	[redacted]	[redacted]	[redacted]	[redacted]
Reference	(143)	Impower110 (as per protocol)	(152)	Impower110 (as per protocol)

Mg = milligrams, m2 = body surface area; AUC = area under curve.

To inform the PFS of patients with metastatic recurrence and who proceed with first-line treatment, a SLR was conducted to identify the efficacy and safety of first-line interventions for advanced-stage NSCLC.

1. <u>Pembrolizumab</u>

The SLR identified four sources that present evidence on the efficacy and safety of first-line pembrolizumab monotherapy derived from the KEYNOTE-024 and KEYNOTE-042 studies (143, 146-148). As Reck et al. (2016) and Mok et al. (2019) present evidence from these studies using earlier clinical cut-offs than do Reck et al. (2021) and de Castro et al. (2023), the study only considers the latter two sources to inform PFS. From these two sources, the model uses de Castro et al. (2023) which

presents evidence from KEYNOTE-042. While the two KEYNOTE studies share certain similarities, KEYNOTE-042 enrolled a large sample of patients who were PD-L1 ≥ 50% than did the KEYNOTE-024 study. Thus, KEYNOTE-042 is deemed more representative to inform the PFS of pembrolizumab monotherapy.

2. Atezolizumab

The SLR identified one source that presents evidence on the efficacy and safety of first-line atezolizumab monotherapy derived from IMpower110(153). As IMpower110 is a Roche sponsored study, IPD were available without the requirement to digitise and transform the published Kaplan-Meier estimates to an approximated dataset.

3. Pembrolizumab + Pemetrexed + Carboplatin

The SLR identified two sources that present evidence on the efficacy and safety of first-line pembrolizumab in combination with pemetrexed and carboplatin derived from the KEYNOTE-021 and KEYNOTE-189 studies (152, 154, 155). The study uses Garassino et al. (2023), since this study presents evidence from the KEYNOTE-189 study and it includes evidence for the PD-L1 ≥ 50% sub-population. A limitation with the use of this evidence to inform PFS is that it is derived using patients who were also treated with cisplatin and carboplatin as part of their treatment.

4. Pemetrexed + Carboplatin

The SLR identified twelve sources that present evidence on the efficacy and safety of first-line pemetrexed and carboplatin plus pemetrexed maintenance therapy (143, 146, 152-154, 156-162). In the model, Spigel et al. (2019) was used to inform Pemetrexed + Carboplatin PFS as it has access to the Impower110 IPD data.

No treatment

To inform the OS of patients with non-metastatic recurrence but who did not receive treatment, the study conducted a targeted literature review (TLR) on the clinical outcomes of patients with non-metastatic recurrence after being diagnosed with resected early-stage NSCLC and who did not receive treatment.

The TLR identified three studies (149-151). The study proceeds with the use of Wong et al. (2016) to inform OS because, in comparison to the other studies, this study uses

a much larger sample size (> 9, 000 patients), and included much less stage I patients. Appendix M presents the OS projections from the exponential and log-normal model (best-fitting model).

B.3.3.7.3 Metastatic recurrence (second-line)

Patients with metastatic recurrence could be treated with second-line treatment or not be treated. The model used this separation to account for the fact that some patients cannot or choose not to be treated. The proportion of patients treated or not treated were informed by UK clinical oncologists (1):

- Treatment: 30%
- No treatment: 70%

Treatment

To inform the OS of patients with metastatic recurrence and who proceed with second-line treatment, the study leverages a 2017 SLR on the efficacy and safety of second-line interventions for advanced stage NSCLC. A limitation of not updating the review is that it may prevent the model from using the most appropriate sources to inform the OS of second-line metastatic treatments. The treatment options were adjusted to use the 4 most common treatment options in the second-line metastatic setting, applying market share data, which was informed by clinicians during the November 2024 Advisory board so that the total market shares of these treatments add up to 100%, as seen in Table 25.

Table 25: Cost-effectiveness analysis – treatment after metastatic recurrence (second-line)

	Option 1	**Option 2**	**Option 3**
Drug 1	Nintendanib	Gemcitabine	Docetaxel
Dose Size	150 mg/fixed	1250mg/m2	75mg/m2
Treatment Interval	3 weeks	3 weeks	3 weeks
Doses per cycle	2	1	1
Drug 2	Docetaxel	Carboplatin	-
Dose Size	75mg/m2	150mg AUC	-
Treatment Interval	3 weeks	3 weeks	-
Doses per cycle	1	1	-
Market Shares			

Adjuvant Immunotherapy (Early-Relapse)	[redacted]	[redacted]	[redacted]
Adjuvant Immunotherapy (Late-Relapse)	[redacted]	[redacted]	[redacted]
Best Supportive Care	[redacted]	[redacted]	[redacted]
Reference	(163)	Impower110 (as per protocol)	OAK (as per protocol)

Nintedanib + Docetaxel

The SLR identified one source that presents evidence on the efficacy and safety of second-line nintedanib plus docetaxel derived from LUME-Lung 1 (163), which was used in the model to inform OS for Nintedanib + Docetaxel.

Gemcitabine + Carboplatin

The SLR did not identify any sources that present evidence on the efficacy and safety of second-line gemcitabine plus pemetrexed. Therefore, the gemcitabine + carboplatin OS is informed by the nintedanib plus docetaxel OS.

Docetaxel

The SLR identified more than fifty sources that present evidence on the efficacy and safety of second-line docetaxel. One source presents evidence derived from OAK. Since the company has access to the IPD data, OAK was used to inform.

No treatment

To inform the OS of patients with non-metastatic recurrence but who did not receive treatment, the study conducted a targeted literature review (TLR) on the clinical outcomes of patients with non-metastatic recurrence after being diagnosed with resected early-stage NSCLC and who did not receive treatment.

The TLR identified three studies (149-151). The study proceeds with the use of Wong et al. (2016) to inform OS because, in comparison to the other studies, this study uses a much larger sample size (> 9, 000 patients), and included much less stage I patients. Appendix M presents the OS projections from the exponential and log-normal model (best-fitting model).

B.3.3.8 Type of progression-free events in the non-metastatic and metastatic setting

Literature was used to inform the type of events patients (on treatment) experience if they have a non-metastatic or metastatic recurrence (first-line). While the model allows this split to differ by treatment option and attempts to inform it with the same sources that it uses to inform their efficacy, most of these sources did not provide this information.

To inform the types of events that patients can experience when on chemoradiotherapy with or without durvalumab, the model uses the PACIFIC NICE committee papers (TA798) (164). It also uses this source to inform the split in events associated with pembrolizumab and radiotherapy. There are two limitations inherent with this approach. First, the PACIFIC study enrolled patients into the trial after they had completed chemoradiotherapy. Thus, these estimates may not completely reflect the relative difference in events that patients would experience who are followed from the initiation of chemoradiotherapy.

To inform the types of events that patients can experience when they experience an event on atezolizumab monotherapy or carboplatin plus pemetrexed, the study uses evidence derived from IMpower010. It also uses this source to inform the split in events for pembrolizumab with or without carboplatin plus pemetrexed. Table 26 presents the evidence that is used by the study to inform the split in events for these treatments.

Table 26: Cost-effectiveness analysis - Types of progression-free events

Non-metastatic recurrence				
PFS Event	**Chemoradiotherapy + Durvalumab**	**Chemoradiotherapy**	**Radiotherapy**	**Pembrolizumab**
Total Events	**63**	**108**	**108**	**63**
Death	12 (19.1%)	27 (25.0%)	27 (25.0%)	12 (19.1%)
Progression	51 (80.9%)	81 (75.0%)	81 (75.0%)	51 (80.9%)
Reference	**(165)**			
Metastatic recurrence (First-Line)				
PFS Event	**Pembrolizumab**	**Atezolizumab**	**Pembrolizumab + Carboplatin + Pemetrexed**	**Carboplatin + Pemetrexed**

Total Events	**67**	**67**	**67**	**79**
Death	20 (29.9%)	20 (29.9%)	20 (29.9%)	20 (25.3%)
Progression	47 (70.1%)	47 (70.1%)	47 (70.1%)	59 (74.7%)
Reference	Data on File (Primary CSR of IMpower110)*			

*N.R. = not reported; *These results can be found in the following output t_ef_lm_pfsinv_33_ITWT derived from the TC3/IC3 patients (i.e. PD-L1 high) who are part of the ITT (Primary CSR of Impower110; using the clinical cut-off date of 10 September 2018).*

B.3.3.9 Treatment discontinuation

The study allows patients to discontinue adjuvant treatment, and treatment received after recurrence, if they experience recurrence, disease progression, death, or cannot tolerate the treatment (e.g. toxicity).

B.3.3.9.1 Adjuvant treatment

In the base case, treatment duration for atezolizumab is based on time-to-off treatment (TTOT) from IMpower010. Table 27 provides an overview of the proportion of patients who discontinue treatment during each treatment cycle.

Table 27: Treatment discontinuation - adjuvant atezolizumab (IMpower010; Stage II–IIIA, PD-L1 ≥ 50% (excluding EGFR-positive and ALK-positive) [CCOD 26 Jan 24]

Cycle	Proportion	Cycle	Proportion	Cycle	Proportion
1	3.8%	7	2.9%	13	1.0%
2	2.9%	8	1.0%	14	0.0%
3	4.8%	9	0.0%	15	1.0%
4	1.9%	10	2.9%	16	74.0%
5	1.9%	11	1.0%		
6	0.0%	12	1.0%		

No unexpected results were observed in the treatment discontinuation rates. 74% of patients completed their treatment (patients receive 16 cycles of atezolizumab). 18.2% of patients discontinued their treatment due to atezolizumab related adverse events, however, no unexpected adverse events were recorded that led to a disproportionate number of patients not completing their treatment. Clinicians confirmed that no unexpected adverse events were observed in the 26th January 2024 data cut.

B.3.3.9.2 Treatment after recurrence

To inform treatment discontinuation after recurrence, the model uses the same sources that it used to inform the efficacy of the treatment options with a few exceptions.

For non-metastatic recurrence, the model assumed the treatment discontinuation period from Antonia, et al., 2017. For metastatic-recurrence first-line, the study uses (143) for pembrolizumab and for pembrolizumab + carboplatin + pemetrexed. For atezolizumab (152) and carboplatin + pemetrexed the model uses the discontinuation rates from IMpower110. To estimate the treatment duration for metastatic second-line, nintedanib + docetaxel and cisplatin + pemetrexed, (163) was used as the source. To inform the treatment duration of docetaxel, the OAK trial was used. Table 28 presents the evidence that the model uses on median treatment duration (i.e. months/cycles).

Table 28: Treatment discontinuation – treatment after recurrence

Non-metastatic recurrence	**Median number of months**	**Reference**
Chemoradiotherapy + Durvalumab	10.0	(142)*
Chemoradiotherapy	n.r.	(142)
Radiotherapy	n.r.	(142)
Pembrolizumab	10.0	(142)*
Metastatic recurrence (first-line)	**Median number of months**	**Reference**
Pembrolizumab	7.0	(143)
Atezolizumab	5.3	Primary CSR of IMpower110***
Pembrolizumab + Carboplatin + Pemetrexed	10.0	(152)**
Carboplatin + Pemetrexed	3.5	Primary CSR of IMpower110***
Metastatic recurrence (second-line)	**Median number of weeks**	**Reference**
Nintedanib + Docetaxel	14.8	(163)
Cisplatin + Pemetrexed	14.8	(163)
Docetaxel	9.1	Primary CSR of OAK

*N.R. = not reported; *Antonia et al. (2017) present the median number of months on treatment, but the median number of infusions administered. As the median number of infusions were 20 and administered every 2 weeks, the study estimates the median number of months on treatment to be 10.; ** Ghandi et al. (2018) present the median number of months separately for pembrolizumab, cisplatin/carboplatin and pemetrexed. The study uses the results on the median number of months on pembrolizumab to inform the median number of months on treatment with the pembrolizumab combination therapies.; *** This output can be found in table 39 of the primary*

CSR of IMpower110, using the clinical cut-off date of 10 September, 2018. The study uses the results presented on the median number of months on treatment with pemetrexed to inform the median number of months of cisplatin + pemetrexed treatment.; §This output can be found in table 9 of the final CSR of OAK, using the clinical cut-off date of 20 June, 2019.

B.3.3.10 Adverse events

B.3.3.10.1 Safety

Based on the number of occurrences per adverse event (AE) for a given period and across treatment options, the study calculates a probability of experiencing an AE. The calculation is performed using this formula:

$$P(adverse\ event_x) = 1 - e^{-occurence_x / follow-up}$$

where x is the AE, $occurence$ is the number of times it occurred, and $follow-up$ is follow-up in months. The model does not consider grade 1-2 AEs as these are events that are defined by mild to moderate symptoms which may not require any medical attention. It attempts to only considers Grade 3–5 treatment emergent AEs as these events that are treatment related and produce severe to life threatening symptoms that may require invasive and/or immediate emergency intervention. However, this is not entirely possible due to the different definitions used by the different sources when publishing evidence on adverse events.

B.3.3.10.2 Adjuvant treatment

In order to determine which AEs should be included in the model, the AE event rates should be Grade >3 treatment-related AEs with an incidence of >2%. Previous appraisals within this therapy area have utilised the criteria of all Grade >3 treatment related AEs with an incidence of > 2% – > 5% in either treatment arm to include in the economic model (TA531 (136), TA428 (137), TA520 (166), TA584 (167)). The treatment-related AEs are presented in Table 29.

Using this cut-off criteria, no AEs from the IMpower010 trial were included in the economic model for the DFS health state, as the proportion of patients experiencing treatment-related AEs/SAEs of Grade 3 and above were all below 2% (in the atezolizumab arm, as BSC arm was active monitoring only).

B.3.3.10.3 Treatment after recurrence in the non-metastatic setting

Using the cut-off criteria mentioned in Section 3.3.10.2, no AEs from the IMpower010 trial were included in the economic model for the non-metastatic health state, as the proportion of patients experiencing treatment-related AEs/SAEs of Grade 3 and above were all below 2% (in the atezolizumab arm, as BSC arm was active monitoring only).

B.3.3.10.4 Treatment after recurrence in the metastatic setting

To inform the AEs of treatments after recurrence in the metastatic setting, the model uses the same sources that it uses to inform the treatment discontinuation of the different treatment options. While the study would have used the most recent sources for each clinical study that it uses to inform efficacy, only earlier publications contain adverse events incidence rates. Table 29 presents all Grade >3 treatment-related AEs with an incidence of >2% in the first-line and second line metastatic setting.

Table 29: Occurrence of Grade 3–5, incidence of >2% treatment emergent adverse events – treatment after metastatic recurrence

	Metastatic recurrence (first-line)			
	Pembrolizumab	**Atezolizumab**	**Pembrolizumab + Carboplatin + Pemetrexed**	**Carboplatin + Pemetrexed**
Median Follow-Up	11.2 months	13.4 months	10.5 months	13.4 months
Sample Size	154	286	294	263
Anemia	3	5	51	48
Asthenia	N.R.	2	15	5
Decreased appetite	0	2	3	0
Decreased neutrophil count	0	0	N.R.	10
Decreased platelet count	0	0	N.R.	11
Diarrhea	6	N.R.	17	2
Dyspnea	N.R.	N.R.	12	0
Fatigue	2	2	18	6
Febrile neutropenia	N.R.	0	N.R.	9
Hyperglycemia	N.R.	N.R.	N.R.	4
Hypokalemia	N.R.	6	11	3
Hyponatremia	N.R.	6	N.R.	6
Leukopenia	N.R.	N.R.	N.R.	4
Nausea	0	1	9	5
Nephritis	1	N.R.	6	N.R.
Neutropenia	0	2	48	46

Pneumonia	N.R.	7	0	10
Pneumonitis	4	N.R.	9	0
Rash	N.R.	N.R.	6	2
Severe skin reactions	6	N.R.	6	N.R.
Thrombocytopenia	0	1	24	19
Urinary tract infection	N.R.	N.R.	5	3
Vomiting	1	N.R.	10	2
Reference	(143)	(168)	(152)	(168)
	Metastatic Recurrence (Second-Line)			
	Nintedanib + Docetaxel	**Gemcitabine + Carboplatin**	**Docetaxel**	
Median Follow-Up	31.7 months	31.7 months	26.3 months	
Sample Size	652	652	578	
Asthenia	15	15	2	
Decreased neutrophils	209	209	5	
Decreased white blood cell count	107	107	N.R.	
Diarrhoea	43	43	6	
Dysnpnoea	32	32	N.R.	
Fatigue	37	37	N.R.	
Febrile neutropenia	46	46	36	
Hypokalaemia	10	10	N.R.	
Hyponatraemia	14	14	N.R.	
Increased alanine aminotransferase	51	51	N.R.	
Increased aspartate aminotransferase	22	22	N.R.	
Increased gamma glutamyltransferase	10	10	N.R.	
Leucopenia	19	19	N.R.	
Neutropenia	79	79	3	
Pneumonia	20	20	10	
Reference	(163)	(163)	Data on File (Final CSR of OAK)**	

**The PACIFIC study administered chemoradiotherapy before randomization. As such, the adverse events presented in the Antonia et al. (2017) publication may not capture all the grade 3-4 treatment related adverse events associated with chemoradiotherapy.; ** This output can be found in table 39 of the Final CSR of OAK, using the clinical cut-off date of 20 June, 2019.*

B.3.4 Measurement and valuation of health effects

- **The IMpower010 trial did not collect patient-reported outcome data**
- **The model sourced health state utility values from published literature**
- **Disutilities associated with AEs were not included to avoid double-counting**
- **The HRQoL SLR identified 4 full publications which had utility values which were deemed appropriate to be used for the DFS health state in the model. Grutters et al. (2010) (91, 96, 101, 103) was used in the base case as it gave the most clinically plausible utility values**
- **For the remaining health states, the following sources were used:**
  - **Non-metastatic recurrence, treatment – Chouaid et al. 2013**
  - **First-line metastatic recurrence, treatment – Chouaid et al. 2013 (119)**
  - **Second-line metastatic recurrence, treatment – Chouaid et al. 2013 (119)**

B.3.4.1 Health-related quality-of-life data from clinical trials

The IMpower010 trial did not collect patient reported outcomes, therefore the model sources evidence on health state utility values from published literature. The decision on the most appropriate source of evidence is challenging due to differences in the sample of patients and methodological approach used and there is considerably different estimations of utility values across studies.

B.3.4.2 Health-related quality-of-life studies

A total of 39 unique cost utility analyses were identified by the current review (published economic evaluations, n=31 (78-81, 84-87, 89, 91, 92, 95-98, 101, 103, 105, 106, 108-118); NG122 evidence reviews, n=1 (169, 170); HTA submissions, n=7 (120-125, 171). Utility values were obtained from a range of sources, as detailed in Appendix J. The most commonly cited published source of utility values across the included studies was Chouaid et al (2013) (119); however, this study reported utilities for health states associated with advanced stages of NSCLC. This indicated a lack of

suitable utility values, specifically for patients with early-stage NSCLC for use in economic evaluations.

B.3.4.2.1 Disease-free survival

Four studies were identified for consideration to inform disease-free health state utility Sharples, et al., 2012, Grutters et al. (2010), Khan, et al., 2016 and Naik, et al., 2017. Grutters et al. (2010) was selected as the base case to estimate the utility values for patients in the DFS health state as it appears to be the only source that presents evidence separately for patients with early- and -stage NSCLC. Specifically, it uses estimates presented in the publication for patients whose initial treatment modality was surgery plus adjuvant chemotherapy. Thus, it assumes these patients realise a health state utility value (HSUV) of 0.81 as can be seen in Table 30. Table 30 also breaks down the health-related quality of life for some of the sub-groups presented in Grutters et al. (2010) study.

Table 30: Health state utility values – disease-free survival (172)

Study	Population/Instrument/ Tariffs	Results	
(172)	Dutch Patients / EQ-5D-3L/ UK	Initial tumour Stage: I	0.77
		Initial tumour Stage: II	0.74
		Initial tumour Stage: III	0.70
		Initial tumour Stage I-IV without recurrence	0.76
		Initial tumour Stage I-IV with recurrence	0.61
		Initial treatment modality: surgery + chemotherapy	0.81

Grutters et al. (2010) present health-state utility values for additional sub-groups that are not presented in this table.

B.3.4.2.2 Non-metastatic and metastatic recurrence

The HRQoL SLR revealed a lack of studies on the health state utility value of non-metastatic recurrence, thus the model includes utility values from Chouaid et al. 2013(173), as a regression analysis allowed the model to isolate the effect that

disease severity of this health state has on utility for patients who were treated. The study was prospective in nature and considered a sample of 319 patients with locally advanced and metastatic NSCLC across 25 centres. Table 31 provides the multivariate regression output on the drivers of health-related utility from the study. As a result, the most representative utility value for the non-metastatic recurrent health state is 0.70, progression free and progressed fist-line metastatic 0.77 and 0.73, progression free and progressed second-line metastatic 0.74 and 0.66.

Table 31: Multivariate regression - utility values

Variable	Estimate	Standard error	p-value
Intercept	0.77	0.03	<0.01
Stage IV	-0.07	0.04	0.029
1L progression free	-0.04	NA	NA
2L progression free	0.03	0.04	0.47
2L progressive disease	-0.11	0.08	0.18

B.3.4.3 Health state utilities used in the economic analysis

Once the appropriate studies had been identified the appropriate utility values were allocated for each health state. In the DFS health state, HSUV for patients were differentiated between atezolizumab on-treatment and off-treatment, informed by Grutters et al. (2010). To inform the HSUV of patients in the non-metastatic and metastatic setting, the values from the regression analysis by Chouaid et al. 2013 were used. The non-metastatic patients are assumed to have a HSUV of 0.77. Patients who are in the 1st line or 2nd line metastatic setting are assumed to have a HSUV of 0.70 (Intercept + Stage IV = metastatic HSUV).

Table 32: Utility values for each health state

Health state		Utility value	Reference
Disease-free survival	Atezolizumab, on-treatment	0.77	Grutters et al. (2010)
	Atezolizumab, off-treatment	0.81	Grutters et al. (2010)
Disease-free survival (BSC)		0.81	Grutters et al. (2010)
Locoregional (non-metastatic)		0.77	Chouaid et al. 2013

1st line metastatic (Stage IV)	0.70	Chouaid et al. 2013
2nd line metastatic (Stage IV)	0.70	Chouaid et al. 2013

Disutilities associated with AEs were not included to avoid double counting, as impact on utilities from AEs may have already been accounted for in the identified utility sources. Not including disutilities in the model is expected to only have a minor impact as adverse events were only included for progressed states.

B.3.4.4 Adjusting utility values

The sourced utility values in Section B.3.4.2.1 and B.3.4.2.2 were based on a static period. As these utility values are used over a long time horizon within the model, it was appropriate to adjust the values so that they did not exceed general population values, given that HRQoL and utility were expected to decline due to the NSCLC population age increase and comorbidities (174).

$$HSUV\ x\ (\frac{(General\ Population\ Utility\ Value(age-adjusted))}{(General\ Population\ Utility\ Value\ (Age-average\ age\ cohort))}$$

This approach multiplies the HSUV by the general population utility value (equal to age of cohort in cycle X), and then divides this value by the general population utility value equal to the age of the cohort at the beginning (i.e. average age of the cohort when entering the model). This approach has been used in other submissions and was deemed appropriate such as TA1014 (174). As result, the model uses an approach that allows the utility values to be converted to time-variant values by multiplying them by age/sex-adjusted general population utility values.

B.3.5 Cost and healthcare resource use identification, measurement and valuation

- **An SLR was conducted to identify cost and resource use data for early NSCLC**

- **The studies identified in the SLR showed that costs increase as the disease progresses and in the early stages of disease, surgery was the predominant cost driver**
- **Estimation of subsequent treatment use was obtained from a survey of 6 UK clinical oncologists during the 4th November 2024 advisory board**

An SLR was conducted in August 2024 to identify recent studies presenting cost and resource use data associated with early-stage resectable NSCLC receiving treatment in the adjuvant or neoadjuvant settings, to inform the economic model for atezolizumab in adults with fully resected NSCLC after platinum-based therapy.

Although few studies reported costs associated with adjuvant therapy, this appears to be an important driver of costs across all early stages of disease. One study reported few differences in regimen or health care resource use by disease stage associated with adjuvant treatment of patients with Stage IB to IIIA NSCLC treated in community oncology practices in the US; the total monthly median cost per patient during adjuvant treatment was US$17,389.75 (IQR: US$8,815.61 to US$23,360.85) whereas the monthly cost from diagnosis until the end of the initial systemic therapy regimen after recurrence or the end of medical record was US$1,185.08 (IQR: US$250.60 to US$2,535.99) (175). Unsurprisingly, there are international differences in the implementation of adjuvant therapy, which is reflected in the cost data; in one multi-national study assessing the economic burden of resected Stage IB–IIIA NSCLC, the largest monthly direct costs per patient in the UK were for the adjuvant treatment period (€2,490 based on 98 patients) whereas in France and Germany, monthly direct costs per patient were highest during the distant metastasis/terminal illness phase followed by the adjuvant phase (176). As treatment burden is found to vary markedly across patients and treatment types, future work should identify opportunities to further understand and ameliorate this burden (177). Understanding international and regional variations in costs and resource utilisation will also be important with respect to delivering optimal treatments in cost-effective strategies (178).

Full details on the cost SLR can be found in Appendix K.

B.3.5.1 Intervention and comparator costs and resource use

B.3.5.1.1 Drug acquisition costs

Drug acquisition costs for the treatment regimens included in the economic model are summarised in Table 33. Prices for generic medicines were taken from the 2024 electronic market information tool (eMIT), which reports the average price paid by the NHS for a generic medicine for the last period. For medicines only available to the NHS as proprietary medicines, prices were taken as the list price stated in the 2024 British National Formulary (BNF). Health care resource use costs were taken from NHS Reference Costs 2022-2023 and the Personal Social Services Research Unit 2023. Note that for the atezolizumab treatment cost only the subcutaneous (subcut) injection cost is presented as the subcut formulation is used in the base case.

Atezolizumab has a patient access scheme (PAS) which offers a discount of [redacted]. All other treatments are assumed to be list price. Although it should be noted that pembrolizumab, durvalumab and nivolumab have confidential PAS discounts within the UK.

The average weight (kg) and BSA (m^2 using the Dubois formula) from the IMpower010 study (74.03 kg and 1.84 m^2) were used to estimate the average cost per dose per patient for the treatments with dosing according to weight or BSA.

Table 33: Drug acquisition unit costs

Drug	Dose per vial/pack (large vial, mg)	Cost per vial/pack (£)	Source
Atezolizumab	1875	£3,807.69 (list price) [redacted] (PAS price)	BNF
Cisplatin	50	£19.69	eMIT
	100	£37.34	
Vinorelbine	10	£76.45	eMIT
	50	£181.95	
Gemcitabine	1200	£18.17	eMIT
	2200	£45.96	
Pembrolizumab	100	£2,630	BNF
Pemetrexed	100	£18.34	eMIT

	500	£28.76	
Carboplatin	50	£6.71	eMIT
	600	£38.93	
Docetaxel	20	£4.49	eMIT
	160	£19.70	
Nintedanib	60	£2,151.00	BNF
Nivolumab	40	£439.00	BNF
	240	£2,633.00	
Durvalumab	120	£592.00	BNF
	500	£2,466.00	

B.3.5.1.2 Administration costs

The administration costs for all therapies across all health states, apart from atezolizumab and nintedanib, are sourced from the NHS reference costs 22-23 and are assumed to be for delivering simple parenteral chemotherapy at first attendance (NHSE reference costs 2022-2023, Day case/ Reg night). To take a conservative approach and simplify the model, we have applied the higher “at first attendance” administration costs to all treatment cycles.

In the model it is assumed that atezolizumab is administered as a subcutaneous injection (subcut). This assumption is expected to be in-line with real world practice should atezolizumab receive a positive recommendation in this indication. In terms of administration cost for the injection, it was assumed that a qualified nurse (band 5) can administer the injection in 7 minutes. According to the PSSRU 2023 cost report, qualified Band 5 nurses earn £53 per hour, therefore, administering subcut for 7 minutes costs £6.18 per administration.

Nintedanib is an oral therapy and in line with TA1014, it was assumed that it would take a pharmacist (Band 6) 12 minutes to administer the drug, which costs £10 per administration (179).

Table 34: Drug administration costs

Drug	Type of administration		NHS reference code	Cost per administration	Source
Atezolizumab	Subcutaneous formulation		-	£6.18	Qualified nurse Band 5, 1 hour salary (£53), subcut administation (7 minutes), PSSRU 2023
All therapies (apart from nintedanib*)	Deliver simple parenteral chemotherapy at first attendance	Daycase and Reg day/night	SB12Z	£313.91	NHSE reference costs 2022-2023, Day case/ reg night
Nintedanib	Oral		-	£10.00	PSSRU 2023, 12 minutes pharmacist time every 4 weeks, hospital pharmacist (band 6)

B.3.5.1.3 PD-L1 testing

The model assumes that patients who receive either atezolizumab or BSC have an associated cost of a PD-L1 test. Table 35 shows the cost of a PD-L1 test.

Table 35: PD-L1 testing

PD-L1 test cost	£42.61

B.3.5.2 Health-state unit costs and resource use

B.3.5.2.1 Disease-free survival

Patients in the atezolizumab arm of the model started on treatment in the DFS health state. Treatment duration was limited to 16 cycles (three weeks per cycle) as per trial protocol. Patients could discontinue treatment before this point due to disease progression or death. Table 36 shows the cost of atezolizumab each month (list and

PAS price) over one year. There are no treatment acquisition costs associated for BSC, only resource use costs, which will be discussed in the *Follow-up costs* sections.

Table 36: Treatment acquisition costs per cycle – DFS health state – atezolizumab

Cycle	Cost per month, PAS price (£) (atezolizumab)	Cost per month, list price (£) (atezolizumab)
1	1,053.29	3,813.87
2	1,012.78	3,667.18
3	982.40	3,557.17
4	931.76	3,373.81
5	911.51	3,300.46
6	891.25	3,227.12
7	891.25	3,227.12
8	860.87	3,117.11
9	850.74	3,080.43
10	850.74	3,080.43
11	820.35	2,970.42
12	810.23	2,933.75
13	800.10	2,897.07
14	789.97	2,860.40
15	789.97	2,860.40
16	779.84	2,823.73
17	-	-
Total treatment cost per year	[redacted]	50,790.48

Follow-up costs

Patients in all arms of the model received the same follow-up healthcare. The current standard of care after surgery plus adjuvant chemotherapy for NSCLC consists of active monitoring. The resource use associated with active monitoring was informed by UK clinical oncologists. Based on feedback, it was assumed that follow-up care is restricted to 5 years as most patients are considered to be cured at 5 years and not follow-up anymore. Note that the same resource use is assumed for treatment and no treatment.

Table 37: Other healthcare resource use while disease-free

Healthcare resource	Use (Yearly)	Resource use reference	Unit cost (£)	Unit cost reference
Chest radiography	1.4 scans	Clinical expert opinion (UK)	40.81	NHS reference costs 2022-2023, DADS, Diagnostic Imaging Service, DAPF
Outpatient visit	1.4 visits	Clinical expert opinion (UK)	217.00	Band 8a, Cost per hour. Personal Social Service Research Unit in UK, 2023, p. 36
Community nurse	1.18 visits	Clinical expert opinion (UK)	82.00	Band 8a, p. 61, Cost per hour. Personal Social Service Research Unit in UK, 2023
Clinical nurse specialist	1.7 visits	Clinical expert opinion (UK)	94.00	Band 8b, p.61, Cost per hour. Personal Social Service Research Unit in UK, 2023
GP surgery	2.8 visits	Clinical expert opinion (UK)	50.50	average cost per surgery consultation lasting 10 minutes. Personal Social Service Research Unit in UK, 2023.
Total monthly cost (per cycle)	£63.24			

B.3.5.2.2 Non-metastatic recurrence

Treatment cost

The model allowed the choice of different treatment options and for the choice of no treatment. The treatment options and information on the dose size and treatment schedule of chemotherapy and radiotherapy were used to calculate the treatment cost of each type of treatment. This is presented in Table 38 and Table 39 presents the cost of chemoradiation each month (3 months in total).

Table 38: Treatment options - non-metastatic recurrence

	Cisplatin	Vinorelbine	Durvalumab	Pembrolizumab	Radiotherapy
Dose size	80mg/m2	60mg/m2	10mg/m2	200/fixed	66 grays
# Of cycles	4	4	24	7	5
Doses per cycle	1	1	1	1	2 grays
Weeks between cycles	3	3	2	3	1
Chemotherapy inclusion	Yes	Yes	Yes	No	Yes

Table 39: Treatment acquisition costs – non-metastatic health state

Month	Cost per month Drug 1 (£) (Cisplatin + Vinorelbine + Durvalumab + Conformal 3-dimensional radiotherapy)	Cost per month Drug 2 (£) (Cisplatin + Vinorelbine + Conformal 3-dimensional radiotherapy)	Cost per month Drug 3 (£) (Conformal 3-dimensional radiotherapy)	Cost per month Drug 4 (£) (Pembrolizumab)
1	8172.79	7677.00	6133.80	11147.82
2	5254.36	4758.57	3986.97	5573.91
3	1986.16	771.60	0.00	11147.82
4	809.71	0.00	0.00	5573.91
5	809.71	0.00	0.00	5573.91
6	809.71	0.00	0.00	0.00
7	809.71	0.00	0.00	0.00
8	809.71	0.00	0.00	0.00

9	1214.56	0.00	0.00	0.00
10	809.71	0.00	0.00	0.00
11	809.71	0.00	0.00	0.00
Total treatment cost per year	22,295.82	13,207.16	10,120.77	39,017.37
Market Shares				
Adjuvant Immunotherapy (Early-Relapse)	[redacted]	[redacted]	[redacted]	[redacted]
Adjuvant Immunotherapy (Late-Relapse)	[redacted]	[redacted]	[redacted]	[redacted]
Best Supportive Care	[redacted]	[redacted]	[redacted]	[redacted]

Follow-up costs

Patients who have non-metastatic recurrence receive follow-up healthcare regardless of treatment status. Table 40 summarises follow-up healthcare resource use. The model assumes that patients use these resources until disease progression. The model sourced information on the use of the resources from UK clinical oncologists. Based on feedback, it was assumed that follow-up care is restricted to 5 years. Note that the same resource use is assumed for treatment and no treatment.

Table 40: Other healthcare resource use after non-metastatic recurrence

Healthcare resource	Treatment – use (yearly)	Resource use reference	Unit costs (£)	Unit cost reference
Ct chest scan	4.00 scans	UK clinical expert opinion	128.31	NHS reference costs 22-23, DADS RD24Z, Diagnostic Imaging Service
Chest radiography	1.20 scans	UK clinical expert opinion	40.81	NHS reference costs 2022-2023, DADS, Diagnostic Imaging Service, DAPF
Outpatient visit	4.76 visits*	UK clinical expert opinion	217.00	Band 8a, Cost per hour. Personal Social Service Research Unit in UK, 2023, p. 36
Community nurse	1.96 visits*	UK clinical expert opinion	82.00	Band 8a, p. 61, Cost per hour. Personal Social Service Research Unit in UK, 2023

Clinical nurse specialist	8.50 visits*	UK clinical expert opinion	94.00	Band 8b, p.61, Cost per hour. Personal Social Service Research Unit in UK, 2023
GP surgery	4.3 visits	UK clinical expert opinion	50.50	average cost per surgery consultation lasting 10 minutes. Personal Social Service Research Unit in UK, 2023.
Total monthly cost (per cycle)	£188.23	-	-	-

**UK clinical oncologists assumed that a visit would be ~1 hour, therefore we assumed one hour per visit.*

B.3.5.2.3 First-line/second-line metastatic recurrence

Treatment cost

As described in Section 3.3.7, the model allowed the choice of four separate options for first- and second-line metastatic treatment. Table 41 and Table 42 show the estimated monthly cost for first-line and second-line metastatic treatment and the associated market share.

Table 41: Estimated monthly cost first-line metastatic treatment and market share

Inputs	Option 1	Option 2	Option 3	Option 4
Drug 1	Pembrolizumab	Atezolizumab	Pembrolizumab	Pemetrexed
Dose size	200mg/ fixed	1875 mg/ fixed	200mg/ fixed	500mg/m^2
Doses per cycle	1	1	1	1
Weeks btw. cycles	3	3	3	3
Drug 2	n/a	n/a	Pemetrexed	Carboplatin
Dose size	n/a	n/a	500mg/m^2	6
Doses per cycle	n/a	n/a	1	1
Weeks btw. cycles	n/a	n/a	3	3
Drug 3	n/a	n/a	Carboplatin	n/a
Dose size	n/a	n/a	6	n/a
Doses per cycle	n/a	n/a	1	n/a
Weeks btw. cycles	n/a	n/a	3	n/a
Estimated monthly cost	£7,623.87	[redacted]	£7,785.37	£161.50
Market Shares				

Adjuvant Immunotherapy (Early-Relapse)	[redacted]	[redacted]	[redacted]	[redacted]
Adjuvant Immunotherapy (Late-Relapse)	[redacted]	[redacted]	[redacted]	[redacted]
Best Supportive Care	[redacted]	[redacted]	[redacted]	[redacted]

Table 42: Estimated monthly cost second-line metastatic treatment and market share

Inputs	Option 1	Option 2	Option 3
Drug 1	Docetaxel	Gemcitabine	Docetaxel
Dose size	75 mg/m^2	1250 mg/m^2	75 mg/m^2
Doses per cycle	1.00	1.00	1.00
Weeks btw. cycles	3.00	3.00	3.00
Drug 2	Nintendanib	Carboplatin	n/a
Dose size	14.00 fixed	6 AUC	n/a
Doses per cycle	1.00	1	n/a
Weeks btw. cycles	1.00	3	n/a
Estimated monthly cost	£2,207.05	£156.13	£24.68
Market Shares			
Adjuvant Immunotherapy (Early-Relapse)	[redacted]	[redacted]	[redacted]
Adjuvant Immunotherapy (Late-Relapse)	[redacted]	[redacted]	[redacted]
Best Supportive Care	[redacted]	[redacted]	[redacted]

Follow-up costs

Patients who had metastatic recurrence received follow-up healthcare regardless of treatment status. The model assumes that patients use these resources until disease progression or death (in the second-line metastatic setting). Table 43 summarises follow-up healthcare resource use. Based on feedback, it was assumed that follow-up care is restricted to 5 years. Note that the same resource use is assumed for treatment and no treatment.

Table 43: Healthcare resource use after metastatic recurrence

Healthcare resource	1L treatment - visits/hours per year	2L treatment – visits/hours per year	Resource use reference	Unit costs (£)	Unit cost reference
Ct chest scan	4 scans	0 scans	UK clinical expert opinion	128.31	NHS reference costs 22-23, DADS RD24Z, Diagnostic Imaging Service
Chest radiography	6.79 scans	6.50 scans	UK clinical expert opinion	40.81	NHS reference costs 2022-2023, DADS, Diagnostic Imaging Service, DAPF
Electrocardiogram	1.04 scans	0.88 scans	UK clinical expert opinion	119.85	NHS Reference costs 2022-2023, DADS, Diagnostic Imaging Service, EY50Z
Outpatient visit	9.61 visits*	7.91 visits*	UK clinical expert opinion	217.00	Band 8a, Cost per hour. Personal Social Service Research Unit in UK, 2023, p. 36
Community nurse	8.70 visits*	8.70 visits*	UK clinical expert opinion	82.00	Band 8a, p. 61, Cost per hour. Personal Social Service Research Unit in UK, 2023
Clinical nurse specialist	12 visits*	12 visit*	UK clinical expert opinion	94.00	Band 8b, p.61, Cost per hour. Personal Social Service Research Unit in UK, 2023
GP surgery	12 visits	0 visits	UK clinical expert opinion	50.50	average cost per surgery consultation lasting 10 minutes. Personal Social Service Research Unit in UK, 2023.

GP home visit	0 visits	26.09 visits	UK clinical expert opinion	123.43	PSSRU 2016, p.145: Cost per home visit including 11.4 minutes for consultations and 12 minutes for travel (from TA531, inflated using the Bank of England inflation calculator)
Therapist visit	0 visits	26.09 visits	UK clinical expert opinion	52.00	PSSRU 2023, Community occupational therapist (local authority) with qualifications, page 77
Total monthly cost (per cycle)	£411.21	£327.38	-	-	-

**UK clinical oncologists assumed that a visit would be ~1 hour, therefore we assumed one hour per visit*

B.3.5.3 Adverse reaction unit costs and resource use

AEs for adjuvant atezolizumab and subsequent therapies in progressive health states have been outlined in Section B.3.3.10. Adverse event management costs and resource use are presented below in Sections B.3.5.3.1 to B.3.5.3.2.

B.3.5.3.1 Adjuvant Atezolizumab and non-metastatic recurrence

Since no adverse events in the adjuvant and non-metastatic setting met the AE definition, Grade >3 treatment-related AEs with an incidence of >2%, no adverse events costs were attributed to the adjuvant and non-metastatic setting.

B.3.5.3.2 First-line metastatic metastatic recurrence adverse events costs

Table 44 shows the costs associated with Grade 3–5 treatment emergent adverse events, >2% incidence in the 1st line metastatic state. All costs were either sourced from the latest NHSE reference costs (22–23) or the PSSRU 2023 unit cost report (179). Any costs sourced from the NHSE include the associated code. Where costs couldn't be sourced a GP visit was assumed (£217), which was sourced from the PSSRU 2023 unit cost report (179).

Table 44: Costs of Grade 3–5 treatment, >2% incidence emergent adverse events – treatment in the first-line metastatic setting

	Metastatic recurrence (first-line)					
	Pembrolizumab	**Atezolizumab**	**Pembrolizumab + Carboplatin + Pemetrexed**	**Carboplatin + Pemetrexed**	**Unit Cost (£)**	**Reference**
Median Follow-Up	11.2 months	13.4 months	10.5 months	13.4 months	-	
Sample Size	154	286	294	263	-	
Anemia	3	5	51	48	860.83	SA50J
Asthenia	N.R.	2	15	5	1,084.67	WH17C
Decreased appetite	0	2	3	0	126.00	654
Decreased neutrophil count	0	0	N.R.	10	217.00	GP visit, PSSRU 2023
Decreased platelet count	0	0	N.R.	11	217.00	GP visit, PSSRU 2023
Diarrhea	6	N.R.	17	2	1,032.62	TA705, 2018/19 inflated to 2024 using the BoE inflation calculator
Dyspnea	N.R.	N.R.	12	0	533.77	TA812, inflated from 2022 to 2024 using the BoE inflation calculator
Fatigue	2	2	18	6	302.12	JC43C
Febrile neutropenia	N.R.	0	N.R.	9	217.00	GP visit, PSSRU 2023
Hyperglycemia	N.R.	N.R.	N.R.	4	466.24	WH13C
Hypokalemia	N.R.	6	11	3	366.68	KC05N
Hyponatremia	N.R.	6	N.R.	6	366.68	KC05N
Leukopenia	N.R.	N.R.	N.R.	4	302.12	JC43C
Nausea	0	1	9	5	217.00	GP visit, PSSRU 2023
Nephritis	1	N.R.	6	N.R.	217.00	GP visit, PSSRU 2023
Neutropenia	0	2	48	46	217.00	GP visit, PSSRU 2023
Pneumonia	N.R.	7	0	10	1,130.67	DZ19N
Pneumonitis	4	N.R.	9	0	1,130.67	DZ19N

Rash	N.R.	N.R.	6	2	302.12	JC43C
Severe skin reactions	6	N.R.	6	N.R.	217.00	GP visit, PSSRU 2023
Thrombocytopenia	0	1	24	19	470.10	SA12K
Urinary tract infection	N.R.	N.R.	5	3	3,072.28	SA12K
Vomiting	1	N.R.	10	2	813.47	TA683, inflated from 2021 to 2024 using the BoE inflation calculator
Reference	(143)	(168)	(152)	(168)	-	

Table 45 shows the monthly associated adverse costs for each treatment in the first-line metastatic setting.

Table 45: Monthly associated adverse events cost for each treatment in the first-line metastatic state

	Monthly associated cost for each treatment option
Pembrolizumab	£38.16
Atezolizumab	£23.17
Pembrolizumab + Pemetrexed + Carboplatin	£6.96
Pemetrexed + Carboplatin	£45.14

B.3.5.3.3 Second-line metastatic metastatic recurrence adverse events costs

Table 46 shows the costs associated with Grade 3–5 treatment emergent adverse events, >2% incidence in the 2nd line metastatic state. All costs were either sourced from the latest NHSE reference costs (22–23) or the PSSRU 2023 unit cost report. Any costs sourced from the NHSE include the associated code. Where costs couldn't be sourced a GP visit was assumed (£217), which was sourced from the PSSRU 2023 unit cost report (179).

Table 46: Costs of Grade 3–5 treatment, >2% incidence emergent adverse events – treatment in the second-line metastatic setting

	Metastatic Recurrence (Second-Line)				
	Nintedanib + Docetaxel	**Gemcitabine + Carboplatin**	**Docetaxel**	**Unit Cost (£)**	**Reference**
Median Follow-Up	31.7 months	31.7 months	26.3 months	-	
Sample Size	652	652	578	-	
Asthenia	15	15	2	1,084.67	WH17C
Decreased neutrophils	209	209	5	217.00	GP visit, PSSRU 2023
Decreased white blood cell count	107	107	N.R.	217.00	GP visit, PSSRU 2023
Diarrhoea	43	43	6	1,032.62	TA705, 2018/19 inflated to 2024 using the BoE inflation calculator
Dysnpnoea	32	32	N.R.	533.77	TA812, inflated from 2022 to 2024 using the BoE inflation calculator
Fatigue	37	37	N.R.	302.12	JC43C
Febrile neutropenia	46	46	36	217.00	GP visit, PSSRU 2023
Hypokalaemia	10	10	N.R.	366.68	KC05N
Hyponatraemia	14	14	N.R.	366.68	KC05N
Increased alanine aminotransferase	51	51	N.R.	217.00	GP visit, PSSRU 2023
Increased aspartate aminotransferase	22	22	N.R.	217.00	GP visit, PSSRU 2023
Increased gamma glutamyltransferase	10	10	N.R.	217.00	GP visit, PSSRU 2023
Leucopenia	19	19	N.R.	302.12	JC43C

Neutropenia	79	79	3	9,434.99	TA683, inflated from 2017 to 2024 using the BoE inflation calculator
Pneumonia	20	20	10	1,130.67	DZ19N
Reference	(163)	(163)	Data on File (Final CSR of OAK)**	-	

Table 47 presents the monthly associated adverse events cost for each treatment option.

Table 47: Monthly associated adverse events cost for each treatment in the second-line metastatic state

	Monthly associated cost for each treatment option
Nintendanib + Docetaxel	£46.46
Gemcitabine + Carboplatin	£46.46
Docetaxel	£5.13

B.3.5.4 Miscellaneous unit costs and resource use

An end of life/terminal care cost was included in the model and applied to patients who enter the death state as a one-off cost, in line with NICE appraisal TA705, atezolizumab monotherapy for untreated advanced NSCLC (180).

The model differentiated end-of-life cost based on whether the death was all-cause or disease related. Patients in the DFS health state who died incurred the all-cause death related end-of-life cost, while patients in the post-DFS health states incurred the disease-related death end-of-life cost.

Table 48: End of life cost

Death	AE management cost
All-cause	£0
Disease related (179)	£19,943 per episode

B.3.6 Summary of base-case analysis inputs and assumptions

B.3.6.1 Summary of base-case analysis inputs

Table 49 summarises all key variable applied in the base case of the economic model.

Table 49: Summary of variables applied in the base case setting of the economic model

Variable	Value	Measurement of uncertainty and distribution: CI (distribution)	Reference to section in submission
General model parameters			
Time horizon	40 years	Fixed	Section B.3.2
Discount rate – efficacy	3.5%	Fixed	
Discount – costs	3.5%	Fixed	
Population parameters			
Age	61.20 years	Fixed	Baseline characteristics section
Body weight	74.03 kg	Fixed	
Height	168.82 cm	Fixed	
Body surface area	1.84 m^2	Fixed	
Proportion of males (%)	66.90%	Fixed	
Population in Analysis	PD-L1 high Stage II–IIIA, no ALK- and EGFR-positive mutation	Fixed	
Efficacy inputs			
Disease-free survival			
Parametric distribution – atezolizumab arm	Gompertz	Fixed	Section B.3.3.3
Parametric distribution – BSC arm	Log-normal	Fixed	
First event occurrence by type – trial data to use to inform recurrence type split	Pooled	Fixed	
First event occurrence by type – Atezo arm: proportion of patients with non-metastatic recurrence	37.6% (pooled)	Fixed	

First event occurrence by type – Atezo arm: proportion of patients with first line metastatic recurrence	45.9% (pooled)	Fixed	
First event occurrence by type – BSC arm: proportion of patients with non-metastatic recurrence	37.6% (pooled)	Fixed	
First event occurrence by type – BSC arm: proportion of patients with first line metastatic recurrence	45.9% (pooled)	Fixed	
Treatment effect – Duration of atezo treatment effect	Limited to 60 months	Fixed	
Cured patients – maximum proportion of cured patients	79%	Fixed	Section B.3.3.4
Cure point	5 years	Fixed	
Excess mortality of long-term survivors – standardised mortality ratio	1.25	Fixed	
Non-metastatic recurrence			
Treatment setting - % of patients treated	70%	UK clinical expert opinion	Section B.3.3.7
Treatment setting - % of patients not treated	30%	UK clinical expert opinion	
Treatment setting - treatment regimen: treatment regimen drug 1	Cisplatin	Fixed	
Treatment setting - treatment regimen: treatment regimen drug 2	Vinorelbine	Fixed	
Treatment setting - treatment regimen: treatment regimen drug 3	Durvalumab	Fixed	
Treatment setting - treatment regimen: treatment regimen drug 4	Pembrolizumab	Fixed	
Efficacy by treatment intent - use result from survival analysis or calculation (based on median)	Exponential extrapolation	Fixed	
First-line metastatic recurrence			
Treatment setting - % of patients treated	60%	UK clinical expert opinion	Section B.3.3.7

Treatment setting - % of patients not treated	40%	UK clinical expert opinion	
Treatment setting – Treatment option 1	Pembrolizumab	Fixed	
Treatment setting – Treatment option 2	Atezolizumab	Fixed	
Treatment setting – Treatment option 3	Pembrolizumab + Pemetrexed + Carboplatin	Fixed	
Treatment setting – Treatment option 4	Pemetrexed + Carboplatin	Fixed	
Treatment setting – Re-challenging with immunotherapy allowed after treatment initiation	6 months	Fixed	
Efficacy by treatment intent – Use result from survival analysis or calculation (based on median)	Exponential extrapolation	Fixed	
Second-line metastatic setting			
Treatment setting - % of patients treated	60%	UK clinical expert opinion	Section B.3.3.7
Treatment setting - % of patients not treated	40%	UK clinical expert opinion	
Treatment setting – Treatment option 1	Nintendanib + Docetaxel	Fixed	
Treatment setting – Treatment option 2	Gemcitabine + Carboplatin	Fixed	
Treatment setting – Treatment option 3	Docetaxel	Fixed	
Efficacy by treatment intent – Use result from survival analysis or calculation (based on median)	Exponential extrapolation	Fixed	
Cost inputs			
Drug costs			
Drug costs – Atezolizumab: Composition (mg) subcutaneous injection = 1825 mg – List Price (PAS price)	£3,807.69 [redacted]	Fixed	
Administration costs			
Subcut administration cost	£6.18	Fixed	Section B.3.5.1
Disease-free survival cost and resource use			

Estimated monthly cost, resource use, treatment	£63.24	Fixed	Section B.3.5.2
Estimated monthly cost, resource use, no treatment	£63.24	Fixed	
Non-metastatic recurrence cost and resource use			
Estimated monthly cost, resource use, treatment	£188.23	Fixed	Section B.3.5.2
Estimated monthly cost, resource use, no treatment	£188.23	Fixed	
First-line metastatic recurrence cost and resource use			
Estimated monthly cost, resource use, treatment	£411.21	Fixed	Section B.3.5.2
Estimated monthly cost, resource use, no treatment	£411.21	Fixed	
Estimated monthly cost, adverse events (Pembrolizumab)	£38.16	Fixed	Section B.3.5.3
Estimated monthly cost, adverse events (Atezolizumab)	£23.17	Fixed	
Estimated monthly cost, adverse events (Pembrolizumab + Pemetrexed + Carboplatin)	£6.96	Fixed	
Estimated monthly cost, adverse events (Pemetrexed + Carboplatin)	£45.14	Fixed	
Second-line metastatic recurrence cost and resource use			
Estimated monthly cost, resource use, treatment	£327.38	Fixed	Section B.3.5.2
Estimated monthly cost, resource use, no treatment	£327.38	Fixed	
Estimated monthly cost, adverse events (Nintendanib + Docetaxel)	£46.46	Fixed	Section B.3.5.3
Estimated monthly cost, adverse events (Gemcitabine + Carboplatin)	£46.46	Fixed	
Estimated monthly cost, adverse events (Docetaxel)	£5.13	Fixed	
End of life costs			
Disease-related death	£19,943	Fixed	Section B.3.5.4
Utilities – base case			
Disease-free survival			

On-treatment atezolizumab	0.81	Grutters at al. 2010	Section B.3.4.1
Off-treatment atezolizumab	0.77	Chouaid et al. 2013	
Off-treatment BSC	0.77	Chouaid et al. 2013	
Non-metastatic recurrence			
Intercept	0.77	Chouaid et al. 2013	Section B.3.4.2
First-line metastatic recurrence			
Stage IV	-0.07	Chouaid et al. 2013	Section B.3.4.2
Second-line metastatic recurrence			
Stage IV	-0.07	Chouaid et al. 2013	Section B.3.4.2

B.3.7 Base-case results

Summary of base-case cost effectiveness results

- **Atezolizumab is cost-effective with an ICER of 2,428 per QALY.**
- **Atezolizumab is cost-effective with an ICER of 22,777 per QALY against BSC.**

B.3.7.1 Base-case incremental cost effectiveness analysis results

Base case results of the economic model are presented in Table 50 (list price) and Table 51 (PAS price; [redacted] discount) for the Stage II–IIIA patients with completely resected NSCLC which expressed PD-L1 on 50% or more of tumour cells, who do not have EGFR-positive or ALK-positive NSCLC and has not progressed after platinum based chemotherapy In these comparisons, all comparators (and therapies included in the treatment pathway) are at list price.

Table 50: Base case cost effectiveness results – Stage II–IIIA population, PD-L1 on 50% or more of tumour cells, who do not have EGFR-positive or ALK-positive NSCLC and has not progressed after platinum based chemotherapy – list price

Technologies	Total costs	Total LYG	Total QALYs	Incremental costs	Incremental LYG	Incremental QALYs	ICER incremental (£/QALY)
Atezolizumab	69,795	10.598	8.160	-			
BSC	30,059	8.325	6.416	39,737	2.273	1.745	22,777

Table 51: Base case cost effectiveness results – Stage II–IIIA population, PD-L1 on 50% or more of tumour cells, who do not have EGFR-positive or ALK-positive NSCLC and has not progressed after platinum based chemotherapy – PAS price

Technologies	Total costs	Total LYG	Total QALYs	Incremental costs	Incremental LYG	Incremental QALYs	ICER incremental (£/QALY)
Atezolizumab	[redacted]	[redacted]	[redacted]	[redacted]			
BSC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	2,428

Observing the results with the PAS price for BSC, atezolizumab provided [redacted] QALYs and [redacted] life years at a total overall cost of [redacted] In contrast, BSC provided [redacted] QALYs and [redacted] life years, at a total cost of [redacted]. The resulting base case ICER when comparing atezolizumab to BSC is atezolizumab is £2,428 per QALY gained over BSC.

These results are relevant for the UK standard of care as the current treatment for early NSCLC is adjuvant chemotherapy followed by best supportive care (active monitoring). At PAS price, adjuvant atezolizumab is cost-effective with an ICER of 2,428 per QALY against BSC. At list price, adjuvant atezolizumab is cost-effective with an ICER of 22,777 per QALY against BSC. In both scenarios (PAS and list price), adjuvant atezolizumab provides good value for money to the NHS.

It should be noted that the with-PAS analysis does not account for confidential discounts of therapies used in the treatment pathway, such as pembrolizumab, durvalumab and nivolumab. The clinical outcomes from the model and the disaggregated results of the base-case cost effectiveness analysis are presented in Appendix N.

B.3.8 Sensitivity analyses

Summary of the sensitivity analysis effectiveness results

- **To assess the uncertainty surrounding the variables included in the cost effectiveness model, a PSA was undertaken using 1,000 iterations to ensure results had converged.**
- **At list price, the deterministic base case ICER for atezolizumab vs. BSC is £22,777.**
- **At list price, the PSA ICER for atezolizumab vs. BSC is £24,523.**
- **At PAS price, the deterministic base case ICER for atezolizumab vs. BSC is £2,428 per QALY gained.**
- **At PAS price, the PSA ICER for atezolizumab vs. BSC are £3,005.**
- **For the comparison to BSC, atezolizumab (PAS price) was cost-effective in 100% of simulations of the PSA.**
- **Scenario analyses were conducted to test the sensitivity of the ICER. In all scenarios atezolizumab (PAS price) remains cost-effective against BSC.**
- **Based on the deterministic sensitivity analyses at PAS price, the most influential parameters appear to be the utility values DFS - off- and on-treatment, discount costs and effects, and the model time horizon**

B.3.8.1 Probabilistic sensitivity analysis

To assess the uncertainty surrounding the variables included in the cost effectiveness model, a PSA was undertaken using 1,000 iterations to ensure results had converged. Results of the PSA compared to deterministic results at list price are presented in Table 52. The with-PAS equivalent comparison is presented in Table 53. Deterministic and probabilistic results are similar, therefore not indicating any signs of non-linearity in the model.

Table 52: PSA results compared to base-case (list price)

	Incremental Costs		Incremental QALYs		ICERs	
	Deterministic base case	PSA	Deterministic base case	PSA	Deterministic base case	PSA
Atezolizumab	-	-	-	-	-	-
BSC	39,737	40,519	1.745	1.745	22,777	24,523

Table 53: PSA results compared to base-case (with PAS)

	Incremental Costs		Incremental QALYs		ICERs	
	Deterministic base case	PSA	Deterministic base case	PSA	Deterministic base case	PSA
Atezolizumab	-	-	-	-	-	-
BSC	[redacted]	[redacted]	[redacted]	[redacted]	2,428	3,005

The incremental cost effectiveness planes in Figure 25 and Figure 26 show the individual PSA iterations for the comparisons of atezolizumab to BSC at list and PAS price, respectively. For BSC, atezolizumab was cost-effective in 100% of simulations at PAS price, supporting the view that atezolizumab is a cost-effective option.

Figure 25: Incremental cost effectiveness plane – atezolizumab vs BSC, list price

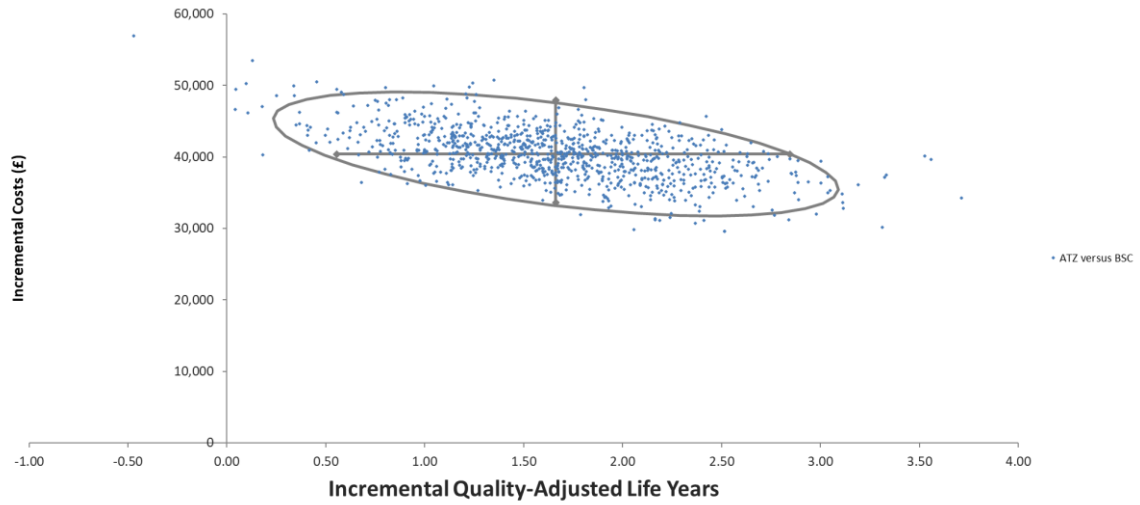


Figure 26: Incremental cost effectiveness plane – atezolizumab vs BSC, PAS price

[redacted]

Cost effectiveness acceptability curves (CEAC) for the comparisons of atezolizumab to BSC at list and PAS price are presented in Figure 27 and

Figure 28. For BSC at PAS price, atezolizumab is deemed the most likely cost-effective treatment option beyond a willingness-to-pay (WTP) of approximately £5,000 per QALY at a £20,000 and £30,000 WTP, the likelihood of atezolizumab being the most cost-effective treatment option rises 98% to 99% at PAS price, respectively.

Figure 27: Cost effectiveness acceptability curve – atezolizumab vs BSC, list price

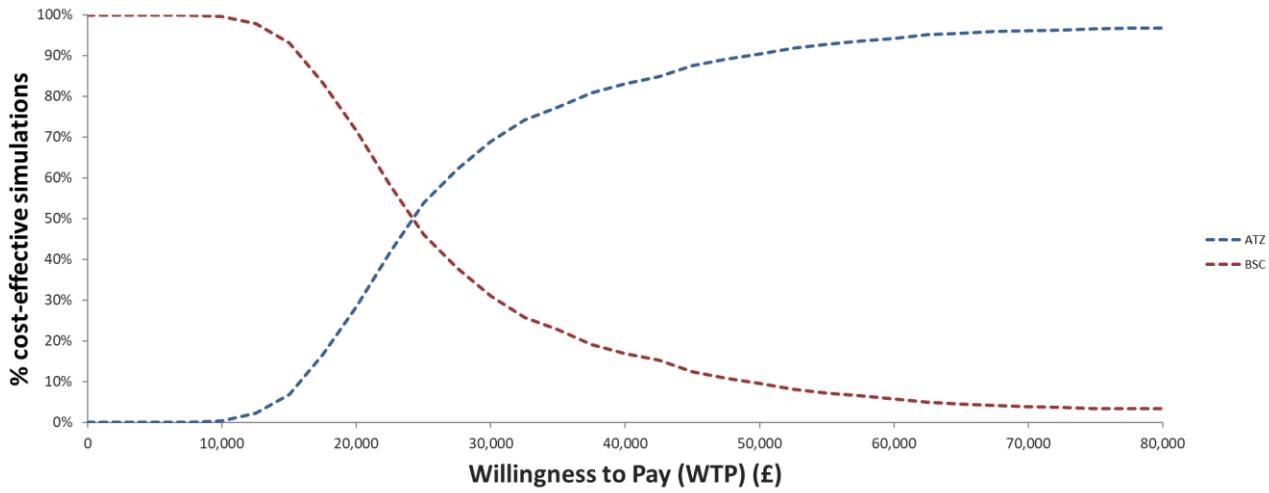


Figure 28: Cost effectiveness acceptability curve – atezolizumab vs BSC, PAS price

[redacted]

B.3.8.2 Deterministic sensitivity analysis

Scenario analyses were conducted to assess uncertainty around parameter inputs and structural assumptions in the model. Deterministic sensitivity analyses with-PAS results are presented Figure 29. Based on the deterministic sensitivity analyses, for the BSC arm, the most influential parameters appear to be the utility values while disease-free – off-treatment (atezolizumab) and utility values while disease-free – on-treatment (BSC) and the % of DFS events being death for atezolizumab and BSC. All results remained significantly below the-cost effectiveness threshold for BSC.

The results of the deterministic sensitivity analyses were as expected due to the number of parameters included within the model and number of progressive states – no individual input would be expected to have a significantly large impact.

Figure 29: Tornado diagram – atezolizumab vs. BSC, PAS price

B.3.8.3 Scenario analysis

Scenario analyses as seen in Table 54 were conducted to assess uncertainty around parameter inputs and structural assumptions in the model. Scenarios demonstrating changes in the following parameters were explored:

Model settings

- Time horizon
- Discount rate outcomes
- Discount rate costs

Clinical inputs

- Alternative plausible DFS extrapolations
- Pooled vs separate treatment recurrence
- Treatment effect duration
- Cure proportion
- Cure point
- Standardised mortality rate

Health state utilities

- Source of utility inputs for disease-free survival

Table 54: Parameter values for univariate sensitivity analysis (atezolizumab vs. BSC) with PAS

Parameter	Base case value	Value	ICER results	% change in ICER base case
Base case			2,428	n/a
Parametric distribution, DFS, ATZ	Gompertz	Exponential	3,103	27.8%
Parametric distribution, DFS, ATZ	Gompertz	Weibull	3,150	29.7%
Parametric distribution, DFS, ATZ	Gompertz	Log-normal	2,626	8.2%
Parametric distribution, DFS, ATZ	Gompertz	Generalized Gamma	2,565	5.7%
Parametric distribution, DFS, ATZ	Gompertz	Log-logistic	2,684	10.6%
Parametric distribution, DFS, ATZ	Gompertz	Gompertz	2,428	0.0%
Parametric distribution, DFS, ATZ	Gompertz	Gamma	3,263	34.4%
Parametric distribution, DFS, BSC	Log-normal	Exponential	3,803	56.7%
Parametric distribution, DFS, BSC	Log-normal	Weibull	3,171	30.6%

Parametric distribution, DFS, BSC	Log-normal	Log-normal	2,428	0.0%
Parametric distribution, DFS, BSC	Log-normal	Generalized Gamma	2,312	-4.7%
Parametric distribution, DFS, BSC	Log-normal	Log-logistic	2,278	-6.2%
Parametric distribution, DFS, BSC	Log-normal	Gompertz	2,503	3.1%
Parametric distribution, DFS, BSC	Log-normal	Gamma	3,495	44.0%
DFS dataset from trial, ATZ and BSC (pooled or separate by arm)	Pooled across borth arms	Separate across both arms	2,219	-8.6%
Treatment effect duration	Stops after 5 years	Maintained over time	1,366	-43.7%
Cure proportion	79%	95% (clinical expert opinion)	1,711	-29.5%
Cure point	5 years	6 years	2,905	19.6%
		7 years	3,318	36.7%
Standardised mortality rate	1.25	1	2,319	-4.5%
		1.5	2,539	4.6%
Model time horizon	40	10	4,642	91.2%
		20	2,679	10.3%
Discount rate outcomes	3.5%	0%	1,597	-34.2%
		5%	2,845	17.2%
Discount rate costs	3.5%	0%	2,226	-8.3%
		5%	2,525	4.0%
Utility values DFS –on-treatment atezolizumab	0.77	0.661	2,556	5.3%
		0.862	2,326	-4.2%
Utility values DFS - off-treatment - treatment atezolizumab	0.81	0.695	5,049	107.9%
		0.908	1,674	-31.1%

Utility values DFS –off - treatment BSC	0.81	0.695	1,721	-29.1%
		0.908	3,771	55.3%
Utility values – non-metastatic	0.77	0.773	2,401	-1.1%
		0.809	2,453	1.0%
Utility values - 1st line metastatic	-0.07	-0.101	2,417	-0.5%
		-0.025	2,442	0.6%
Utility values - 2nd line metastatic	-0.07	-0.101	2,417	-0.5%
		-0.025	2,442	0.6%

Based on the deterministic sensitivity analyses at PAS price, the most influential parameters for atezolizumab and BSC appear to be DFS - off-treatment utility values, discount costs and effects, and the model time horizon. All results remained significantly below the cost effectiveness threshold (£30,000). The results of the deterministic sensitivity analyses were as expected due to the number of parameters included within the model and number of progressive states.

B.3.9 Interpretation and conclusions of economic evidence

Conclusions of economic results evidence

- **The cost effectiveness analysis used the best available evidence and methods to inform the model, as well as extensive scenario and sensitivity analyses**
- **There are uncertainties in the extrapolation of DFS and heterogeneity literature and utility sources for the different health states, however, extensive scenario and sensitivity analyses have been provided, showing that atezolizumab is cost-effective in all scenarios (PAS and list price)**
- **In a potentially curative setting, preventing early lung cancer recurrence or progression to metastatic disease has significant benefits for both patients and society**

B.3.9.1 Relevance of the economic evaluation for decision problem

The populations included in the economic evaluation are consistent with the population in the IMpower010 trial and the UK NSCLC population.

The analysis is applicable to clinical practice in England since:

- The patient population in IMpower010 trial and the economic evaluation are reflective of patients following resection and platinum-based chemotherapy with NSCLC whose tumours have PD-L1 expression on ≥ 50% of tumour cells excluding patients with an EGFR-positive and ALK-positive mutation. Advice from clinical experts suggest that the IMpower010 trial is broadly consistent with UK patients treated in clinical practice. Therefore, the outcomes observed in the trial are expected in UK patients.
- The economic structure is consistent with the model structure TA1014, ID5120 and ID390 in a similar indication.
- The resource utilisation and unit costs are reflective of UK clinical practice and were mainly derived from the NHS reference costs, PSSRU, BNF and eMIT and previous NICE submissions in NSCLC, as well as from clinical expert opinion.
- Extensive scenario and sensitivity analyses were conducted in the economic model, considering alternative approaches to the extrapolation of DFS, alternative parameter inputs and data sources.
- The outputs of the model were validated against available published sources and UK clinical expert opinion to ensure the clinical plausibility of the model and its applicability to the UK.

B.3.9.2 Strengths and weaknesses of the evaluation

The key strengths associated with the cost effectiveness analysis are related to the use of the best available evidence and methods to inform the model, as well as extensive scenario and sensitivity analyses as mentioned in Section B.3.8.

- IMpower010 RCT: IMpower010 is a randomised, multicentre, open-label, Phase III trial, with the comparator being current standard of care in the UK. As

a result, the data used in this cost-effectiveness analysis is a reliable source to inform decision-making.

- Modelling and validation: The modelling approach and structure was extensively validated in 2022 and in 2024 to ensure the validated of our assumptions through literature and leading UK oncologists during multiple Advisory boards.

- DFS curve adjustment: Numerous assumptions have been made to address any uncertainty in DFS and a conservative approach was taken to resolve this uncertainty such as the treatment waning effect was applied, the cure proportion (79% literature vs. 95% UK clinical opinion), SMR 1.25.

- SLRs and evidence: Numerous SLRs, such as cost-effectiveness, clinical, costs SLRs, were run within the appropriate time-frame to inform key parameters and inputs of the model.

- Scenario and sensitivity analysis: Extensive sensitivity and scenario analyses were conducted at PAS price and list price to test the sensitivity of atezolizumab and atezolizumab remains cost-effective or dominant in all scenarios.

The economic evaluation is also associated with some limitations. These are considered below:

- Extrapolation – Best efforts were made to ensure the methods were statistically sound, clinically plausible, and reflective of real-world clinical practice. Where uncertainty remains extensive sensitivity and scenario analyses were conducted to inform the impact of alternative extrapolation models and assess the long-term plausibility and appropriateness of each scenario. In all scenarios, adjuvant atezolizumab remains cost-effective below the cost-effectiveness threshold at PAS and list price.

- PRO data – No PRO data was collected as part of IMpower010. The systematic literature review (Appendix J showed that there is a lack of published literature capturing long-term QoL data relevant for the model health states of interest. The published literature used to provide the health state utility values could

impact the results given the heterogeneity of the different sources, however, Roche has provided extensive scenario analyses to show the minor impact on the ICER when varying the values and where possible, the same source was used for multiple progressive states. In all scenarios, adjuvant atezolizumab remains cost-effective below the cost-effectiveness threshold at PAS and list price.

- DFS as a surrogate for OS – In the absence of long-term OS data (the 'gold standard' in terms of outcomes for oncology), DFS is used in the model. We validated this with UK clinical oncologists who considered that the adjuvant setting means measurable disease and recurrence which could correlate well with OS.
- Subsequent therapies – Based on UK clinical oncologists' opinion, subsequent treatments in the non-metastatic, first-line and second-line metastatic were derived. Efficacy and safety for these subsequent treatments were informed by literature, NICE TAs and RCTs.

Roche have aimed to address limitations by adopting conservative assumptions and following robust methodology where possible, testing the impact on the ICER, providing thorough sensitivity and scenario analyses, and ultimately providing an appropriate cost effectiveness analysis to assist decision-making.

B.3.9.3 Conclusions

In 2022, atezolizumab was recommended for access in the CDF [TA823] to ensure further data collection would resolve some of the uncertainty identified as part of the appraisal (141). The present submission [ID6324] addresses many of these uncertainties and demonstrates why adjuvant atezolizumab should be reimbursed through routine commissioning.

Currently, there is a high unmet need for NSCLC patients in the adjuvant setting. Atezolizumab offers an innovative approach to adjuvant therapy through a distinct mechanism of action versus the current standard of care. Through the IMpower010 study, atezolizumab has demonstrated robust evidence of its clinical effectiveness and safety, with data reflecting an additional 36 months of follow-up (a total of five years). The five-year follow-up data confirms a maintained DFS benefit from January 2021

(CCOD presented in the original company submission [NICE TA823]) to January 2024 (CCOD presented in the current CDF exit). At the advisory board on 4th November, six clinicians expressed confidence in the stability of HRs, with most patients beyond the high-risk relapse period and less censoring at five years for both DFS and OS. Finally, atezolizumab maintains a consistent and well-tolerated safety profile, further supporting the effectiveness of atezolizumab in this indication. These positive findings suggest that adjuvant atezolizumab offers a promising treatment option that extends DFS in patients with completely resected NSCLC which expressed PD-L1 on 50% or more of tumour cells, without ALK- positive and EGFR-positive mutation, and has not progressed after platinum-based chemotherapy, even beyond the treatment period.

In the economic analysis, the results show that atezolizumab offers an innovative, highly cost-effective treatment option for adjuvant patients at PAS and list price. The analyses demonstrate that earlier intervention with atezolizumab could both delay and prevent disease progression, which is associated with a reduction in both the costs and clinical burden of NSCLC, whilst also delivering less progression to the metastatic setting. In addition, the modelling approach and structure in this appraisal [ID6324] is broadly consistent with the modelling approach that was taken in TA823 and the original approach was deemed suitable to recommend adjuvant atezolizumab (via the CDF). Furthermore, the modelling approach and structure of ID6324 is consistent with other NICE appraisals looking at a similar early NSCLC population: alectinib for untreated ALK-positive advanced non-small-cell lung cancer [TA1014] (recommended) (50), osimertinib for adjuvant treatment of EGFR mutation-positive NSCLC after complete tumour resection [ID5120] (49) and pembrolizumab for adjuvant treatment of resected non-small-cell lung cancer [ID3907] . The methodology described above has adhered to the NICE Guide to the methods of technology appraisal and any instances where Roche has deviated from this guide has been highlighted and justified. Finally, ID6324, has used conservative assumptions such as applying the treatment waning effect at 5 years, assuming a significantly lower cure proportion and applying a higher excess mortality to the cured population.

In sum, atezolizumab in the adjuvant setting offers an overall safe, effective and cost-effective treatment option for patients in an area of high unmet need. Any uncertainties in the appraisal have been tested extensively in scenario analyses and the ICERs

remain significantly below the cost-effectiveness threshold, evidencing further the cost-effective potential of atezolizumab in the adjuvant setting. Therefore, we believe that atezolizumab in the adjuvant setting should be considered a cost-effective use of scarce NHS resources.

B.10 References

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NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single technology appraisal

Atezolizumab for adjuvant treatment of resected non-small-cell lung cancer (CDF review of TA823) [ID6324]

Summary of Information for Patients (SIP)

December 2024

File name	Version	Contains confidential information	Date
ID6324_adjuvent atezolizumab for NSCLC_SIP_v1.0	1.0	Yes	4th Dec 2024

Summary of Information for Patients (SIP):

The pharmaceutical company perspective

What is the SIP?

The Summary of Information for Patients (SIP) is written by the company who is seeking approval from NICE for their treatment to be sold to the NHS for use in England. It is a plain English summary of their submission written for patients participating in the evaluation. It is not independently checked, although members of the public involvement team at NICE will have read it to double-check for marketing and promotional content before it is sent to you.

The **Summary of Information for Patients** template has been adapted for use at NICE from the Health Technology Assessment International – Patient & Citizens Involvement Group (HTAi PCIG). Information about the development is available in an open-access IJTAHC journal article

SECTION 1: Submission summary

1a) Name of the medicine (generic and brand name):

Atezolizumab (Tecentriq®)

1b) Population this treatment will be used by. Please outline the main patient population that is being appraised by NICE:

Adults with non-small cell lung cancer (NSCLC) that has been completely removed through surgery, where the tumour shows programmed death-ligand 1 (PD-L1) expression on 50% or more of its cells, who do not have specific genetic changes known as epidermal growth factor receptor (EGFR) mutations or anaplastic lymphoma kinase (ALK)-positive alterations. Additionally, their disease has not reoccurred after receiving platinum-based chemotherapy.

1c) Authorisation: Please provide marketing authorisation information, date of approval and link to the regulatory agency approval. If the marketing authorisation is pending, please state this, and reference the section of the company submission with the anticipated dates for approval.

On 27th January 2022, as part of Project Orbis, the MHRA approved an additional indication for atezolizumab as a standalone treatment (monotherapy) for adult patients with Stage II to IIIA NSCLC, according to the 7th edition of the UICC/AJCC staging system. This approval applies to patients whose tumours have PD-L1 expression on 50% or more of tumour cells (TC), and whose disease has not reoccurred after platinum-based adjuvant chemotherapy. Under the Windsor Framework, the updated MHRA license specifies atezolizumab as monotherapy for the adjuvant treatment (following surgery) of adults with NSCLC at high risk of recurrence. This treatment is intended for patients whose tumours have PD-L1 expression on 50% or more of tumour cells, following complete surgical removal and platinum-based chemotherapy, and who do not have EGFR mutations or ALK-positive NSCLC.

1d) Disclosures. Please be transparent about any existing collaborations (or broader conflicts of interest) between the pharmaceutical company and patient groups relevant to the medicine. Please outline the reason and purpose for the engagement/activity and any financial support provided:

We are committed to being transparent about all existing collaborations and potential conflicts of interest between Roche and patient groups. Below is an outline of the purpose, scope, and financial support provided for these engagements:

Patient organisation	Reason for engagement	Amount
ALK Positive UK	Supported ALK+ UK 2024 Conference	£11,897
Roy Castle Lung Cancer Foundation	Provided a grant (grant request) to support 2024 lung cancer awareness campaign in November, *Let Go of the Labels*, aimed to improve early diagnosis of lung cancer by eradicating the labels of smoker, ex-smoker, non-smoker and never-smoker	£10,000
Roy Castle Lung Cancer Foundation	Invited as a speaker at a Roche internal event for Lang Cancer Awareness Month	£1,050
Roy Castle Lung Cancer Foundation	Invited as a speaker at a Roche organised meeting for healthcare professionals involved in the management of Lung Cancer (LCEF 2024)	£787.50
Roy Castle Lung Cancer Foundation	Invited as a speaker at a Roche organised meeting for healthcare professionals involved in the management of Lung Cancer (LCEF 2023)	£525

SECTION 2: Current landscape

2a) The condition – clinical presentation and impact

Please provide a few sentences to describe the condition that is being assessed by NICE and the number of people who are currently living with this condition in England.

Please outline in general terms how the condition affects the quality of life of patients and their families/caregivers. Please highlight any mortality/morbidity data relating to the condition if available. If the company is making a case for the impact of the treatment on carers this should be clearly stated and explained.

Atezolizumab is a treatment that helps the immune system fight cancer by blocking a protein called PD-L1, which is found on tumour cells and immune cells within the tumour. PD-L1 allows cancer to evade the immune system, but by targeting this protein, atezolizumab enables the immune system to recognize and attack cancer cells. Atezolizumab is used to treat NSCLC, which is the most common type of lung cancer, making up 92% of all lung cancer cases in England (1). Lung cancer is the third most common cancer in the UK, representing 13% of all new cancer diagnoses, with approximately 49,229 cases reported annually between 2017 and 2019. It is also the leading cause of cancer-related deaths, responsible for 21% of all cancer fatalities during the same period (2). Survival rates for NSCLC depend on the stage of the disease. In early-stages, survival is higher: 68–92% for Stage I, 53–60% for Stage II, and 13–36% for Stage III (3). However, 57% of lung cancer cases are diagnosed at an advanced stage because early NSCLC often has no symptoms and is found by chance (4). This shows the need for better screening programs to catch the disease earlier.

Patients with early NSCLC usually have fewer symptoms than those with advanced cancer. However, as the disease progresses, symptoms like chest pain, back pain and breathlessness get worse. Even in early-stages, quality of life (QoL) can be lower than in healthy people due to other health problems, older age, and the effects of smoking (5). Treatments like surgery and chemotherapy for early NSCLC can also affect QoL. Many patients feel worse in the weeks after surgery, with fatigue, pain, and breathing problems. Chemotherapy contributes to side effects like nausea and tiredness, though some pain may improve. While some aspects of life improve over time, lung cancer survivors often have shorter lives and lower QoL compared to people of the same age without cancer (6).

2b) Diagnosis of the condition (in relation to the medicine being evaluated)

Please briefly explain how the condition is currently diagnosed and how this impacts patients. Are there any additional diagnostic tests required with the new treatment?

Diagnosing NSCLC involves several steps, starting with a patient's medical history and physical exam, followed by advanced tests. These include chest X-rays, computed tomography (CT) scans, magnetic resonance imaging (MRI) scans, positron emission tomography (PET) scans, sputum analysis, and lung biopsies (4). These tests not only confirm the presence of NSCLC but also help determine the stage, guide treatment decisions, and provide a prognosis.

The Tumour, Node, Metastasis (TNM) system, created by the Union for International Cancer Control (UICC) and the American Joint Committee on Cancer (AJCC), is used to stage NSCLC from Stage 0 to IV (7, 8). The latest version, the 8th edition, is the standard in clinical practice. About half of all NSCLC cases are diagnosed at an early-stage (Stages I–III), which generally has a better outlook than Stage IV (3).

Testing also includes looking for specific markers in the tumour using immunohistochemistry (IHC) and genetic tests. These include PD-L1 expression, ALK rearrangements, and EGFR mutations (9). These tests are important for tailoring treatments to each patient. For early-stage NSCLC, PD-L1 testing is conducted through a reflex testing system, which means every sample taken from a patient suspected of having lung cancer is automatically tested for PD-L1. This approach ensures that results are ready quickly and are accurate. This, along with next-generation sequencing (NGS), is part of the National Optimal Lung Cancer Pathway (NOLCP), which streamlines testing and supports treatment planning through discussions with a multidisciplinary team (MDT) (10).

2c) Current treatment options:

The purpose of this section is to set the scene on how the condition is currently managed:

- What is the treatment pathway for this condition and where in this pathway the medicine is likely to be used? Please use diagrams to accompany text where possible. Please give emphasis to the specific setting and condition being considered by NICE in this review. For example, by referencing current treatment guidelines. It may be relevant to show the treatments people may have before and after the treatment under consideration in this SIP.
- Please also consider:
    - if there are multiple treatment options, and data suggest that some are more commonly used than others in the setting and condition being considered in this SIP, please report these data.
    - are there any drug–drug interactions and/or contraindications that commonly cause challenges for patient populations? If so, please explain what these are.

Treating early-stage NSCLC in the UK follows guidelines from NICE. Surgery is the main treatment, aimed at curing the disease, but fewer UK patients have surgery compared to other countries. Only 18% of NSCLC patients had surgery in 2022 (1). For patients with Stage IB (tumours larger than 4 cm) to Stage III, NICE recommends chemotherapy with cisplatin after surgery (11).

Even with surgery and chemotherapy, many patients see their cancer return: 17–29% for Stage I, 38–46% for Stage II, and 47–64% for Stage III (12-14). This shows the need for better treatments to reduce the risk of recurrence and improve survival rates. Advances in identifying biomarkers like PD-L1, ALK, and EGFR mutations have led to new targeted treatments, some of which are being reviewed under the Cancer Drugs Fund (CDF).

Tyrosine Kinase Inhibitors (TKIs):

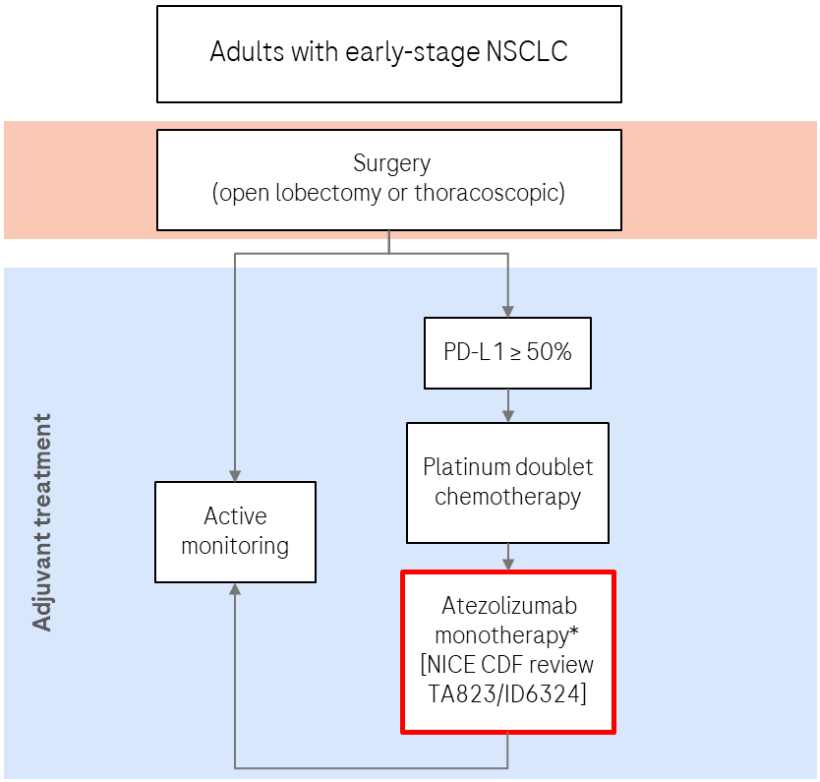
- Osimertinib: A treatment for patients with EGFR mutations, shown to reduce the risk of cancer returning (DFS HR = 0.23) (15) and improve survival (OS HR = 0.49) (16) in the ADAURA trial. While included in NICE guidance, a draft update in 2024 does not recommend it (17), and it is excluded from this review because atezolizumab's license does not cover EGFR-mutant tumours.
- Alectinib: A treatment for ALK-positive NSCLC, shown to lower the risk of recurrence by 76% in the ALINA trial (HR = 0.24). NICE approved it in 2024 (18), but it is not included in this review as atezolizumab's license excludes ALK-positive tumours.

Immunotherapy:

- Pembrolizumab: A PD-1 inhibitor that improved disease-free survival (HR = 0.81) in the KEYNOTE-091 trial, though it did not show a clear benefit in patients with high PD-L1 levels (HR = 0.83) (19). Draft guidance published in August 2024 does not recommend pembrolizumab, therefore, it is not included in this CDF review (20).
- Atezolizumab: A PD-L1 inhibitor shown to improve survival outcomes in the IMpower010 trial. It reduced the risk of cancer returning across groups: ITT (HR = 0.70), PD-L1 ≥ 50% Stage II–IIIA (HR = 0.48), and patients without EGFR or ALK mutations (HR = 0.49). Atezolizumab is recommended by NICE within the Cancer Drug Fund (21), ESMO (22, 23) and NCCN (24) and has a manageable safety profile.

The current CDF review focuses on atezolizumab for adults with resected, high-risk NSCLC whose tumors express PD-L1 ≥ 50%, without EGFR or ALK abnormalities, and whose disease have not reoccurred after chemotherapy. It offers a treatment option that has potential to reduce recurrence and improve survival.

Figure 1: Proposed positioning for adjuvant atezolizumab for early-stage NSCLC patients



The red box indicates the proposed positioning of adjuvant atezolizumab.

Abbreviations: NSCLC, non-small cell lung cancer; PD-L1, programmed death-ligand 1.

2d) Patient-based evidence (PBE) about living with the condition

Context:

- **Patient-based evidence (PBE)** is when patients input into scientific research, specifically to provide experiences of their symptoms, needs, perceptions, quality of life issues or experiences of the medicine they are currently taking. PBE might also include carer burden and outputs from patient preference studies, when conducted in order to show what matters most to patients and carers and where their greatest needs are. Such research can inform the selection of patient-relevant endpoints in clinical trials.

In this section, please provide a summary of any PBE that has been collected or published to demonstrate what is understood about **patient needs and disease experiences**. Please include the methods used for collecting this evidence. Any such evidence included in the SIP should be formally referenced wherever possible and references included.

No patient-based evidence has been collected or published for this submission.

SECTION 3: The treatment

3a) How does the new treatment work?

What are the important features of this treatment?

Please outline as clearly as possible important details that you consider relevant to patients relating to the mechanism of action and how the medicine interacts with the body

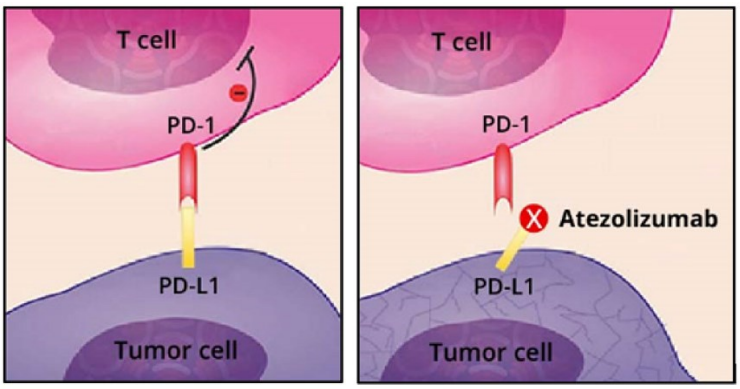
Where possible, please describe how you feel the medicine is innovative or novel, and how this might be important to patients and their communities.

If there are relevant documents which have been produced to support your regulatory submission such as a summary of product characteristics or patient information leaflet, please provide a link to these.

Atezolizumab is a monoclonal antibody (a type of targeted drug therapy); designed to target a specific protein called PD-L1. This protein is found on the surface of tumour cells and certain immune cells within tumours (25). PD-L1 normally binds to other proteins, PD-1 and B7.1, on T cells (a type of immune cell), which reduces the T cells' ability to fight cancer (26-28). By blocking PD-L1, atezolizumab helps reactivate the immune system to attack cancer cells.

Importantly, atezolizumab is designed so it does not trigger a process called antibody-dependent cell-mediated cytotoxicity (ADCC), which can harm tumour-specific T cells and potentially worsen autoimmune conditions (27, 29). This design ensures that the treatment focuses on boosting the immune response against cancer while minimising the risk of damaging healthy immune cells.

Figure 2: How atezolizumab works



Left frame: Normally, tumour cells (purple) evade the immune system's T cells (pink) by expressing a protein known as PD-L1. Right frame: Atezolizumab binds to PD-L1 and blocks it from binding to another protein, PD-1. This helps T cells regain their ability to kill tumour cells.

3b) Combinations with other medicines

Is the medicine intended to be used in combination with any other medicines?

- Yes / No

If yes, please explain why and how the medicines work together. Please outline the mechanism of action of those other medicines so it is clear to patients why they are used together.

If yes, please also provide information on the availability of the other medicine(s) as well as the main side effects.

If this submission is for a combination treatment, please ensure the sections on efficacy (3e), quality of life (3f) and safety/side effects (3g) focus on data that relate to the combination, rather than the individual treatments.

No, atezolizumab is not used in combination with other medicines in this indication.

3c) Administration and dosing

How and where is the treatment given or taken? Please include the dose, how often the treatment should be given/taken, and how long the treatment should be given/taken for.

How will this administration method or dosing potentially affect patients and caregivers? How does this differ to existing treatments?

The recommended dose of atezolizumab for treating NSCLC depends on the method of administration:

- **Intravenous (IV) infusion** (30, 31):
  - 840 mg every two weeks (Q2W)
  - 1,200 mg every three weeks (Q3W)
  - 1,680 mg every four weeks (Q4W)
- **Subcutaneous (SC) injection** (32):
  - 1,875 mg every three weeks (Q3W)

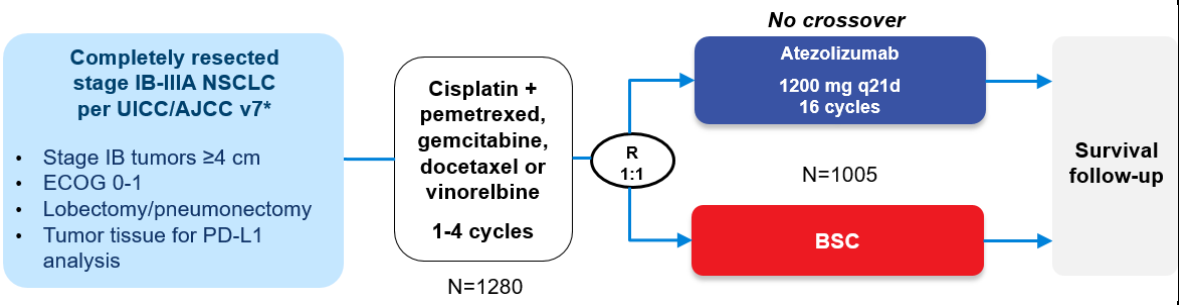
Treatment continues for up to one year, or until the cancer returns or side effects become unmanageable.

3d) Current clinical trials

Please provide a list of completed or ongoing clinical trials for the treatment. Please provide a brief top-level summary for each trial, such as title/name, location, population, patient group size, comparators, key inclusion and exclusion criteria and completion dates etc. Please provide references to further information about the trials or publications from the trials.

The randomised controlled trial (RCT) data used to assess the clinical effectiveness of atezolizumab in this appraisal is based on the IMpower010 trial, a large, global study that tested how well atezolizumab works compared to best supportive care (BSC) in adults with early-stage NSCLC (33). The study focused on patients whose cancer was completely removed through surgery and who had already received chemotherapy. It aimed to find out if atezolizumab could help prevent the cancer from coming back.

Figure 3: IMpower010 study schema for adult patients



** Stage II–IIIA in the AJCC 7th edition became IIB–IIIA and select IIIB in the AJCC 8th edition.*
Both arms included observation and regular scans for disease recurrence on the same schedule.
Abbreviations: AJCC, American Joint Committee on Cancer; BSC, Best Supportive Care; DFS, Disease Free survival; ECOG, Eastern Cooperative Oncology Group; IC, tumour-infiltrating immune cells; ITT, intent to treat; OS, Overall Survival; PD-L1, Programmed death-ligand 1; TC, tumour cells; UICC, Union for International Cancer Control.

IMpower010 study overview

- Design: Phase III, global, multi-centre, open-label randomised study
- Population: Adults with early-stage NSCLC (Stage IB tumours ≥ 4 cm to Stage IIIA) who were healthy enough to handle treatment (ECOG performance status of 0 or 1)
- Treatment: Atezolizumab
- Comparator: BSC – active follow-up without additional drugs, following cisplatin-based adjuvant chemotherapy

IMpower010 study phases

- Enrolment Phase:
    - Patients had their lung cancer surgically removed and were screened to see if they qualified
    - Eligible patients received one of four chemotherapy regimens (cisplatin combined with vinorelbine, docetaxel, gemcitabine, or pemetrexed), chosen by the investigator (doctor)
    - Up to four cycles of chemotherapy were given unless side effects became too severe, the cancer returned, or the patient decided to stop
- Randomisation Phase: Patients who finished chemotherapy and still met the requirements were randomly assigned to receive either atezolizumab or BSC

IMpower010 recruitment and treatment details

The study ran from February 2016 to January 2019 across 227 hospitals in 22 countries. A total of 1269 patients were enrolled and received up to 4 cycles of adjuvant chemotherapy (186 patients to the cisplatin + docetaxel regimen, 205 patients in the cisplatin + gemcitabine regimen, 472 patients in the cisplatin + pemetrexed regimen, and 406 patients in the cisplatin + vinorelbine regimen); and 1005 patients were subsequently randomised in a 1:1 ratio to receive atezolizumab or BSC.

Other ongoing trials

In addition to IMpower010, atezolizumab is being studied in several clinical trials, to evaluate its effectiveness as a stand-alone treatment (monotherapy) or in combination with other cancer therapies. Key ongoing studies in early-stage NSCLC include:

- IMpower030: A Phase III trial investigating the safety and effectiveness of using atezolizumab along with platinum-based chemotherapy before surgery (neoadjuvant treatment) in patients with resectable early-stage NSCLC. The goal is to see if this combination improves surgical outcomes and long-term survival.
- IMscin002: A Phase III trial assessing subcutaneous atezolizumab in two groups: patients with resected Stage IIB-IIIB NSCLC and chemotherapy-naïve Stage IV NSCLC. The study aims to confirm whether subcutaneous administration works as well as intravenous delivery in controlling disease progression.

3e) Efficacy

Efficacy is the measure of how well a treatment works in treating a specific condition.

In this section, please summarise all data that demonstrate how effective the treatment is compared with current treatments at treating the condition outlined in section 2a. Are any of the outcomes more important to patients than others and why? Are there any limitations to the data which may affect how to interpret the results? Please do not include academic or commercial in confidence information but where necessary reference the section of the company submission where this can be found.

The IMpower010 study is the first Phase III trial to show that adjuvant immunotherapy with atezolizumab can improve disease-free survival (DFS) in patients with early-stage NSCLC after surgery and chemotherapy. In early results from 2021, atezolizumab reduced the chance of the cancer returning, new lung cancer developing, or death by 34% compared to BSC in patients with PD-L1 levels of 1% or higher. (HR = 0.66) (34). By January 2024, after about five years of follow-up, atezolizumab continued to show benefits in DFS compared to BSC in certain groups of patients. The study looked at three subgroups based on how advanced the cancer was (stage) and levels of PD-L1. Two of these groups showed clear benefits from atezolizumab. However, in the group with smaller tumours (Stage Ib) and all levels of PD-L1, the results were not statistically significant.

The study's secondary goal, overall survival (OS), was not formally tested at the time of the final DFS analysis. This was due to the study's statistical design, which only allows for OS to be tested if the last DFS was not positive. The data were also not yet mature, with only about 31% of patients in both groups having experienced death. Future analyses will continue to observe survival trends.

For patients with PD-L1 levels of 50% or higher, both the interim and final analyses showed significant DFS benefits with atezolizumab (HR = 0.48). Further analysis also showed strong DFS and OS benefits in patients with high PD-L1 expression who did not have EGFR or ALK mutations (DFS HR = 0.49; OS HR = 0.44). These benefits were consistent across most patient subgroups.

In cases where cancer did come back, patients treated with atezolizumab were less likely to need further immunotherapy (17.9% vs. 40.4%) or surgery (10.7% vs. 19.1%) in this trial. This suggests that the introduction of immunotherapy for the resected stages of NSCLC will have implications for the treatment algorithms in the advanced stages. Using atezolizumab for earlier-stage NSCLC could also change how advanced lung cancer is treated in the future.

3f) Quality of life impact of the medicine and patient preference information

What is the clinical evidence for a potential impact of this medicine on the quality of life of patients and their families/caregivers? What quality of life instrument was used? If the EuroQol-5D (EQ-5D) was used does it sufficiently capture quality of life for this condition? Are there other disease specific quality of life measures that should also be considered as supplementary information?

Please outline in plain language any quality of life related data such as **patient reported outcomes (PROs).**

Please include any **patient preference information (PPI)** relating to the drug profile, for instance research to understand willingness to accept the risk of side effects given the added benefit of treatment. Please include all references as required.

The IMpower010 study did not include patient-reported outcomes (PROs) because these measures were not commonly used when the study was designed. Additionally, since many patients in the trial already had other health issues (co-morbidities) and did not have the same QoL as the general population; it was expected to be challenging to show the impact of atezolizumab on QoL. This was especially true because patients in the BSC arm were largely

without symptoms related to lung cancer and were not receiving any active control treatment for comparison.

3g) Safety of the medicine and side effects

When NICE appraises a treatment, it will pay close attention to the balance of the benefits of the treatment in relation to its potential risks and any side effects. Therefore, please outline the main side effects (as opposed to a complete list) of this treatment and include details of a benefit/risk assessment where possible. This will support patient reviewers to consider the potential overall benefits and side effects that the medicine can offer.

Based on available data, please outline the most common side effects, how frequently they happen compared with standard treatment, how they could potentially be managed and how many people had treatment adjustments or stopped treatment. Where it will add value or context for patient readers, please include references to the Summary of Product Characteristics from regulatory agencies etc.

The safety profile of atezolizumab in the IMpower010 study was consistent with previous clinical trials (35-38). As of January 2024, atezolizumab continued to demonstrate a manageable safety profile. Although adverse events (AEs) were more common in the atezolizumab group compared to BSC, these side effects were in line with what has been observed in other studies of atezolizumab for different conditions.

No new Grade 5 AEs (fatal events) have been reported since earlier analyses, with rates remaining at 1.8% in the atezolizumab group and 0.6% in the BSC group. These Grade 5 events were rare, scattered across different organ systems, and only a few were considered treatment-related. Common side effects, such as mild-to-moderate hepatitis, rash, and hypothyroidism, were effectively managed by pausing treatment or using supportive care. Most side effects resolved, suggesting that atezolizumab's side effects are typically reversible and not long-term for most patients.

While more toxicity was observed with atezolizumab compared to BSC (which involved only active monitoring), these risks need to be considered alongside the treatment benefits. In the PD-L1 ≥ 50% Stage II–IIIA population, the overall benefit-risk balance was favourable. Roche consulted clinicians with experience in treating NSCLC and they noted the risk-benefit profile of atezolizumab was favourable and they had no additional concerns after longer follow up of patients on this treatment (39).

In a setting where the goal is a potential cure and treatment options are limited, adjuvant atezolizumab has the potential to significantly reduce the risk of early lung cancer recurrence or progression to metastatic disease, offering meaningful benefits for both patients and society.

3h) Summary of key benefits of treatment for patients

Issues to consider in your response:

- Please outline what you feel are the key benefits of the treatment for patients, caregivers and their communities when compared with current treatments.
- Please include benefits related to the mode of action, effectiveness, safety and mode of administration

- Atezolizumab selectively targets the PD-L1 protein, reactivating the immune system to fight cancer cells effectively.
- As an adjuvant therapy, atezolizumab addresses potential residual disease post-surgery, targeting small collection of cancer cells (micrometastases) that could lead to recurrence.
- In the IMpower010 study, atezolizumab demonstrated a 34% reduction in the risk of disease recurrence, new NSCLC, or death in patients with PD-L1 ≥ 1%, and an even greater benefit in patients with PD-L1 ≥ 50% without EGFR or ALK alterations. This is a significant improvement over BSC, which offers no active prevention against recurrence.
- Atezolizumab has a manageable safety profile.
- Common side effects like rash, hypothyroidism, and mild-to-moderate hepatitis are typically reversible and manageable with standard supportive care or temporary treatment pauses.
- By reducing the risk of recurrence and delaying progression to metastatic disease, atezolizumab reduces the physical and emotional burden of advanced cancer on patients and their families.

3i) Summary of key disadvantages of treatment for patients

Issues to consider in your response:

- Please outline what you feel are the key disadvantages of the treatment for patients, caregivers and their communities when compared with current treatments. Which disadvantages are most important to patients and carers?
- Please include disadvantages related to the mode of action, effectiveness, side effects and mode of administration
- What is the impact of any disadvantages highlighted compared with current treatments

- Atezolizumab is approved for patients with high PD-L1 expression (≥ 50%) and excludes those with EGFR or ALK alterations. Although this restricts its use to a subset of early-stage NSCLC patients, the targeted nature of atezolizumab ensures that treatment is provided to those most likely to benefit.
- In the IMpower010 trial, while atezolizumab has demonstrated clear DFS benefits, OS data remain immature. The sustained DFS improvements observed over time strongly suggest that atezolizumab delays cancer relapse, which is likely to translate into OS benefits as the data mature.

3i) Value and economic considerations

Introduction for patients:

Health services want to get the most value from their budget and therefore need to decide whether a new treatment provides good value compared with other treatments. To do this they consider the costs of treating patients and how patients' health will improve, from feeling better and/or living longer, compared with the treatments already in use. The drug manufacturer provides this information, often presented using a health economic model.

In completing your input to the NICE appraisal process for the medicine, you may wish to reflect on:

- The extent to which you agree/disagree with the value arguments presented below (e.g., whether you feel these are the relevant health outcomes, addressing the unmet needs and issues faced by

patients; were any improvements that would be important to you missed out, not tested or not proven?)

- If you feel the benefits or side effects of the medicine, including how and when it is given or taken, would have positive or negative financial implications for patients or their families (e.g., travel costs, time-off work)?
- How the condition, taking the new treatment compared with current treatments affects your quality of life.

How the model reflects the condition

- The economic case presented in this submission is based on an analysis assessing the use of adjuvant atezolizumab in adults with completely resected NSCLC which expressed PD-L1 on 50% or more of tumour cells, who do not have EGFR mutant or ALK-positive NSCLC and have not progressed after platinum based chemotherapy compared to best supportive care.
- The approach taken to model costs and health benefits is done by splitting patients into 8 different health states: disease-free survival, non-metastatic recurrence (treatment and no treatment), metastatic recurrence (first-line: treatment and no treatment), metastatic recurrence (second-line: treatment and no treatment) and death. This is a common approach used to model the lifetime benefits and costs of treatments used to treat different types of cancer.
- The data used to predict how long patients exposed with each treatment would remain in each health state, which informs the amount of costs and health gains they would accrue, is based on the IMpower010 clinical trial data and literature published.

Modelling how much a treatment extends life

- The IMpower010 trial aimed to study the effect of atezolizumab on patient outcomes against current standard of care for patients with early-stage NSCLC, after surgery. The results of the study showed that atezolizumab significantly reduces disease recurrence or death compared to best supportive care.
- Disease-free survival (DFS), healthcare related quality of life and adverse events are used in the economic model. Given the relatively short median follow-up period in the IMpower010 trial, and the fact that a large proportion of events had not occurred by the end of the available follow-up period, extrapolation techniques were used to model DFS over a (lifetime) time horizon of 40 years.

Modelling how much a treatment improves quality of life

- In IMpower010 trial, no patient-reported outcomes (PRO) data was collected from patients, therefore, literature was used to inform PROs in the HTA submission.

Modelling how the costs of treatment differ with the new treatment and cost-effectiveness results

- The total costs of atezolizumab are expected to be greater than active monitoring driven mainly by increased treatment costs.
- In addition to the clinical benefits of atezolizumab to patients, it is also a highly cost effective treatment when compared to active monitoring reporting an ICER (Incremental

Cost Effectiveness Ratio) well below the conventional NICE thresholds of £30,000 per QALY (Quality Adjusted Life Year).

Uncertainty

Due to limited data availability and short-term trial follow-up, there is some uncertainty regarding the efficacy estimates included within the economic model. These are common obstacles in clinical trials and HTA submissions.

3j) Innovation

NICE considers how innovative a new treatment is when making its recommendations.
If the company considers the new treatment to be innovative please explain how it represents a 'step change' in treatment and/ or effectiveness compared with current treatments. Are there any QALY benefits that have not been captured in the economic model that also need to be considered (see section 3f)

Atezolizumab represents a significant advancement in the treatment of early-stage NSCLC by introducing immunotherapy to a setting where curative intent is the primary goal. Until recently, treatment options following surgery and chemotherapy were limited to BSC, leaving high-risk patients vulnerable to recurrence or progression. As demonstrated in the IMpower010 trial, atezolizumab has demonstrated a significant improvement in DFS, especially in patients with PD-L1 ≥ 50%, reducing the risk of cancer recurrence, new NSCLC, or death. While OS data remain immature, the sustained DFS benefit strongly suggests a reduction in progression to metastatic disease, which would result in significant survival and QoL gains over time. Atezolizumab addresses this gap by reducing the risk of recurrence and potentially preventing progression to metastatic disease.

3k) Equalities

Are there any potential equality issues that should be taken into account when considering this condition and this treatment? Please explain if you think any groups of people with this condition are particularly disadvantaged.
Equality legislation includes people of a particular age, disability, gender reassignment, marriage and civil partnership, pregnancy and maternity, race, religion or belief, sex, and sexual orientation or people with any other shared characteristics

More information on how NICE deals with equalities issues can be found in the NICE equality scheme
Find more general information about the Equality Act and equalities issues here

The introduction of atezolizumab as an adjuvant treatment is not considered to present any equality issues.

SECTION 4: Further information, glossary and references

4a) Further information

Feedback suggests that patients would appreciate links to other information sources and tools that can help them easily locate relevant background information and facilitate their effective contribution to the NICE assessment process. Therefore, please provide links to any relevant online information that would be useful, for example, published clinical trial data, factual web content, educational materials etc.
Where possible, please provide open access materials or provide copies that patients can access.

- ALK Positive UK: https://www.alkpositive.org.uk/
- Roy Castle Lung Cancer Foundation: https://roycastle.org/

Further information on NICE and the role of patients:

- Public Involvement at NICE Public involvement | NICE and the public | NICE Communities | About | NICE
- NICE's guides and templates for patient involvement in HTAs Guides to developing our guidance | Help us develop guidance | Support for voluntary and community sector (VCS) organisations | Public involvement | NICE and the public | NICE Communities | About | NICE
- EUPATI guidance on patient involvement in NICE: https://www.eupati.eu/guidance-patient-involvement/
- EFPIA – Working together with patient groups: https://www.efpia.eu/media/288492/working-together-with-patient-groups-23102017.pdf
- National Health Council Value Initiative. https://nationalhealthcouncil.org/issue/value/
- INAHTA: http://www.inahta.org/
- European Observatory on Health Systems and Policies. Health technology assessment - an introduction to objectives, role of evidence, and structure in Europe: http://www.inahta.org/wp-content/themes/inahta/img/AboutHTA_Policy_brief_on_HTA_Introduction_to_Objectives_Role_of_Evidence_Structure_in_Europe.pdf

4b) Glossary of terms

ADCC	Antibody-Dependent Cell-Mediated Cytotoxicity
AJCC	American Joint Committee on Cancer
ALK	Anaplastic Lymphoma Kinase
BSC	Best Supportive Care
CDF	Cancer Drugs Fund
DFS	Disease-Free Survival
ECOG	Eastern Cooperative Oncology Group
EGFR	Epidermal Growth Factor Receptor
ESMO	European Society for Medical Oncology
HTA	Health Technology Assessment
IHC	Immunohistochemistry
ITT	Intention-to-Treat
MDT	Multidisciplinary Team
MHRA	Medicines and Healthcare Products Regulatory Agency
MRI	Magnetic Resonance Imaging
NCCN	National Comprehensive Cancer Network
NHS	National Health Service
NICE	National Institute for Health and Care Excellence
NLCA	National Lung Cancer Audit
NOLCP	National Optimal Lung Cancer Pathway
NSCLC	Non-Small Cell Lung Cancer
PET	Positron Emission Tomography

QALY	Quality-Adjusted Life Year
RCT	Randomised Controlled Trial
TNM	Tumour, Node, Metastasis (staging system)
UICC	Union for International Cancer Control
UKLCC	United Kingdom Lung Cancer Coalition

4c) References

Please provide a list of all references in the Vancouver style, numbered and ordered strictly in accordance with their numbering in the text:

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NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single technology appraisal

Atezolizumab for adjuvant treatment of resected non-small-cell lung cancer (CDF review of TA823) [ID6324]

Company response to clarification questions

January 2025

File name	Version	Contains confidential information	Date
ID6324_adjuvant atezolizumab for NSCLC_CQ response_v1.0	1.0	Yes	21st Jan 2025

Contents

Section A: Clarification on effectiveness data 8
Questions related to literature searching 8
A1. CS Figure 2 (page 101, Appendix I) and Figure 3 (page 107, Appendix H). Can you confirm if the PRISMA diagrams reflect the total number of records retrieved and screened for all years? 8
Questions related to the decision problem and clinical data 17
A2. Priority: CS Section B.1.1. The updated marketing authorisation states that atezolizumab is indicated for patients at a "*high risk of recurrence*". This replaces the previous wording of "stage II to IIIA". Please state what is meant by "high risk" and whether it is equivalent to disease stage II to IIIA. If not equivalent, please justify the focus in the CS of the stage II to IIIA population. 17
A3. Priority: Confirm that the maximum number of cycles of atezolizumab is 16 and not 17 as could be taken within a 12-month period. 18
A4. Priority (NICE technical team highlight this question as highly important): The EAG notes the reasons stated by the company for not including pembrolizumab as a comparator. However, pembrolizumab is in the NICE scope and NICE recommended that pembrolizumab should be included in the submission at the decision problem meeting. Can the company confirm if it will (or will not) be providing any data comparing the clinical- and cost-effectiveness of atezolizumab with pembrolizumab before the first appraisal committee. The EAG believes that this information may be requested by the Appraisal Committee. The NICE technical team notes that the final draft guidance (FDG) for ID3907 "Pembrolizumab for adjuvant treatment of resected non-small-cell lung cancer" is now on the NICE website subject to appeal. The NICE technical team believe pembrolizumab to be the most relevant comparator, given the positive recommendation in the ID3907 FDG. 18
A5. Priority: Figure 1 appears misleading. Please provide a diagram where the doublet chemotherapy has been undertaken and then make the options atezolizumab monotherapy (followed by active monitoring), or active monitoring alone. The PD-L1 ≥ 50% can be added to the title. 18
A6. CS Section B.2.1. The SLR in CS Appendix D identified 67 RCTs of adjuvant treatments for resectable early-stage NSCLC. Please state how many RCTs of adjuvant atezolizumab were identified. If any RCTs of atezolizumab in addition to IMpower010 were identified, please state why they were excluded. 19
A7. CS Section B.2.3.1. Please confirm whether any patients in Impower010 received neoadjuvant therapies. 19
A8. CS Section B.2.3.4 Table 4 (baseline characteristics). In Table 4, the patient demographics and baseline characteristics are summarised for the PD-L1 ≥ 50%, stage II-IIIA group. If available, please provide an update to this table to include a breakdown of patient demographics/baseline characteristics for the target population, namely the PD-L1 ≥ 50%, stage II-IIIA group with no known EGFR or ALK alterations. 20

A9. CS Section B.2.3.4 Table 4 (baseline characteristics). In IMpower010, please explain why no testing of EGFR or ALK status was performed for patients with squamous NSCLC (footnote to Table 4). 20
A10. CS Section B.2.3.4 Table 4 (baseline characteristics). In IMpower010, please explain why 11% of patients had unknown EGFR status despite not having squamous NSCLC, and 19% had unknown ALK status despite not having squamous NSCLC (footnote to Table 4). 20
A11 CS Section B.2.3.4. In Table 5, the patient disposition is reported for the ITT population. Please could this be summarised for the PD-L1 ≥ 50%, stage II-IIIA with no known EGFR or ALK alterations target population.. 21
A12. CS Section B.2.10 (adverse reactions). The AE details per category are provided as text but not as tables, and it is not always clear which data relate to the January 2024 cut-off. Please provide tables of AE data for the following categories, including details of the most common AEs (and those with differing incidence by arm where applicable), for the January 2024 cut-off: 21
A13. CS Section B.2.10 (adverse reactions). Please provide the percentage of participants in IMpower010 with anti-therapeutic antibodies to atezolizumab (as listed as an outcome in the clinicaltrials.gov page for this study). 21
A14. CS Sections B.2.11 and B.3.2.8. Please provide and summarise the evidence for the equivalence in efficacy and safety of subcutaneous versus intravenous atezolizumab. Please include a summary of methods and results for studies IMscin001 and IMscin002 plus any additional relevant studies. Also please clarify whether study IMscin002 is assessing effectiveness (as stated in CS Section B.2.11) or only safety and patient preference. 22
A15. CS Section B.3.3.7 states that pragmatic searches of the literature were conducted to identify PFS/OS evidence for each of the subsequent treatments included within the model for local recurrences and 1L metastatic recurrences. However, a SLR conducted in 2017 was used to inform subsequent therapies for the 2L metastatic recurrence data. Please provide the reference for this SLR or confirm that it is the company's SLR. 23
Questions related to statistical issues 23
A16. CS Section B.2.6.1, page 41. In Table 8, the overview of the efficacy of atezolizumab is summarised for each of the population groups for both cut-offs. Both stratified and unstratified HRs are reported for DFS and OS. Please clarify why the unstratified DFS HR and the stratified OS HR is reported for the target population. .. 23
A17. CS Section B.3.3.3. Please provide the smoothed hazards (by arm) for DFS in IMpower010 along with the presentation of the associated hazards for the parametric models fitted to the data in this section, using the latest available data cut-off. 24

Section B: Clarification on cost-effectiveness data 28
Modelling questions 28
B1. Priority: Provide updated base case and key scenario analyses if there have been any changes made to the modelling based on the clarification process. .. 28

B2. Priority: The EAG believes that the 'cured' proportion within DFS should increase across time as the 'non-cured' population are more likely to have an event. Clarify reasons as to why this would not be the case. Clarify why the approach taken in the submission was preferred to using an explicit cure model with a cure fraction from day zero (using a mixture cure model). Note, the EAG is not asking the company to restructure the model to accommodate a mixture cure approach. Clarify what advantages the present approach (which assumes 79% of patients are cured after 5 years) has compared with using a distribution (for example a Gompertz in both arms) and assuming a 100% cure rate at a specified time point (for example 7 years in both arms). Whilst the EAG may not agree with NICE's position it notes that the FAD for TA823 states "*It agreed that it was appropriate to have differential cure timepoints between the 2 arms. The Cancer Drugs Fund clinical lead suggested that 1 to 2* ..... 29 *years difference is plausible because most disease relapses occur after 12 months or at most after 18 months after the surgery and adjuvant treatment. Therefore, a cure timepoint of 6 years or 7 years for atezolizumab and a cure timepoint of 5 years for active monitoring was a reasonable assumption. The ERG provided analyses, which assumed these alternative cure timepoints. The committee concluded that there was significant uncertainty about the company's cure assumptions, and it would consider both of the ERG's approaches in its decision making.*" Can the company provide functionality in the model to allow differential cure points for atezolizumab and for BSC. 29

B3. Priority: In B.3.3.5 CS Document B, the DFS-derived OS curves are compared with data from the IMpower010 trial using the data cut-off 18 April 2022 (Figure 24). Please provide this comparison using the most recent data cut-off. 32

B4. Priority: Clarify whether the distribution for treatment discontinuation for atezolizumab in the PSA works as intended. The deterministic values in 'PSA parameters D12:D27 sum to 100% as expected, however the probabilistic values (M12:M27) which are sampled using independent Beta distributions add up to different values each time and a range of 92% to 108% has been observed in a small number of samples. We suspect that this is an error and suggest using a Dirichlet distribution, or as an approximate fix all values be multiplied by a common factor to ensure a sum of 100%. 32

B5. Priority: The sum of the proportion of patients 'incident 'off-treatment' do not add up to 100% in the PSA (cells M12:M27 in the 'PSA parameters sheet'). This is because the incident proportions are sampled as independent Beta distributions. Please correct this. 33

B6. Priority: The Dirichlet used in the 'PSA parameters' sheets do not appear to be implemented correctly as the individual values do not sum to 1. For example, see cells M33:M36 or M38:M41. 33

B7. Clarify the rationale for providing list price ICERs. The EAG only intends to present results using the PAS discount. 33

B8. In references 1, 18, and 19 of the CS Document B, advisory board meetings are referenced to validate model assumptions, please could the company provide the minutes or meeting reports from these advisory board meetings? 34

B9. Clarify whether Figure 17 is correct? it implies you can have a second metastatic recurrence when not on treatment which was stated not to be the case and does not occur in the model. 34
B10. Clarify the usefulness of comparing percentages with disease-free survival at 10 and 20 years (as done above Table 19 and Table 20) when a cure proportion is applied at 5 years. The EAG believes that the distributions are likely irrelevant beyond the assumed cure point. 34
B11. Clarify the text in Table 21, The EAG interpreted this as 79% had conditional DFS after 8 years as there had been 3 years disease-free survival and then a further 5 years. If this interpretation is correct, the conditional DFS proportion at 5 years would be 89%. 34
B12. We agree with the company that incorporating potential disutilities associated with AEs in the model, and the administration costs for treatments that aren't atezolizumab or nintedanib into the model will have no material impact on the ICER. However, in order to show this to the committee, provide scenario analyses illustrating this lack of impact. 35
B13. Clarify why correlations were not used in sampling utility values from the multivariate regression model. 37
B14. Clarify the rationale to have different probabilities of death for those with a PFS event dependent on non-metastatic recurrence treatment - this would appear to contradict the decision in the base case to pool rates for atezolizumab and BSC. Perform an analysis where the probabilities are set equal across all options for this group and where the probabilities are set equal across all options in the metastatic recurrence progression. Further, these probabilities should all use the same sample in the PSA. This does not currently happen when treatments are assumed to have the same value, for example in cell M126 and cell M129 in the 'PSA parameters sheet' and also in cells M127:M128. 37
B15. Comment on the appropriateness of assuming the standard error to be 10% of the mean for utility of patients in DFS who are off treatment. There is a large variation in this value and from a small number of samples a range of 0.64 to 0.96 was observed suggesting the standard error is too large. 38
B16. Add functionality so that the period of HRU can be set differently in each arm and use 5 years for BSC and 6 years for ATZ. Clinicians state that patients are likely to be followed up for one additional year if atezolizumab treatment is provided. 40
B17. Clarify why the costs of non-lung cancer death is set to zero as it is likely that other causes also have costs (heart attacks, other cancers, respiratory diseases etc). Provide estimations of these average costs for non-lung cancer death and explore in sensitivity analyses. 40
B18. There appears to be a cell referencing error in DG13 in the 'CMP' sheet where D12 is used instead of D13. This error propagates through all other cells as the formula is dragged down. This makes a very small change to the ICER (£0.07). 41
B19. Perform an analysis assuming 100% of atezolizumab is provided as IV rather than subcutaneous. Comment on the change in the ICER if IV atezolizumab was provided every 4 weeks rather than every 3, but with the same number of cycles, which is a schedule known to be used by clinical advisors to the EAG. 41

B20. Clarify why Life Year Gained values are discounted. Where these values are reported as results, provide undiscounted values. 43
B21. Typo in Table 31, should '1L progression free' be 'first line PD' which has a standard error and *p*-value in the Chouaid paper? Also confirm how the sentence immediately prior to Table 31 which lists values of 0.73, 0.74 and 0.66 relates to the utility values in the model for local recurrence (0.77) and metastatic disease (0.70). Clarify why the utilities associated with the last 3 rows in Table 31 are not included in the modelling. If appropriate, perform a sensitivity analysis incorporating these values. 43
B22. Please provide further details on how SACT data were used within the modelling. Provide an analysis where patient characteristics match those from the SACT dataset. Compare the OS results from the model in this scenario with OS from the SACT data if possible..... 44
B23. For transparency, confirm whether there is a limitation in the methodology used for 'rechallenging' patients after progressing from local recurrence to metastatic recurrence. It is believed that the eligibility of patients for rechallenge is based on time since a DFS event from the initial treatment rather than related to the time to progression from durvalumab or pembrolizumab. The EAG believes that if this is a limitation the impact would be negligible so is not requesting any changes to the model, just clarification that our understanding is correct. 44
B24. The costs for GP Home visits and Therapist visit (cells F60 and F61 in the 'Direct Costs' sheet) are set to zero. Clarify whether it is intentional. If not, please replace with appropriate costs. Clarify how the cost for a 10-minute GP appointment was estimated to be £50.50. Table 9.4.2 of Jones et al (Unit Costs of Health and Social Care 2023) reports a maximum cost of £49. 45

Section C: Textual clarification and additional points 46
Typographical questions 46
C1. Table 36. Should the numbers in the PAS price column be CIC? 46
C2. The EAG believes there is a typographical error in Table 49 relating to utilities in the base case. We believe that the utility for BSC and atezolizumab off treatment should be 0.81, with atezolizumab on-treatment being 0.77 as used in the modelling. 47
C3. The EAG believes there is a typographical error in cell BG13 of the ATZ workbook which contains 'Ref#' and was probably intended to be BG12. This has no impact on the model results. 48

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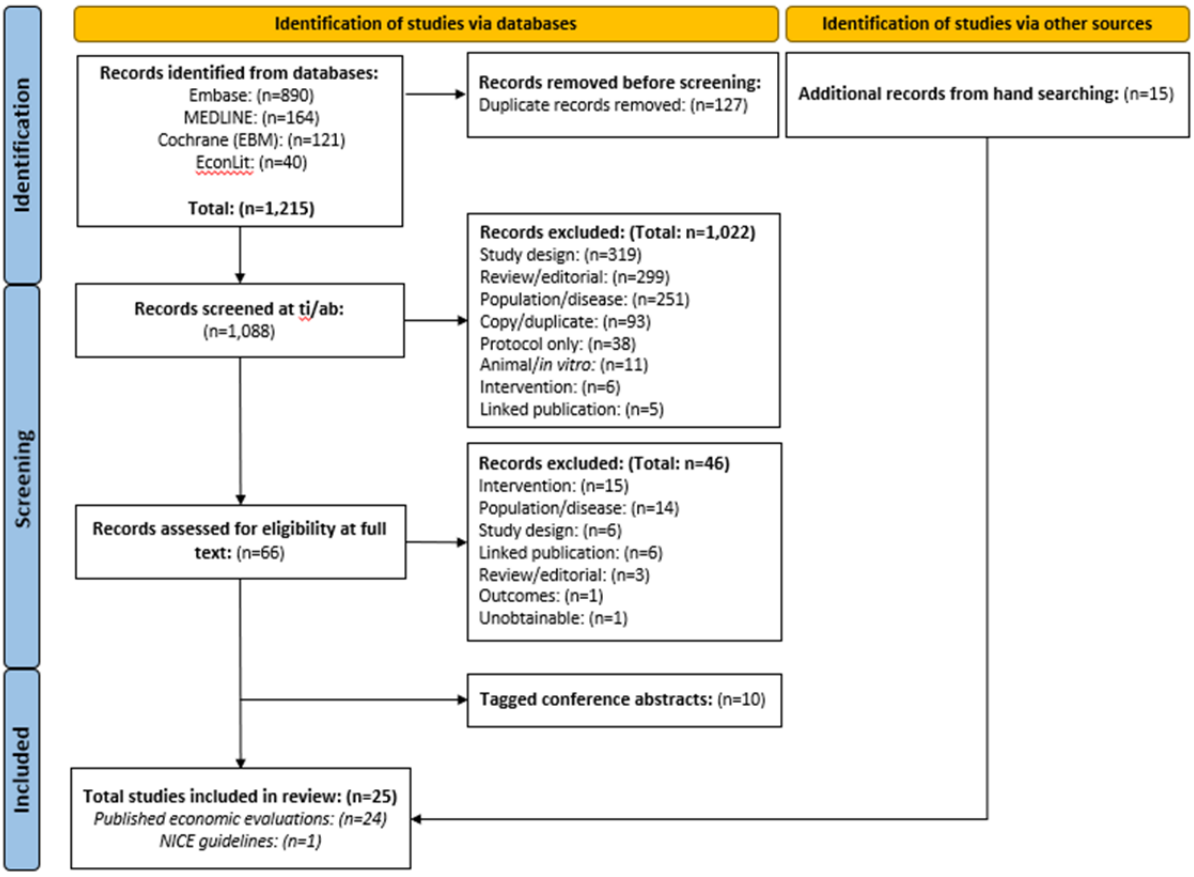
Section A: Clarification on effectiveness data

Questions related to literature searching

A1. CS Figure 2 (page 101, Appendix I) and Figure 3 (page 107, Appendix H). Can you confirm if the PRISMA diagrams reflect the total number of records retrieved and screened for all years?

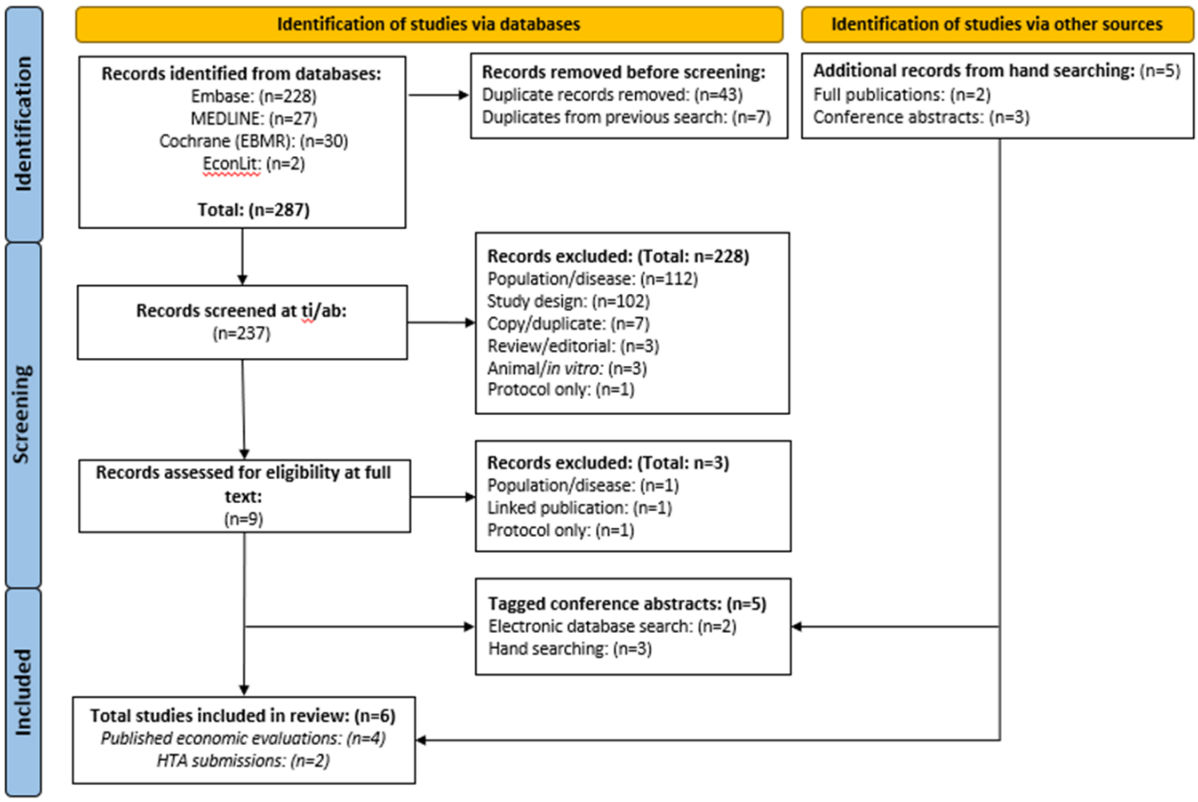
Page 101, Appendix I does not include the total number of records retrieved and screened for all years. Please see Figure 1 to Figure 5 below for the PRISMA diagrams for each year from March 2021 until August 2024.

Figure 1: PRISMA flow diagram of the original (March 2021) SLR



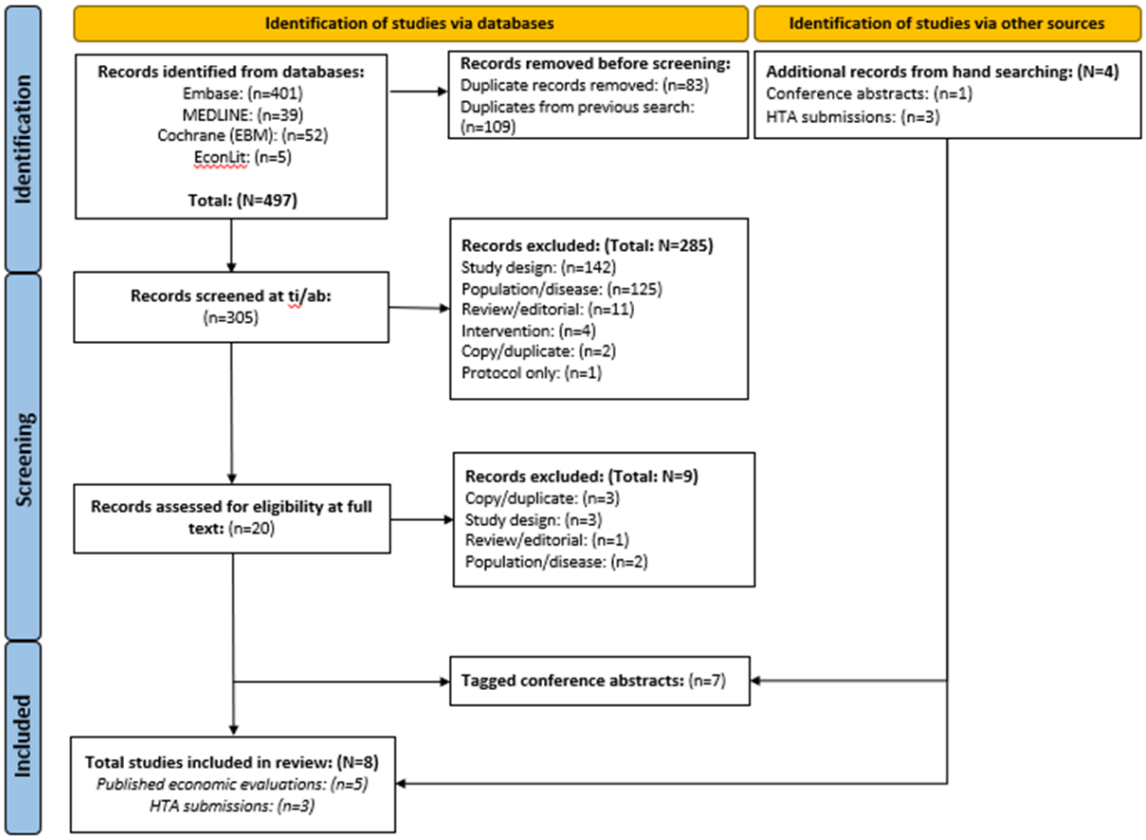
Abbreviations: EBM, evidence-based medicine; NICE, National Institute for Health and Care Excellence; PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-Analyses; SLR, systematic literature review; ti/ab, title/abstract.

Figure 2: PRISMA flow diagram of the July 2022 update



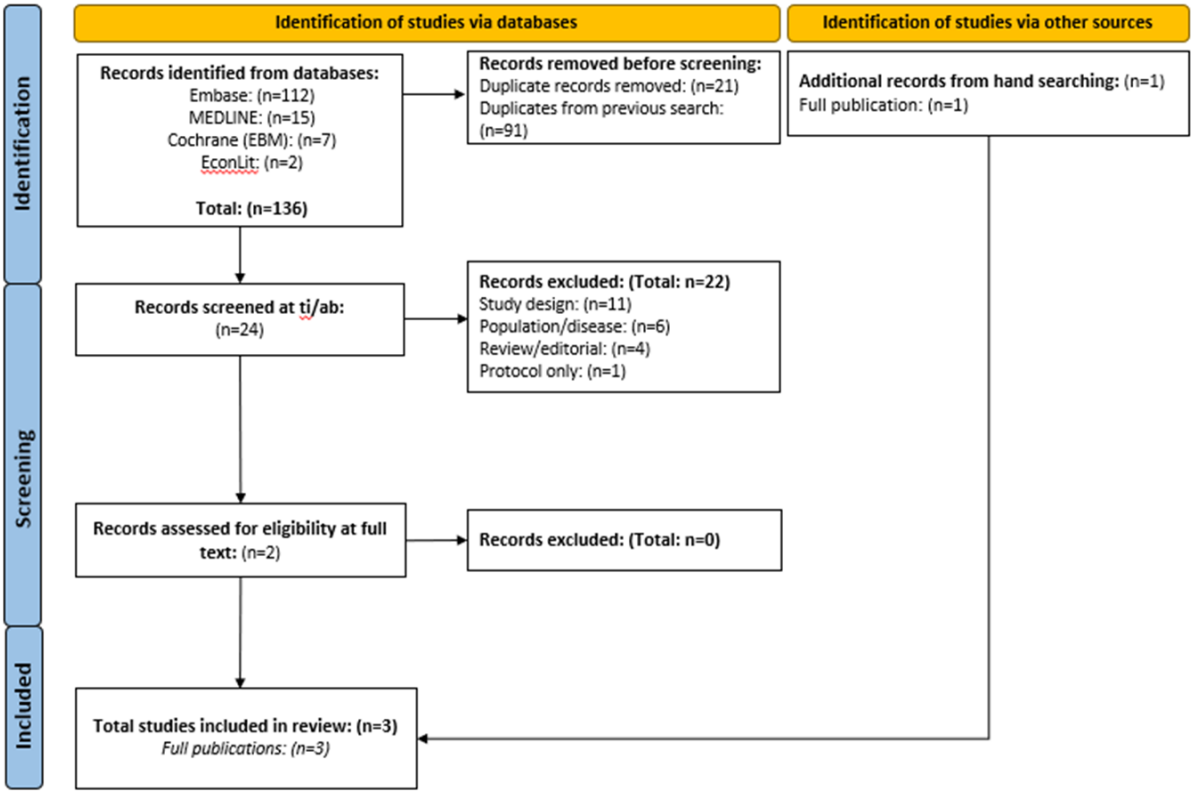
Abbreviations: EBMR, Evidence-based medicine reviews; HTA, health technology assessment; PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-Analyses; ti/ab, title/abstract.

Figure 3: PRISMA flow diagram of the July 2023 update



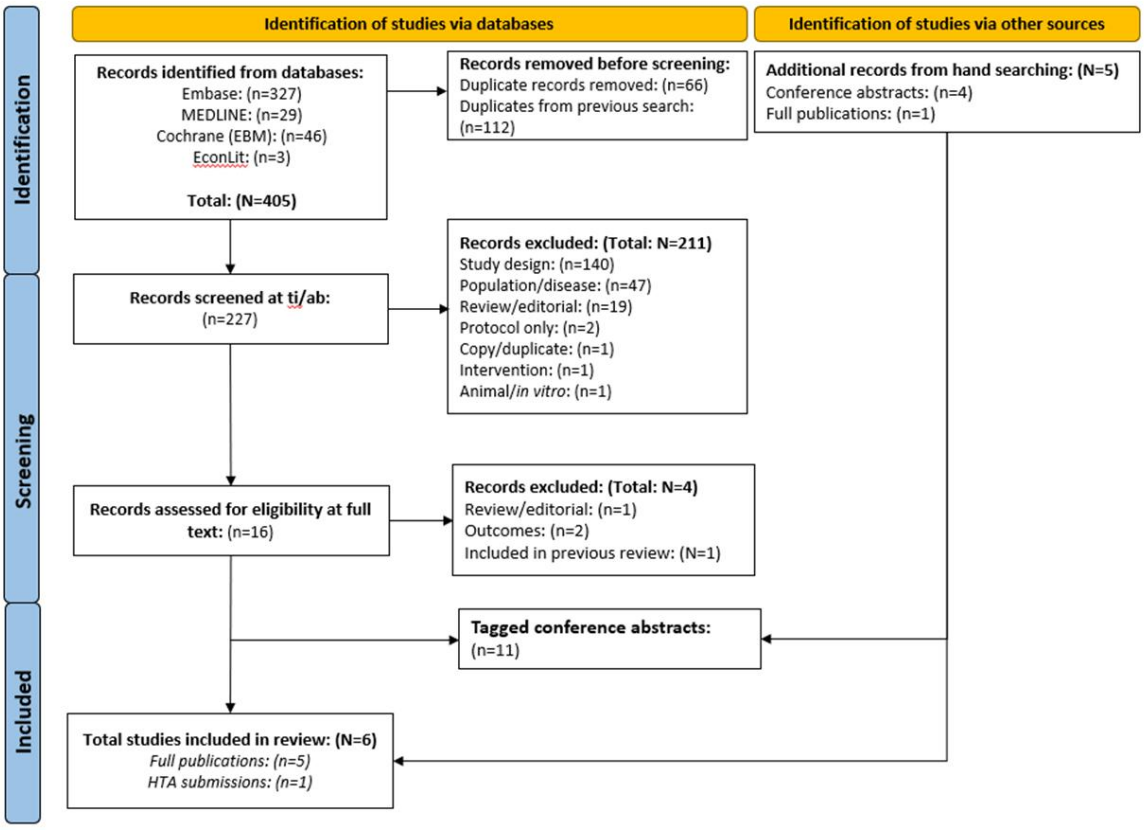
Abbreviations: EBM, evidence-based medicine; HTA, health technology assessment; PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-Analyses; ti/ab, title/abstract.

Figure 4: PRISMA flow diagram of the September 2023 update



Abbreviations: EBM, evidence-based medicine; PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-Analyses; ti/ab, title/abstract.

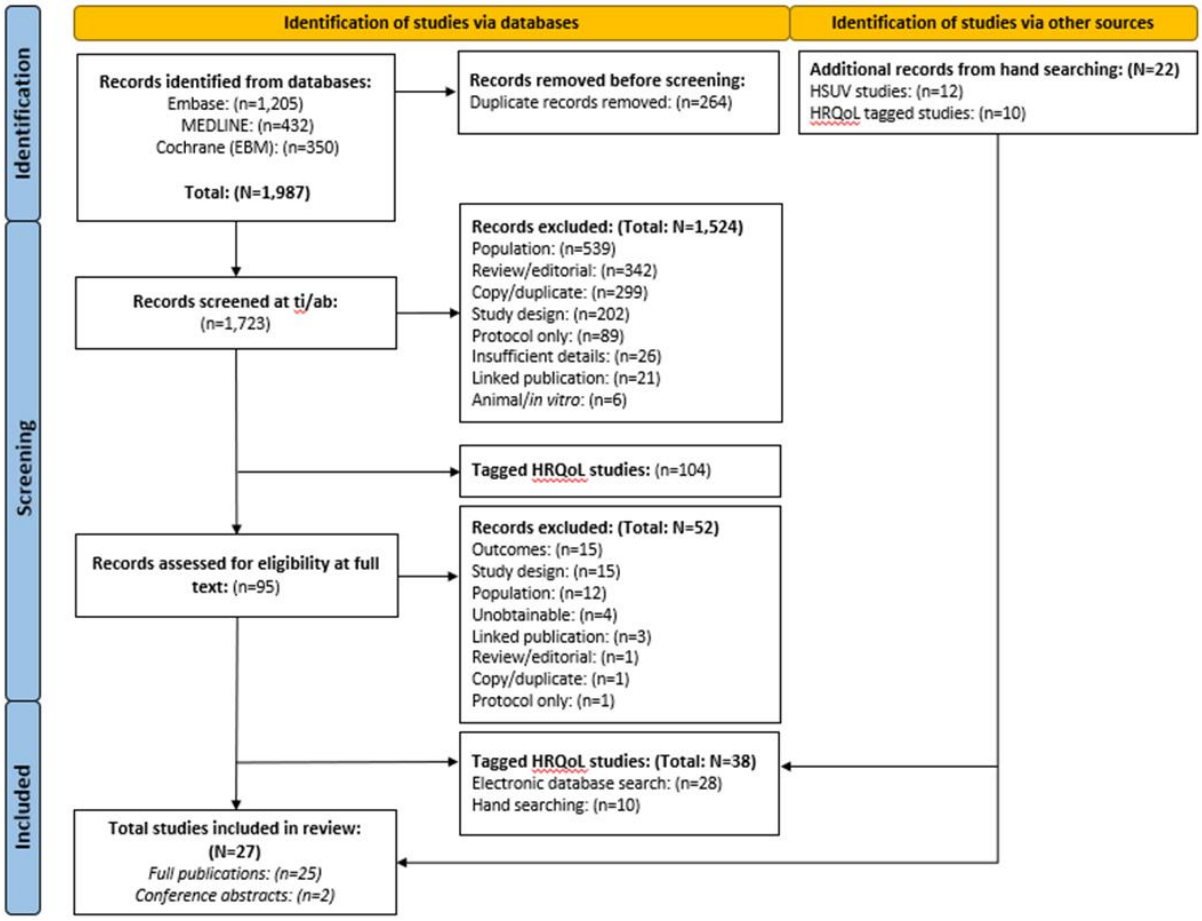
Figure 5: PRISMA flow diagram of the August 2024 update



Abbreviations: EBM, evidence-based medicine; PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-Analyses; ti/ab, title/abstract.

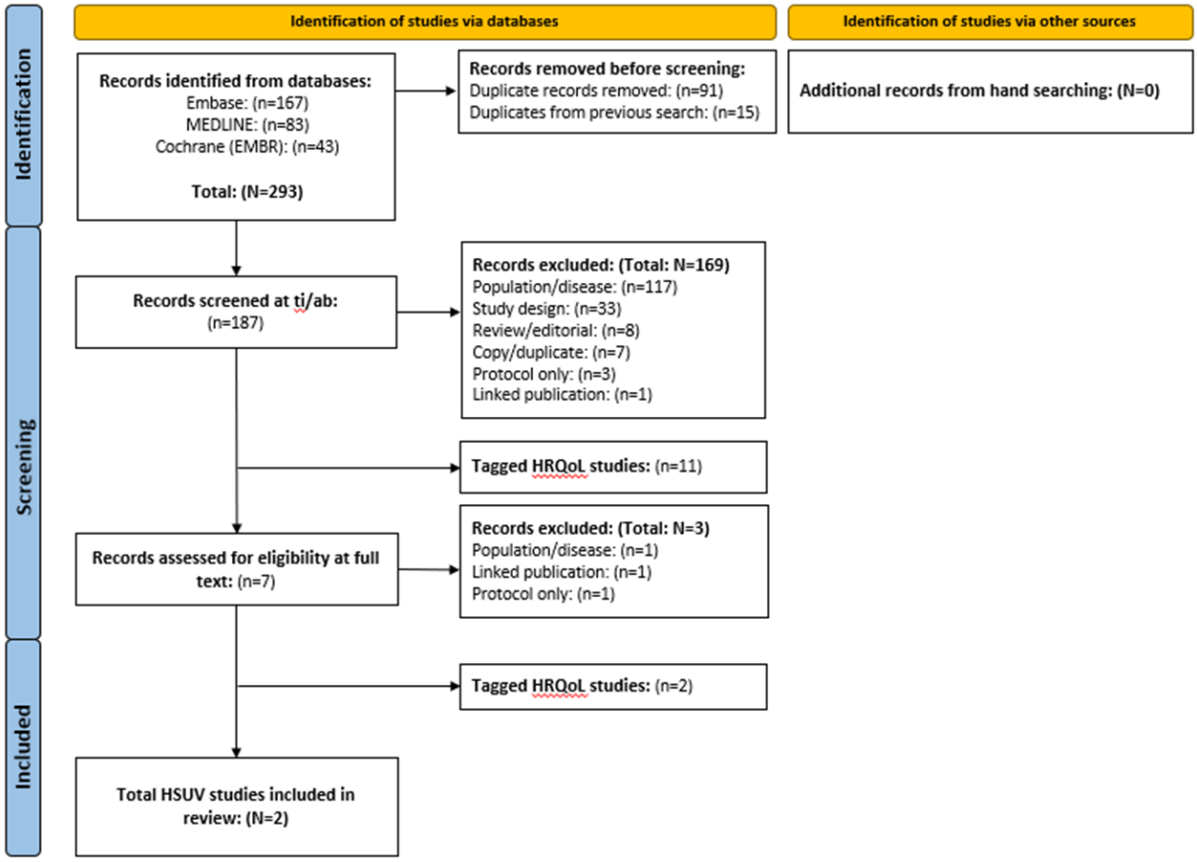
Page 117, Appendix J does not include the total number of records retrieved and screened for all years. Please see Figure 6 to Figure 10 below for the PRISMA diagrams for each year from March 2021 until August 2024.

Figure 6: PRISMA flow diagram of the original (March 2021) SLR



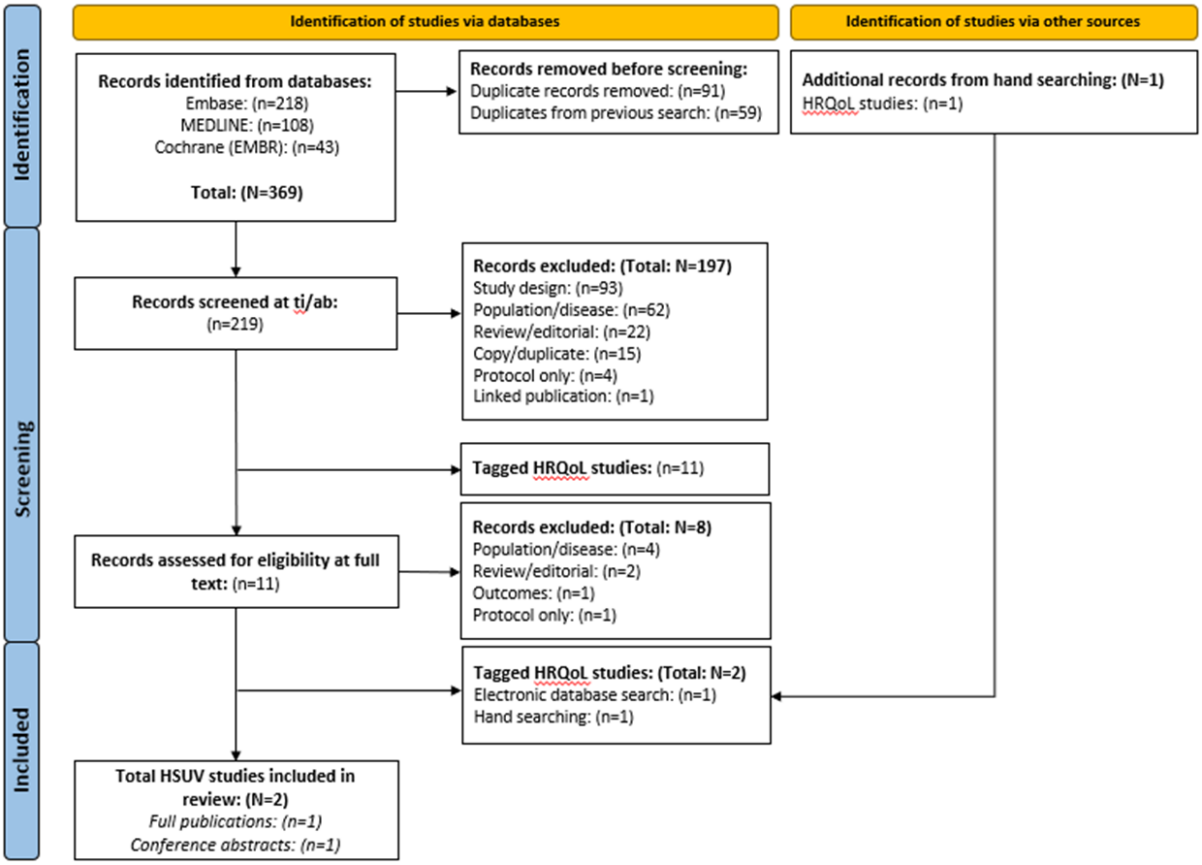
Abbreviations: EBM, Evidence-Based Medicine; HSUV, health state utility value; HRQoL, health related quality of life; PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-Analyses; SLR, systematic literature review; ti/ab, title and abstract.

Figure 7: PRISMA flow diagram of the June 2022 update



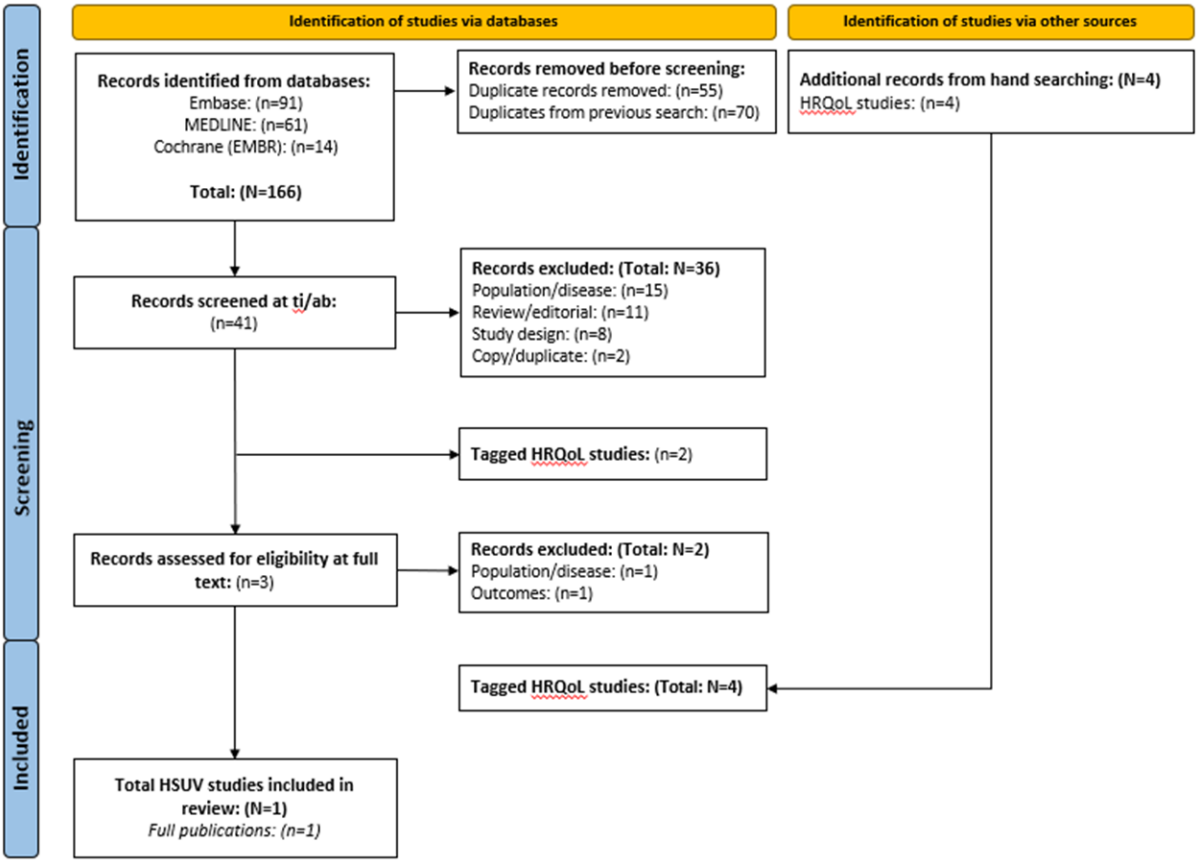
Abbreviations: EMBR, Evidence-Based Medicine Reviews; HRQoL, health related quality of life; HSUV, health state utility value; PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-Analyses; ti/ab, title and abstract.

Figure 8: PRISMA flow diagram of the July 2023 update



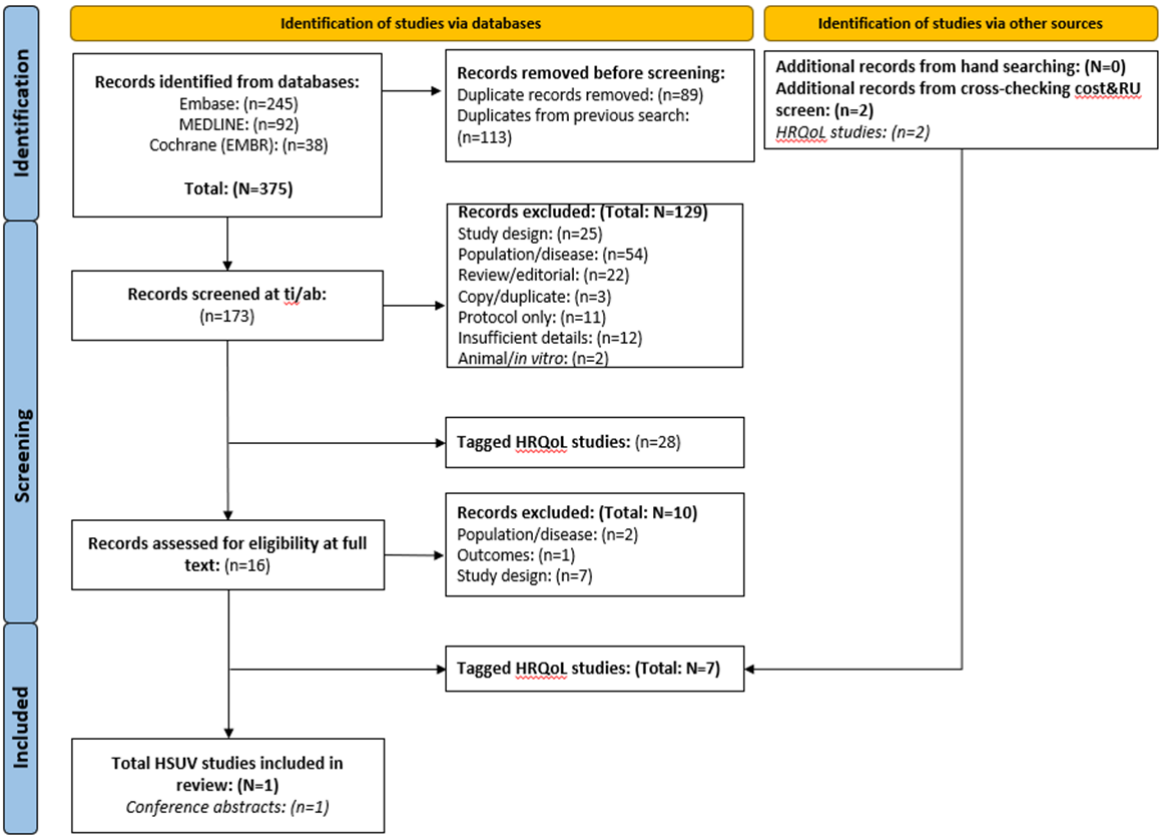
Abbreviations: EMBR, Evidence-Based Medicine Reviews; HSUV, health state utility value; HRQoL, health-related quality of life; PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-Analyses; ti/ab, title and abstract.

Figure 9: PRISMA flow diagram of the September 2023 update



Abbreviations: EMBR, Evidence-Based Medicine Reviews; HSUV, health state utility value; HRQoL, health-related quality of life; PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-Analyses; ti/ab, title and abstract.

Figure 10: PRISMA flow diagram of the August 2024 update



Abbreviations: EMBR, Evidence-Based Medicine Reviews; HSUV, health state utility value; HRQoL, health-related quality of life; PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-Analyses; RU, resource use; ti/ab, title and abstract.

Questions related to the decision problem and clinical data

A2. **Priority:** CS Section B.1.1. The updated marketing authorisation states that atezolizumab is indicated for patients at a "*high risk of recurrence*". This replaces the previous wording of "stage II to IIIA". Please state what is meant by "high risk" and whether it is equivalent to disease stage II to IIIA. If not equivalent, please justify the focus in the CS of the stage II to IIIA population.

The term "high risk of recurrence" is equivalent to disease stage II–IIIA, as defined by the 7th edition of the TNM staging system, and selected Stage II–IIIB disease based on the 8th edition. For further clarity, patient population defined by the "high risk of recurrence" in accordance with the relevant staging system aforementioned are:

- Tumour size ≥ 5 cm, or;
- Tumours of any size that are either accompanied by N1 or N2 status, or;

- Tumours that are invasive of thoracic structures (directly invade the parietal pleura, chest wall, diaphragm, phrenic nerve, mediastinal pleura, parietal pericardium, mediastinum, heart, great vessels, trachea, recurrent laryngeal nerve, oesophagus, vertebral body, carina), or;
- Tumours that involve the main bronchus < 2 cm distal to the carina but without involvement of the carina, or;
- Tumours that are associated with atelectasis or obstructive pneumonitis of the entire lung, or;
- Tumours with separate nodule(s) in the same lobe or different ipsilateral lobe as the primary.

A3. **Priority:** Confirm that the maximum number of cycles of atezolizumab is 16 and not 17 as could be taken within a 12-month period.

As per the IMpower010 protocol, 16 cycles of atezolizumab administered every three weeks (Q3W) were mandated. One patient in the study received 17 cycles of treatment but was excluded from the primary CSR and has not been included in the submission or the model.

A4. **Priority (NICE technical team highlight this question as highly important):** The EAG notes the reasons stated by the company for not including pembrolizumab as a comparator. However, pembrolizumab is in the NICE scope and NICE recommended that pembrolizumab should be included in the submission at the decision problem meeting. Can the company confirm if it will (or will not) be providing any data comparing the clinical- and cost-effectiveness of atezolizumab with pembrolizumab before the first appraisal committee. The EAG believes that this information may be requested by the Appraisal Committee. The NICE technical team notes that the final draft guidance (FDG) for ID3907 “Pembrolizumab for adjuvant treatment of resected non-small-cell lung cancer” is now on the NICE website subject to appeal. The NICE technical team believe pembrolizumab to be the most relevant comparator, given the positive recommendation in the ID3907 FDG.

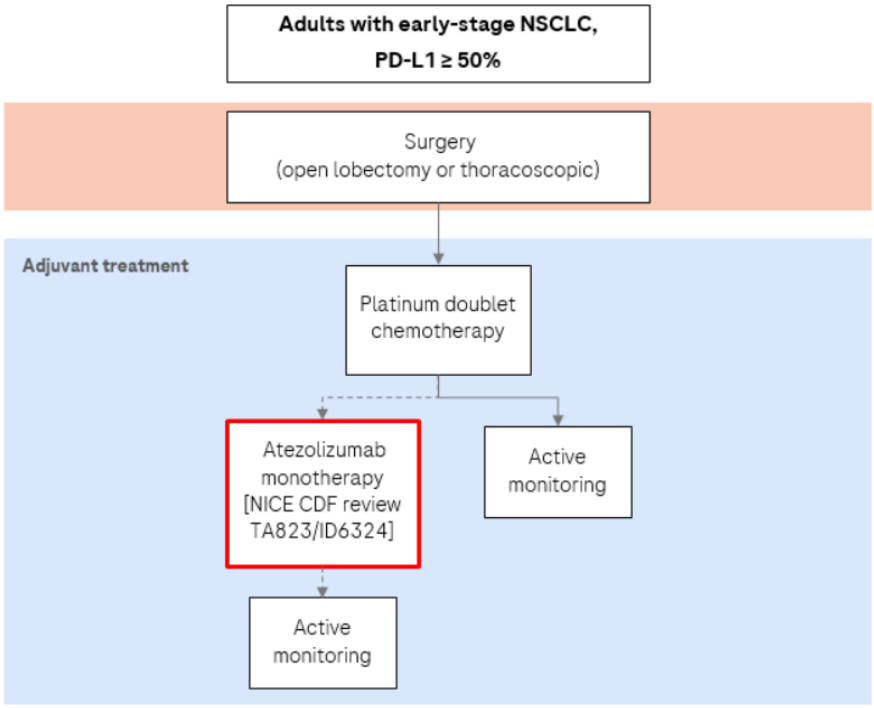
The additional pembrolizumab analysis can be found in the Appendix at the end of this response document. Please note that the headers align with the Doc B section headers for ease of review.

A5. **Priority:** Figure 1 appears misleading. Please provide a diagram where the doublet chemotherapy has been undertaken and then make the options atezolizumab monotherapy

(followed by active monitoring), or active monitoring alone. The PD-L1 ≥ 50% can be added to the title.

As discussed in the clarification call, please see Figure 11 below for the updated pathway diagram.

Figure 11: Proposed positioning for adjuvant atezolizumab for early-stage PD-L1 ≥ 50% NSCLC patients



A6. CS Section B.2.1. The SLR in CS Appendix D identified 67 RCTs of adjuvant treatments for resectable early-stage NSCLC. Please state how many RCTs of adjuvant atezolizumab were identified. If any RCTs of atezolizumab in addition to IMpower010 were identified, please state why they were excluded.

Out of the 67 RCTs identified in the SLR, only the pivotal trial IMpower010 was identified as a RCT of adjuvant atezolizumab and has been included in the present submission. No additional RCTs of adjuvant atezolizumab were identified. Further details can be found in the data extraction spreadsheet from Appendix D.1.4.

A7. CS Section B.2.3.1. Please confirm whether any patients in Impower010 received neoadjuvant therapies.

No patients in the IMpower010 trial received neoadjuvant therapies. As stated in CS Section B.2.3.1 and Appendix E, patients in IMpower010 were only eligible if they were aged ≥18 years, had an ECOG performance status of 0 or 1, and had undergone complete surgical resection of Stage IB (tumours ≥ 4 cm) to Stage IIIA NSCLC. Surgery was the only therapy

patients received. Appendix E explains that patients were excluded if they had received prior systemic chemotherapy (with rare exceptions), hormonal therapy, radiation therapy, or immune checkpoint inhibitors. The full list of inclusion and exclusion criteria can be found in Appendix E.

A8. CS Section B.2.3.4 Table 4 (baseline characteristics). In Table 4, the patient demographics and baseline characteristics are summarised for the PD-L1 ≥ 50%, stage II-IIIA group. If available, please provide an update to this table to include a breakdown of patient demographics/baseline characteristics for the target population, namely the PD-L1 ≥ 50%, stage II-IIIA group with no known EGFR or ALK alterations.

Within the same table (CS Section B.2.3.4, Table 4), EGFR mutation and ALK rearrangement statuses are already provided for the PD-L1 ≥ 50%, Stage II–IIIA group. A further breakdown is not available, as this variation involves the inclusion or exclusion of the EGFR/ALK population, which only comprises fewer than 20 patients.

A9. CS Section B.2.3.4 Table 4 (baseline characteristics). In IMpower010, please explain why no testing of EGFR or ALK status was performed for patients with squamous NSCLC (footnote to Table 4).

Until the FDA approval of adjuvant osimertinib in December 2020, determining EGFR/ALK status in non-metastatic NSCLC was not standard practice. In IMpower010, genomic alteration testing was not required per protocol, and local results were provided only if available. Central testing for EGFR and ALK mutations was conducted for patients with non-squamous histology where tissue was available. It is important to note that the study was initiated in 2015, prior to this approval of osimertinib, and included patients at a time when data on these biomarkers, even in metastatic settings, was limited. Additionally, in squamous NSCLC, testing for EGFR and ALK alterations is typically not mandatory unless there is clinical suspicion, such as in non-smokers or younger patients.

A10. CS Section B.2.3.4 Table 4 (baseline characteristics). In IMpower010, please explain why 11% of patients had unknown EGFR status despite not having squamous NSCLC, and 19% had unknown ALK status despite not having squamous NSCLC (footnote to Table 4).

See response to A9. In addition, the term "unknown" should be corrected to "not tested". Testing for EGFR and ALK was not mandated per the IMpower010 study protocol. Local results were included if available, and central testing was performed only for non-squamous histology when sufficient tissue samples were available. Therefore, patients categorised as "unknown" simply did not undergo testing, rather than their results being inconclusive or unavailable.

A11 CS Section B.2.3.4. In Table 5, the patient disposition is reported for the ITT population. Please could this be summarised for the PD-L1 ≥ 50%, stage II-IIIA with no known EGFR or ALK alterations target population..

As mentioned in A8, we do not have a specific summary for the PD-L1 ≥ 50%, Stage II–IIIA population with no known EGFR or ALK alterations. The main variation involves the inclusion or exclusion of the EGFR/ALK-positive patient population, which comprises fewer than 20 patients.

A12. CS Section B.2.10 (adverse reactions). The AE details per category are provided as text but not as tables, and it is not always clear which data relate to the January 2024 cut-off. Please provide tables of AE data for the following categories, including details of the most common AEs (and those with differing incidence by arm where applicable), for the January 2024 cut-off:

- All AEs and treatment-related AEs
- Fatal AEs and treatment-related fatal AEs
- Serious AEs and treatment-related serious AEs
- Grade 3-4 AEs and treatment-related grade 3-4 AEs [these are not currently described in the CS]
- AEs leading to dose interruption
- AEs leading to discontinuation
- AESIs [as in CS Table 13]
- Fatal AESIs
- Grade 3-4 AESIs.

The AE summary (CS Section B.2.10, Table 22), AE breakdown (CS Section B.2.10, Tables 23 and 24), and the entire AE section in the submission provide a clear overview of the data. The specific breakdown of AE data requested is not available and further analysis has not been planned. It is explained that since the first OS interim analysis (CCOD April 2022), there have been only minor changes in AE updates. Therefore, the updates were summarised in text and in the summary table, with a focus on AEs showing a difference of at least 5% between arms (CS Section B.2.10, Table 24).

A13. CS Section B.2.10 (adverse reactions). Please provide the percentage of participants in IMpower010 with anti-therapeutic antibodies to atezolizumab (as listed as an outcome in the clinicaltrials.gov page for this study).

Anti-therapeutics antibodies (ATAs), also referred to as anti-drug antibodies (ADAs), were one of the secondary outcomes measures in the IMpower010 trial. The observed incidence of

treatment-emergent ADAs was 31.2% (152/487) in the ADA evaluable population (clinical cutoff date 21st January 2021). The ADA analysis was only conducted for CCOD Jan 21, meaning the data presented here is the only data available on ADA. This analysis was included in the primary CSR (Section 5.7.1), which was submitted to NICE in 2021. Please find this attached alongside the response. The present CDF exit submission focuses on safety outcomes (AE measurements) to provide a more comprehensive understanding of the impact of atezolizumab on patients.

A14. CS Sections B.2.11 and B.3.2.8. Please provide and summarise the evidence for the equivalence in efficacy and safety of subcutaneous versus intravenous atezolizumab. Please include a summary of methods and results for studies IMscin001 and IMscin002 plus any additional relevant studies. Also please clarify whether study IMscin002 is assessing effectiveness (as stated in CS Section B.2.11) or only safety and patient preference.

Regarding the equivalence of subcutaneous (SC) vs. intravenous (IV) atezolizumab, the evidence is based on pharmacokinetic (PK) data demonstrating comparable efficacy-exposure and safety-exposure relationships seen in the IMscin001 and IMscin002 studies.

IMscin001 is a 2-part, open-label, global, multicentre, Phase 1b/3 study to evaluate the PK, safety, and efficacy of SC atezolizumab compared with IV atezolizumab in patients with locally advanced or metastatic NSCLC. The objective from Part 1 was to determine the dose of SC atezolizumab that provides a comparable serum concentration (C_{trough}) to that following administration of IV atezolizumab 1200 mg administered once every 3 weeks (1). SC atezolizumab 1800 mg every 3 weeks and 1200 mg every 2 weeks provided similar C_{trough} and area under the curve values (AUC) in cycle 1 to the corresponding IV atezolizumab reference, was well-tolerated, and exhibited a safety profile consistent with the established IV formulation. Part 2 was a randomised phase III, open-label, multicentre, non-inferiority study comparing the drug exposure of atezolizumab SC with atezolizumab IV (2). The study met both of its co-primary endpoints: cycle 1 observed C_{trough} (SC: 89 mg/ml, coefficient of variation [CV]: 43% versus IV: 85 mg/ml, CV: 33%; geometric mean ratio [GMR]: 1.05, 90% confidence interval [CI] 0.88–1.24) and model-predicted AUC0-21 d (SC: 2907 mg d/ml, CV: 32% versus IV: 3328 mg d/ml, CV: 20%; GMR: 0.87, 90% CI 0.83–0.92). Progression-free survival (hazard ratio [HR] 1.08, 95% CI 0.82–1.41), objective response rate (SC: 12% versus IV: 10%), and incidence of anti-atezolizumab antibodies (SC: 19.5% versus IV: 13.9%) were similar between arms. No new safety concerns were identified. C_{trough} and AUC0-21 d for atezolizumab SC were consistent with the other approved atezolizumab IV indications.

IMscin002 was a Phase II, randomised, multicentre, cross over trial investigating patient- and HCP-reported preference for atezolizumab SC vs IV for the treatment of patients with NSCLC (3). IMscin002 assessed patient preference and safety only. The overall safety profile was consistent with prior study (IMscin001). The study also demonstrated that compared with IV, atezolizumab SC demonstrated non-inferior drug exposure at cycle 1. Efficacy, safety, and immunogenicity were similar between arms and consistent with the known profile for atezolizumab IV. After Cycle 6, most patients (79.4%) chose atezolizumab SC for the continuation period. Overall, 85.8% of patients were very satisfied or satisfied with atezolizumab SC vs 75.2% of patients with IV. Similar drug exposure and clinical outcomes following SC and IV administration support the use of atezolizumab SC as an alternative to atezolizumab IV.

Additionally, in August 2023, the MHRA approved atezolizumab SC for all indications in which the IV formulation is authorised, supported by findings from the IMscin001 study. This approval confirms that regulatory authorities have deemed the SC formulation equivalent in safety and efficacy to the IV formation. Access to atezolizumab SC has also been granted in the UK, further demonstrating that payers also recognise its equivalence in safety and efficacy.

A15. CS Section B.3.3.7 states that pragmatic searches of the literature were conducted to identify PFS/OS evidence for each of the subsequent treatments included within the model for local recurrences and 1L metastatic recurrences. However, a SLR conducted in 2017 was used to inform subsequent therapies for the 2L metastatic recurrence data. Please provide the reference for this SLR or confirm that it is the company's SLR.

The company has submitted the SLR in a separate document labelled *Tecentriq_ Non-small Cell Lung Cancer (NSCLC)_2L SLR Report.zip* and can confirm that it is the company's SLR.

Questions related to statistical issues

A16. CS Section B.2.6.1, page 41. In Table 8, the overview of the efficacy of atezolizumab is summarised for each of the population groups for both cut-offs. Both stratified and unstratified HRs are reported for DFS and OS. Please clarify why the unstratified DFS HR and the stratified OS HR is reported for the target population.

This was a typographical error. The HR for 'OS in PD-L1 SP263 ≥ 50% TC Stage II–IIIA' and 'OS in PD-L1 SP263 ≥ 50% TC Stage II–IIIA, excluding EGFR and ALK' populations should be unstratified, as shown in CS Figures 11 and 13. The unstratified HRs are reported because stratified data are typically used for primary analysis populations, while unstratified data are used for subsets of patients, such as exploratory analyses by PD-L1 status.

Note that this typographical error has no impact on the economic analysis or ICER results due to the type of model that was used in the dossier; a parametric survival model rather than cox proportional hazard model.

A17. CS Section B.3.3.3. Please provide the smoothed hazards (by arm) for DFS in IMpower010 along with the presentation of the associated hazards for the parametric models fitted to the data in this section, using the latest available data cut-off.

Figure 12 to

Figure ***18*** show the smoothed hazards by arm for DFS in IMpower010 along with the presentation of the associated hazards for each parametric model.

Figure 12: Hazard functions DFS - Exponential model

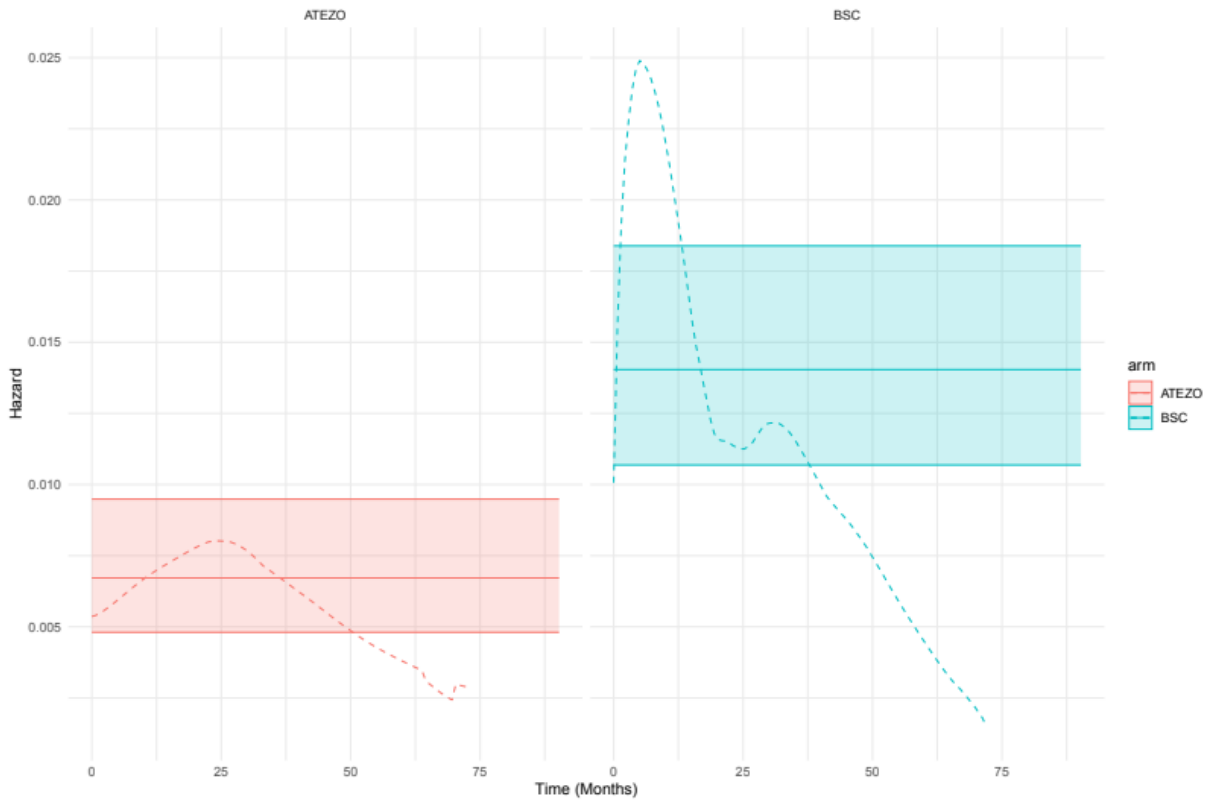


Figure 13: Hazard functions DFS - Weibull model

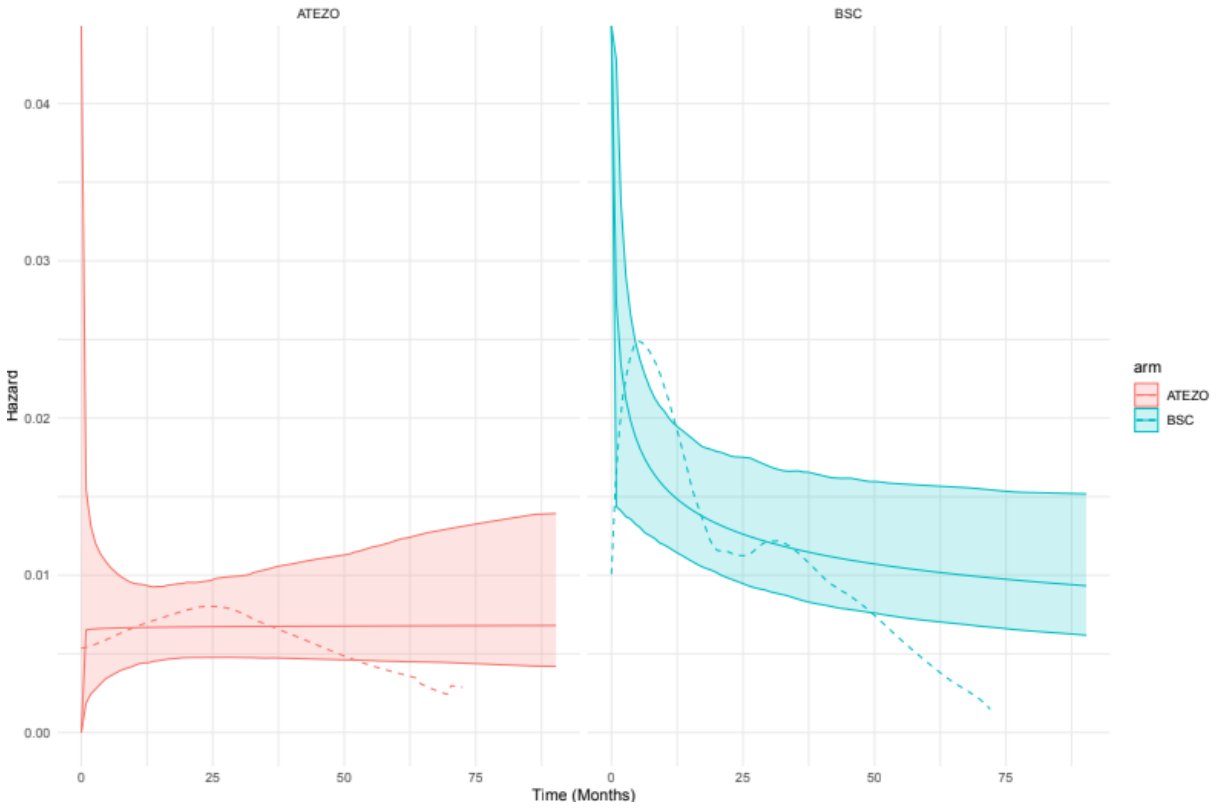


Figure 14: Hazard functions DFS - Gompertz model

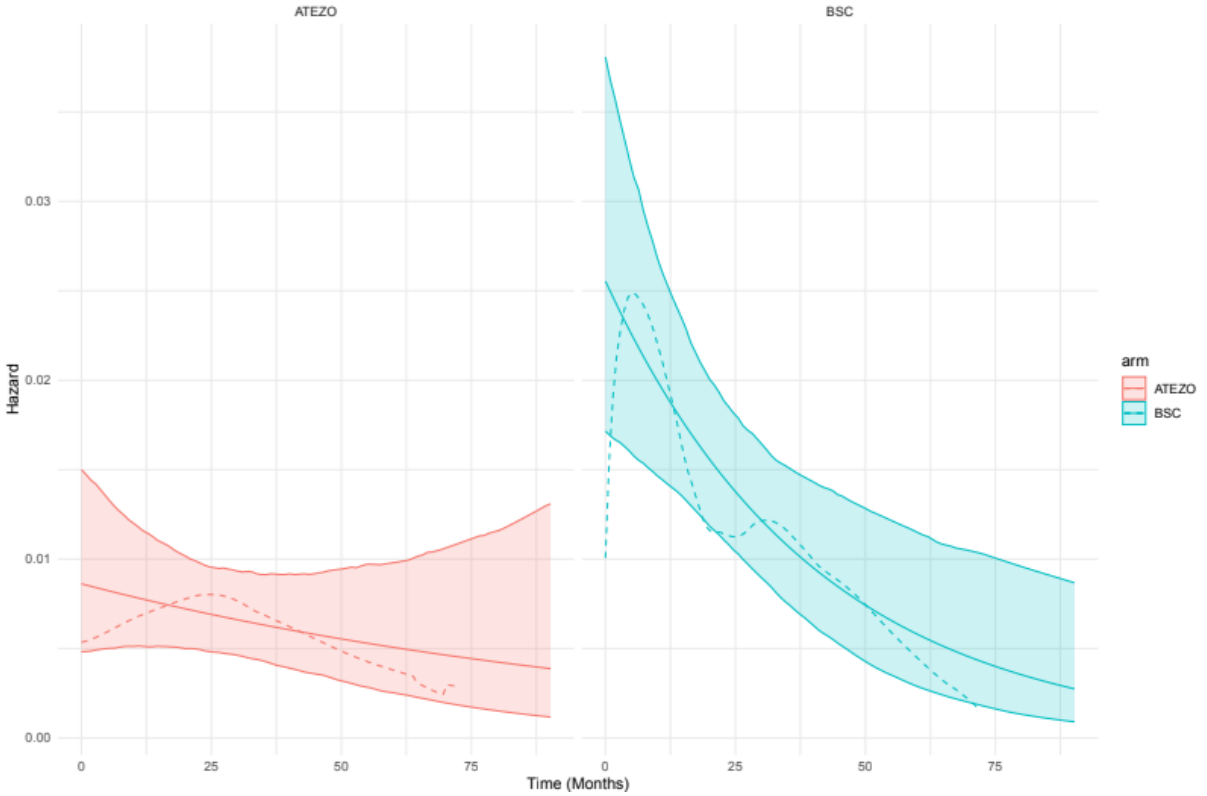


Figure 15: Hazard functions DFS - Gamma model

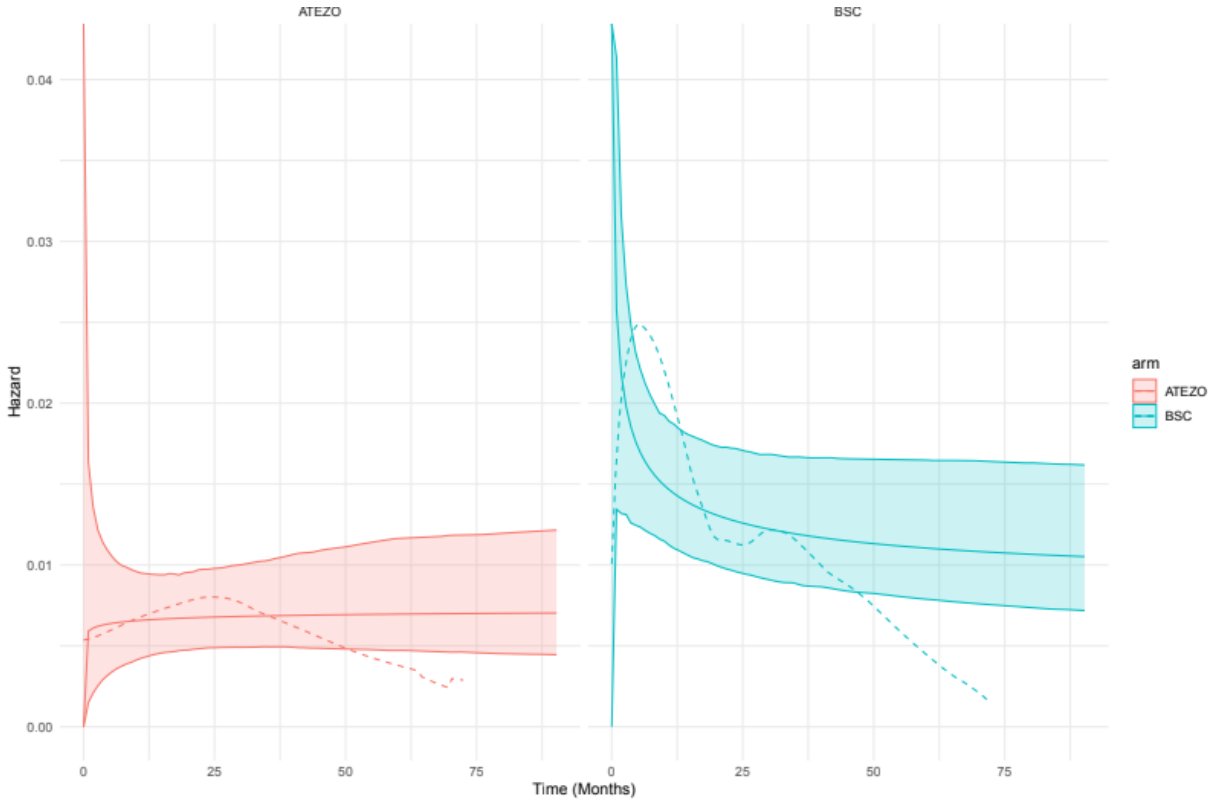


Figure 16: Hazard function DFS - Generalised gamma model

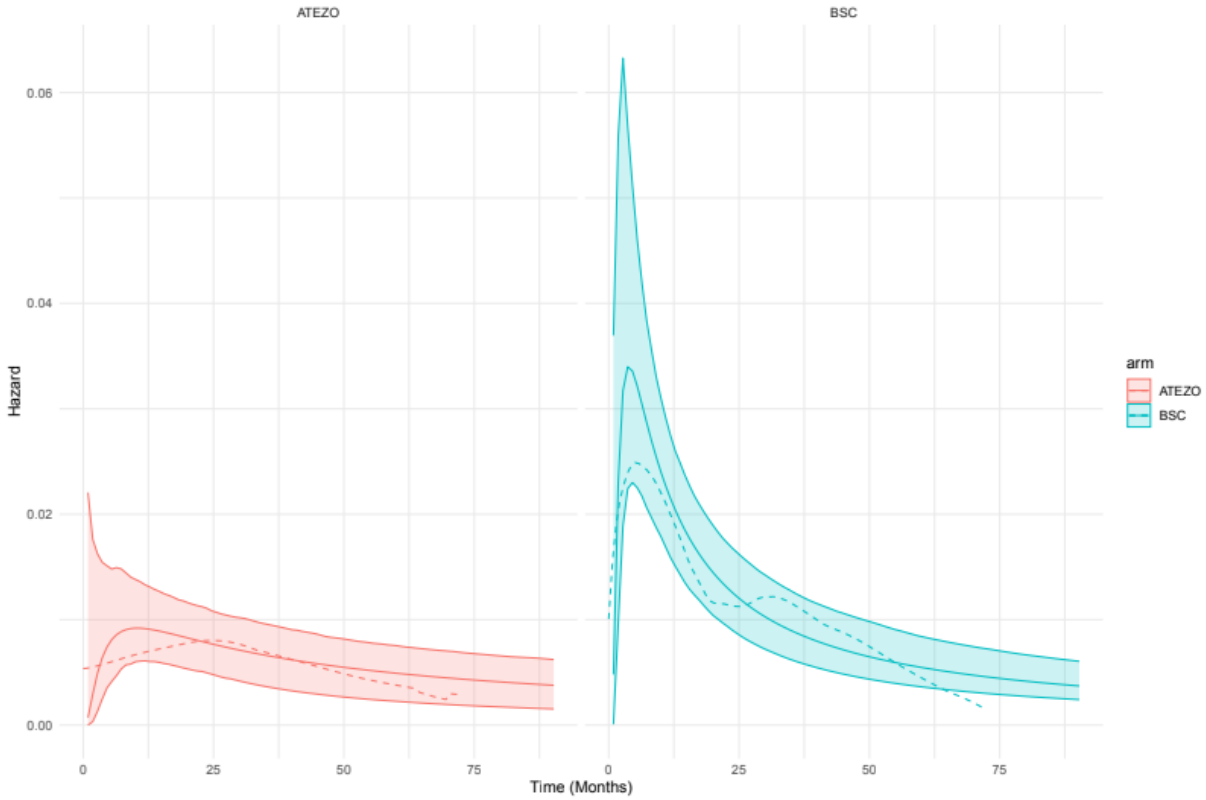


Figure 17: Hazard functions DFS - Log-normal model

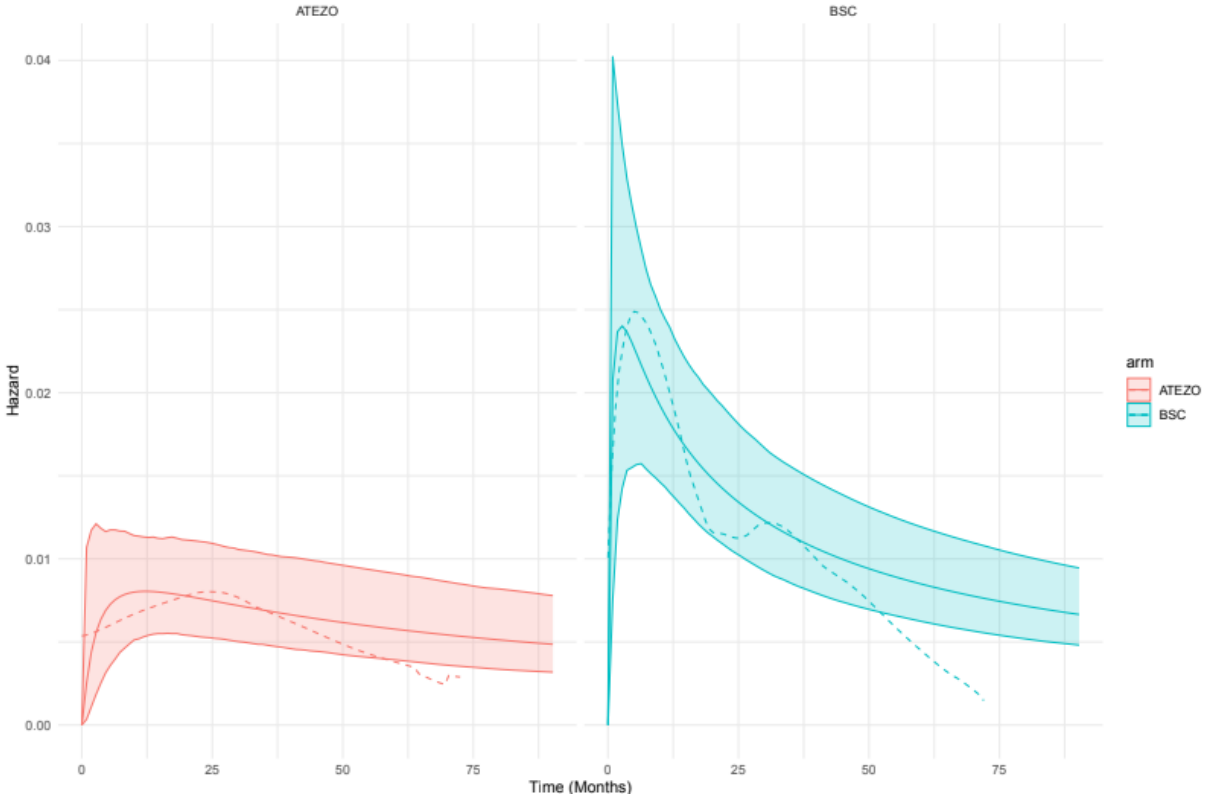
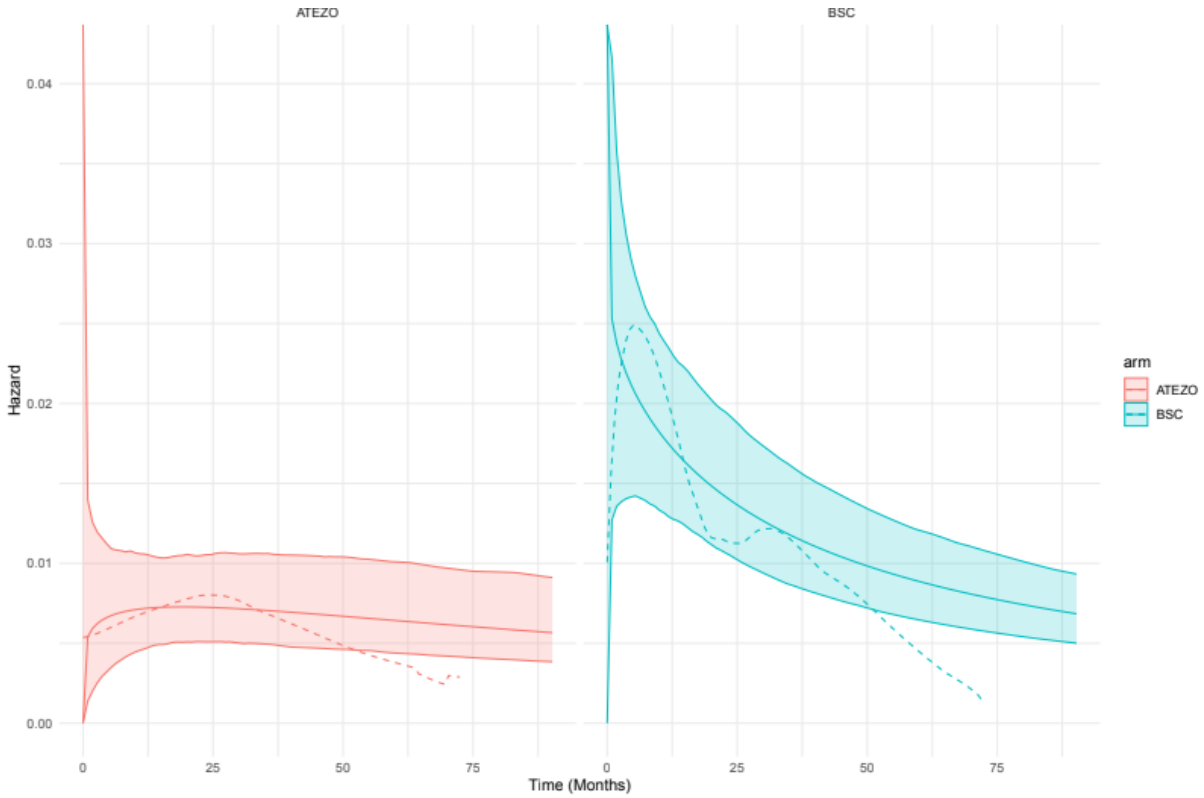


Figure 18: Hazard functions DFS - Log-logistic model



Section B: Clarification on cost-effectiveness data

Modelling questions

B1. **Priority:** Provide updated base case and key scenario analyses if there have been any changes made to the modelling based on the clarification process.

Please note before adapting the company base case based on the EAG questions, a few corrections were made to show the true base case of the company. By correcting B18 (cell referencing in the 'CMP' sheet), B20 (LYG undiscounted) and B24 (missing resource use). In addition, the administration costs were also updated and two different types of administration costs were applied for IV infusions; administration costs for an IV infusion at first attendance (SB12Z, NHSE reference costs 22-23) and subsequent cycles (SB15Z, NHSE reference costs 22-23). The incorrect company base case is presented in Table 1 and the updated company base case is presented in Table 2. The corrected base case will be used throughout questions B2-B24 to showcase either an updated company base case or scenario analyses.

Table 1: Incorrect company base

Technologies	Total costs	Total LYG	Total QALYs	Incremental costs	Incremental LYG	Incremental QALYs	ICER incremental (£/QALY)
Atezolizumab	[redacted]	[redacted]	[redacted]	[redacted]			
BSC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	2,428

Table 2: Corrected company base

Technologies	Total costs	Total LYG	Total QALYs	Incremental costs	Incremental LYG	Incremental QALYs	ICER incremental (£/QALY)
Atezolizumab	[redacted]	[redacted]	[redacted]	[redacted]			
BSC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	2,252
Pembrolizumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	dominant

After correcting the company base case, Table 3 shows the inputs used in the updated company base case. The company has changed 2 inputs: firstly, the cure point and proportion was updated from 5 years, assuming a 79% cure proportion to at 5 years, assuming a 89% cure proportion followed by at 7 years, assuming a 100% cure proportion. Further information on this change can be found in question B2. Secondly, the mode of administration for atezolizumab was adapted. Instead of assuming 100% of patients receive an atezolizumab subcutaneous injection (subcut), the company assumed that 50% of patients would receive subcut and 50% would receive an IV infusion. Further information can be found in question B19. The updated company base case is presented in Table 4. The resulting base case ICER when comparing atezolizumab to BSC is £3,233 per QALY gained and atezolizumab (PAS price) is dominant over pembrolizumab (list price).

Table 3: Input values changed in the updated company base case

Input	Old value	New value
Cure point and proportion	79%	89% at year 5 and 100% at year 7
Mode of administration for atezolizumab	100% subcut	50% subcut, 50% IV infusion

Table 4: Updated company base case

Technologies	Total costs	Total LYG	Total QALYs	Incremental costs	Incremental LYG	Incremental QALYs	ICER incremental (£/QALY)
Atezolizumab	[redacted]	[redacted]	[redacted]			[redacted]	
BSC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	3,233
Pembrolizumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	dominant

B2. Priority: The EAG believes that the 'cured' proportion within DFS should increase across time as the 'non-cured' population are more likely to have an event. Clarify reasons as to why this would not be the case. Clarify why the approach taken in the submission was preferred to using an explicit cure model with a cure fraction from day zero (using a mixture cure model). Note, the EAG is not asking the company to restructure the model to accommodate a mixture cure approach. Clarify what advantages the present approach (which assumes 79% of patients are cured after 5 years) has compared with using a distribution (for example a Gompertz in both arms) and assuming a 100% cure rate at a specified time point (for example 7 years in both arms). Whilst the EAG may not agree with NICE's position it notes that the FAD for TA823 states "*It agreed that it was appropriate to have differential cure timepoints between the 2 arms. The Cancer Drugs Fund clinical lead suggested that 1 to 2 years difference is plausible because most disease relapses occur after 12 months or at most after 18 months after the surgery and adjuvant treatment. Therefore, a cure timepoint of 6 years or 7 years for atezolizumab and a cure timepoint of 5 years for active monitoring was a reasonable assumption. The ERG provided analyses, which assumed these alternative cure timepoints. The committee concluded that there was significant uncertainty about the company's cure assumptions, and it would consider both of the ERG's approaches in its decision making.*" Can the company provide functionality in the model to allow differential cure points for atezolizumab and for BSC?

To respond to question B2, the company has broken up the question into two sections for clarity.

Company approach vs. mixture cure approach

A Markov model was used in the original adjuvant atezolizumab submission (TA823) as the follow-up period of IMpower010 in 2022 was not sufficiently long enough to inform a mixture cure model or the cure fraction. In 2022, NICE and the EAG deemed the company's model structure appropriate for decision-making and since TA823 a number of submissions were evaluated who also used a Markov model; alectinib for untreated ALK-positive advanced non-

small-cell lung cancer [TA1014] (recommended) (4), osimertinib for adjuvant treatment of EGFR mutation-positive NSCLC after complete tumour resection [ID5120] (5) and pembrolizumab for adjuvant treatment of resected non-small-cell lung cancer [ID3907] (recommended) (6). Although TA1014 focused on ALK-positive NSCLC and ID5120 focused EGFR-positive NSCLC, there are a few similarities that can be drawn between these appraisals and atezolizumab, such as the model structure, for adjuvant treatment of resected non-small-cell lung cancer (MA review of TA823) [ID6324].

Given that the follow-up may still not be sufficiently long enough to assess the extent of long-term survivorship, the current approach was not criticised by the EAG or NICE during the initial appraisal in 2022 (apart from criticism on exactly when a patient could be considered cured, and what proportion of patients would be cured [the company aims to resolve this uncertainty as outlined in the next section of this question]) and is consistent with other appraisals in the NSCLC adjuvant setting, a decision was made to not to use another approach to model the cure assumption.

Functionality for different cure points

To address some of the uncertainty regarding the cure point and proportion, the company has decided to take a pragmatic approach. Firstly, the company has updated their proportion at a 5 year cure point due to an incorrect interpretation of the Chaudhry T et al. (2023). Based on the paper, a 89% cure proportion was assumed at 5 years, which correlates with UK clinical expert opinion who estimate a 95% cure proportion at year 5. In addition, the first cure point of 5 years was chosen as clinicians unanimously agreed in a November 2024 clinical advisory board, where 6 clinicians were present, that the cure period starts after surgery and its duration is 5 years.

Nevertheless, to mitigate some of the uncertainty regarding the cure point and proportion, a linear increase was applied from 5 years at a 89% cure proportion to 7 years reaching a 100% cure proportion. This reduces significantly some of the uncertainty mentioned by the EAG. This change in cure point and linear increase in the proportion of patients cured from 5 years to 7 years has been included in the updated company base case. The resulting base case ICER when comparing atezolizumab to BSC is £3,233 per QALY gained and atezolizumab is dominant over pembrolizumab as seen in Table 5.

Table 5: Updated company base case (5 year, 89% proportion; 7 year time point, 100% proportion)

Technologies	Total costs	Total LYG	Total QALYs	Incremental costs	Incremental LYG	Incremental QALYs	ICER incremental (£/QALY)
Atezolizumab	[redacted]	[redacted]	[redacted]			[redacted]	
BSC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	3,233
Pembrolizumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	dominant

To further take a more conservative approach, a scenario analysis is presented below, which assumed no linear increase in cure point and proportion, and only assumed one single cure point and one single proportion; a 100%cure proportion at a 7 year time point. In the scenario analysis, comparing atezolizumab to BSC results in an ICER increase from £3,233 to 3,796 per QALY gained and atezolizumab remains dominant over pembrolizumab as seen in Table 6.

Table 6: Scenario: 7 years, 100% cure proportion

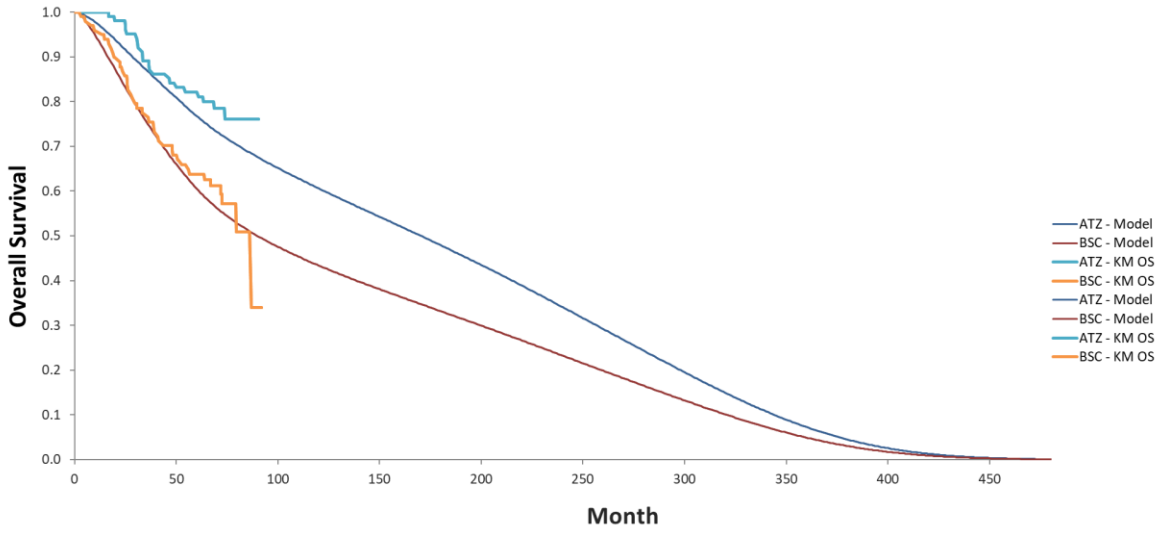
Technologies	Total costs	Total LYG	Total QALYs	Incremental costs	Incremental LYG	Incremental QALYs	ICER incremental (£/QALY)
Atezolizumab	[redacted]	[redacted]	[redacted]			[redacted]	
BSC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	3,796
Pembrolizumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	dominant

B3. Priority: In B.3.3.5 CS Document B, the DFS-derived OS curves are compared with data from the IMpower010 trial using the data cut-off 18 April 2022 (Figure 24). Please provide this comparison using the most recent data cut-off.

Figure 19 presents the updated OS and data cut from 26th January 2024 and compares the modelled and Kaplan Meier (KM) overall survival curves. Based on visual fit, it can be

assumed that the current model slightly underestimates OS. This is likely due to the conservative assumptions taken to adjust DFS; cure assumption, SMR and treatment waning effect.

Figure 19: Modelled OS vs. KM data OS



B4. **Priority:** Clarify whether the distribution for treatment discontinuation for atezolizumab in the PSA works as intended. The deterministic values in 'PSA parameters D12:D27 sum to 100% as expected, however the probabilistic values (M12:M27) which are sampled using independent Beta distributions add up to different values each time and a range of 92% to 108% has been observed in a small number of samples. We suspect that this is an error and suggest using a Dirichlet distribution, or as an approximate fix all values be multiplied by a common factor to ensure a sum of 100%.

The CEM has been updated to ensure that the probabilistic values of the treatment discontinuation parameters for atezolizumab correctly sum up to 100% at the end of the 16 treatment cycles.

The changes made include:

1. Moving the probabilistic values originally generated in PSA Parameters!M12:M27 to PSA Parameters!N12:N27.
2. Generation of new probabilistic values in PSA Parameters!M12:M27 by adjusting the probabilistic values generated in PSA Parameters!N12:N27 by diving the value generated in each cell (e.g. N12) by the sum of the total value (i.e. N12:N27). These are the values that the CEM now uses to inform the treatment discontinuation.

B5. **Priority:** The sum of the proportion of patients 'incident 'off-treatment' do not add up to 100% in the PSA (cells M12:M27 in the 'PSA parameters sheet'). This is because the incident proportions are sampled as independent Beta distributions. Please correct this.

The company believes question B5 can be resolved by B4. Please refer to question B4.

B6. **Priority:** The Dirichlet used in the 'PSA parameters' sheets do not appear to be implemented correctly as the individual values do not sum to 1. For example, see cells M33:M36 or M38:M41.

The CEM already includes the logic needed to ensure that the sum of the probabilistic values for these parameters do not add up to less or greater than 100%. Please refer to the formulas in the following cells:

1. Treatment Description! (G92, J92, M92, P92, G94, J94, M94, P94, G109, J109, M109, P109, G137, J137, M137, P137, G139, J139, M139, P139, G154, J154, M154, P154, G182, J182, M182, P182, G184, J184, M184, P184, G198, J198, M198, P198).
2. Efficacy! (E73:E75, E78:E80, F85:F87, F92:F94).

B7. Clarify the rationale for providing list price ICERs. The EAG only intends to present results using the PAS discount.

The company has provided list price ICERs for completeness, however, for decision-making the company agrees that the PAS discounted ICER results are the relevant ICERs to determine cost-effectiveness of atezolizumab against standard of care. For the pembrolizumab analyses in question A4, only the PAS ICERs were provided.

B8. In references 1, 18, and 19 of the CS Document B, advisory board meetings are referenced to validate model assumptions, please could the company provide the minutes or meeting reports from these advisory board meetings?

The company has provided the advisory board meeting minutes in document Atezolizumab_IMpower010_Advisory_Board_Meeting_Minutes_November_2024.

B9. Clarify whether Figure 17 is correct? it implies you can have a second metastatic recurrence when not on treatment which was stated not to be the case and does not occur in the model.

CS Figure 17 illustrates the structure of the model and theoretically, the model allows for patients who have a 1L metastatic recurrence and are not treated to progress to 2L metastatic recurrence. However, this transition was not activated for this submission, as there is a lack of evidence on the types of events untreated patients experience. Thus, the CEM assumes that the only health state untreated 1L metastatic patients can transition to is Death. It would

be implausible to assume that patients who have a 1L metastatic recurrence and are not treated, progress to 2L metastatic recurrence. Nevertheless, CS Figure 17 presents the overall model structure for completeness.

B10. Clarify the usefulness of comparing percentages with disease-free survival at 10 and 20 years (as done above Table 19 and Table 20) when a cure proportion is applied at 5 years. The EAG believes that the distributions are likely irrelevant beyond the assumed cure point.

The company agrees that there might be limited usefulness in presenting these numbers, however, the company included these for completeness.

B11. Clarify the text in Table 21, The EAG interpreted this as 79% had conditional DFS after 8 years as there had been 3 years disease-free survival and then a further 5 years. If this interpretation is correct, the conditional DFS proportion at 5 years would be 89%.

Upon review of the paper, the company agrees that based on the paper "Conditional survival analysis of patients with resected non–small cell lung cancer". Figure E2 shows that 2Y-CS3 corresponds to 5 year conditional DFS, which is 89%, which is consistent with what the EAG states. CS3 DFS at 5 years was 79%, which corresponds to 8 years DFS and is beyond the cure point the company is assuming. Therefore, in the base case the company will assume that at a 5 year cure point, the proportion of patients that are cured are 89%. In addition, as mentioned in B2 and to take a pragmatic approach, the updated base case will include a second cure point, which assumes 100% cure proportion at year 7. The resulting base case ICER when comparing atezolizumab to BSC is £3,233 per QALY gained and atezolizumab is dominant over pembrolizumab as can be seen in Table 7.

Table 7: Updated company base case

Technologies	Total costs	Total LYG	Total QALYs	Incremental costs	Incremental LYG	Incremental QALYs	ICER incremental (£/QALY)
Atezolizumab	[redacted]	[redacted]	[redacted]			[redacted]	
BSC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	3,233
Pembrolizumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	dominant

B12. We agree with the company that incorporating potential disutilities associated with AEs in the model, and the administration costs for treatments that aren't atezolizumab or

nintedanib into the model will have no material impact on the ICER. However, in order to show this to the committee, provide scenario analyses illustrating this lack of impact.

The CEM has been updated to allow it to consider the disutility of AEs and allow for a split in the use of atezolizumab via IV and subcut to adjust its cost of administration.

The changes made include (AE disutilities):

1. Inclusion of an option that allows the CEM to account for the disutility of AEs (opt_cqb12), variables that calculate the monthly disutility associated with each AE, and variables that calculate the total disutility of AEs associated with each treatment option (d_ae_atz, d_ae_bsc, d_ae_place1, d_ae_place2, d_ae_lr_tx1, d_ae_lr_tx2, d_ae_lr_tx3, d_ae_lr_tx4, d_ae_m1_tx1, d_ae_m1_tx2, d_ae_m1_tx3, d_ae_m1_tx4, d_ae_m2_tx1, d_ae_m2_tx2, d_ae_m2_tx3, d_ae_m2_tx4).
2. Inclusion of additional columns (EU:EY) of the ATZ and CMP tabs that separately calculate QALYs when accounting for the disutility of AEs.
3. Updating of formulas in the Results Table! (G39, G41, G43, G45, G47, H39, H41, H43, H45, H47) to allow the newly calculated QALYs to feed into the results.

A standard disutility rate of 0.1 was assumed and applied to all the health states to test the sensitivity to the results. The ICER remains the same as the company updated base case, £3,233. Atezolizumab remains dominant over pembrolizumab as can be seen in Table 8. Note the ICER does not change when applying disutilities. Refer to tab “ATZ”, columns EN7:ER7 and EU7:EY7 in the model. Applying disutilities has a minute impact on the Quality Adjusted Life Years gained and as a result does not have an impact on the ICER.

Table 8: Scenario analyses disutilities

Technologies	Total costs	Total LYG	Total QALYs	Incremental costs	Incremental LYG	Incremental QALYs	ICER incremental (£/QALY)
Atezolizumab	[redacted]	[redacted]	[redacted]			[redacted]	
BSC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	3,233
Pembrolizumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	dominant

As mentioned in B1, the administration costs were adjusted as part of the corrected and updated company base case. Table 9 shows the updated administration costs.

Table 9: Updated administration costs for all treatments given by IV infusion

Drug	Type of administration		NHS reference code	Cost per administration	Source
All therapies (apart from nintedanib and atezolizumab subcut)	Deliver simple parenteral chemotherapy at first attendance	Daycase and Reg day/night	SB12Z	£431.16	NHSE reference costs 2022-2023, Day case/ reg night
All therapies (apart from nintedanib and atezolizumab subcut)	Deliver Subsequent Elements of a Chemotherapy Cycle	Daycase and Reg day/night	SB15Z	£392.61	NHSE reference costs 2022-2023, Day case/ reg night

The resulting base case ICER when comparing atezolizumab to BSC is £3,233 per QALY gained and atezolizumab is dominant over pembrolizumab as can be seen in Table 10 below.

Table 10: Updated administration costs and company base case

Technologies	Total costs	Total LYG	Total QALYs	Incremental costs	Incremental LYG	Incremental QALYs	ICER incremental (£/QALY)
Atezolizumab	[redacted]	[redacted]	[redacted]			[redacted]	
BSC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	3,233
Pembrolizumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	dominant

B13. Clarify why correlations were not used in sampling utility values from the multivariate regression model.

The health state utility values in the DFS and post-DFS health states were not correlated when sampling values in the PSA as the covariance structure between them is not known. Neither Grutters et al. (2010) or Chouaid et al. (2013) presented this evidence. Therefore, correlations were not used in sampling utility values from the multivariate regression model.

B14. Clarify the rationale to have different probabilities of death for those with a PFS event dependent on non-metastatic recurrence treatment - this would appear to contradict the decision in the base case to pool rates for atezolizumab and BSC. Perform an analysis where the probabilities are set equal across all options for this group and where the probabilities are set equal across all options in the metastatic recurrence progression. Further, these probabilities should all use the same sample in the PSA. This does not currently happen when treatments are assumed to have the same value, for example in cell M126 and cell M129 in the 'PSA parameters sheet' and also in cells M127:M128

The CEM has been updated to reflect the scenario and PSA changes requested by the EAG. In the base case, the CEM now uses the same probabilistic values to inform the proportion of patients who experience progression versus death as their PFS event for treatments who use the same deterministic values for this parameter. In addition, the CEM includes a scenario analysis, which assumes the same probability of death for patients that are progressing in the metastatic setting.

The changes made include to the PSA:

1. The probabilistic values of p_lr_tx1_prog and p_lr_tx4_prog now come from the same source (i.e. PSA Parameters!M126).
2. The probabilistic values of p_lr_tx2_prog and p_lr_tx3_prog now come from the same source (i.e. PSA Parameters!M127)

3. The probabilistic values of p_m1_tx1_prog, p_m1_tx2_prog, and p_m1_tx3_prog now come from the same source (i.e. PSA Parameters!M133).
4. The connections between PSA Parameters! (M128, M129, M134, M135) and Efficacy tab have been removed.

The changes made to the probabilities of death for patients who experience a PDS event:

1. In the Efficacy tab, cells X139:AJ152 and X195:AJ208, a module has been included that consists of an option that allows the model to be restricted to using the same proportions across treatment options within the same health state (opt_cqb14_a), a list of proportions that can be used when this restriction is applied, and options to inform which proportions to use from these lists.

2. The formulas in p_lr_tx1_prog, p_lr_tx2_prog, p_lr_tx3_prog, p_lr_tx4_prog, p_m1_tx1_prog, p_m1_tx2_prog, p_m1_tx3_prog and p_m1_tx4_prog have been amended to allow for the proportions from the restriction to be used.

Table 11 presents a scenario analysis, which assumes the probabilities of death are set equal across all treatment options in the non-metastatic and metastatic setting. The ICER increases slightly from the company updated base case of £3,233 per QALY gained to £3,245 per QALY gained (+£12 ICER) when comparing atezolizumab to BSC. Atezolizumab remains dominant over pembrolizumab.

Table 11: Scenario: probability of death set equal in the non-metastatic and metastatic state

Technologies	Total costs	Total LYG	Total QALYs	Incremental costs	Incremental LYG	Incremental QALYs	ICER incremental (£/QALY)
Atezolizumab	[redacted]	[redacted]	[redacted]			[redacted]	
BSC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	3,245
Pembrolizumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	dominant

B15. Comment on the appropriateness of assuming the standard error to be 10% of the mean for utility of patients in DFS who are off treatment. There is a large variation in this value

and from a small number of samples a range of 0.64 to 0.96 was observed suggesting the standard error is too large.

Note that the appropriate S.E. were sourced from literature and formula was updated to use the correct S.E. values for the scenarios analyses. 0.754 for the lower value input and 0.867 for the higher value input.

The changes made include:

1. Correcting the formula in PSA Parameters!G1399 to =IF(Utility!F14 = "", "", Utility!F14)

These changes result in a scenario can be seen in Table 12. In all scenarios, atezolizumab remains cost-effective compared to BSC. No utility values scenario results are presented for pembrolizumab as in all scenarios atezolizumab is dominant over pembrolizumab. Refer to the Appendix, Section B.3.8.2., for further information on the deterministic sensitivity analysis and the net monetary benefit (NMB) of atezolizumab vs. pembrolizumab.

Table 12: Scenario analyses: utility values

	Lower value	Higher value	Lower value ICER	Higher value ICER
Base case	3,233			
Utility Values while Disease-Free - On-treatment - ATZ	0.716	0.826	3,320	3,149
Utility Values while Disease-Free - Off-treatment - ATZ	0.754	0.0867	4,455	2,523
Utility Values while Disease-Free - Off-treatment - BSC	0.754	0.0867	2,658	4,159
Utility Values after Recurrence - intercept	0.792	0.809	3,195	3,271
Utility Values after Recurrence - stageIV	-0.105	0.025	3,219	3,252

B16. Add functionality so that the period of HRU can be set differently in each arm and use 5 years for BSC and 6 years for ATZ. Clinicians state that patients are likely to be followed up for one additional year if atezolizumab treatment is provided.

The CEM has been updated to allow for follow-up HCRU and costs to be restricted to 5 years follow-up for best supportive care and 6 years for pembrolizumab and atezolizumab.

The changes made include:

1. Inclusion of a module in the Direct Costs tab that contains an option that allows this restriction to be switched on (opt_cqb16), and parameters defining at what time point the restriction should be activated separately for ATZ and BSC (t_hcru_dfs_atz, t_hcru_dfs_bsc).

2. Amendment of formulas in column DI in the ATZ and CMP tab to allow for follow-up HCRU and costs to be restricted up to a certain point in time if opt_cqb16 is switched on."

Table 13 shows the scenario analyses results. The ICER increase slightly from the company updated base case £3,233 to £3,314 (+£81 ICER) when comparing atezolizumab to BSC. Atezolizumab remains dominant over pembrolizumab.

Table 13: Scenario analysis, follow-up costs applied for 6 years to atezolizumab and for 5 years to pembrolizumab and BSC

Technologies	Total costs	Total LYG	Total QALYs	Incremental costs	Incremental LYG	Incremental QALYs	ICER incremental (£/QALY)
Atezolizumab	[redacted]	[redacted]	[redacted]			[redacted]	
BSC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	3,314
Pembrolizumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	dominant

B17. Clarify why the costs of non-lung cancer death is set to zero as it is likely that other causes also have costs (heart attacks, other cancers, respiratory diseases etc). Provide estimations of these average costs for non-lung cancer death and explore in sensitivity analyses.

The end-of-life cost for all-cause mortality was applied in a scenario analysis. This was sourced from the PSSRU 2023 report (8), Table 7.2.2: Cost of hospital and social care services by diagnostic group per decedent in the final year of life. The cost for “all people” was assumed, which results in £12,726. Note that the company has not included all-cause mortality

costs in their base case as this cost was not applied to any other appraisals in the adjuvant setting, therefore, it should also be excluded in ID6324.

When applying the all-cause mortality cost in scenario, the ICER increases slightly from the company updated base case £3,233 to £3,748 (+£515 ICER) when comparing atezolizumab to BSC. Atezolizumab remains dominant over pembrolizumab as can be seen in Table 14.

Table 14: Scenario analysis cost associated with all-cause mortality

Technologies	Total costs	Total LYG	Total QALYs	Incremental costs	Incremental LYG	Incremental QALYs	ICER incremental (£/QALY)
Atezolizumab	[redacted]	[redacted]	[redacted]			[redacted]	
BSC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	3,748
Pembrolizumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	dominant

B18. There appears to be a cell referencing error in DG13 in the 'CMP' sheet where D12 is used instead of D13. This error propagates through all other cells as the formula is dragged down. This makes a very small change to the ICER (£0.07).

The formulas in column DG of the CMP tab have been corrected. These changes result in the Company's corrected base case as mentioned in B1.

Table 15.

Table 15: Corrected company base case analysis

Technologies	Total costs	Total LYG	Total QALYs	Incremental costs	Incremental LYG	Incremental QALYs	ICER incremental (£/QALY)
Atezolizumab	[redacted]	[redacted]	[redacted]			[redacted]	
BSC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	3,233
Pembrolizumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	dominant

B19. Perform an analysis assuming 100% of atezolizumab is provided as IV rather than subcutaneous. Comment on the change in the ICER if IV atezolizumab was provided every 4

weeks rather than every 3, but with the same number of cycles, which is a schedule known to be used by clinical advisors to the EAG.

The changes made include (ATZ administration cost):

1. Inclusion of variables that define the administration cost of IV and subcutaneous (subcut) atezolizumab (Direct Costs!W19:20).
2. Inclusion of variables that define the proportion of patients on IV and subcut atezolizumab (Direct Costs!W23:24).
3. Inclusion of formula in Direct Costs!N14 to allow for the administration cost of atezolizumab to be defined by the mix of patients who would receive atezolizumab via IV and subcut.

Expected proportions of subcut were sourced from company data, [redacted] Therefore, the company has assumed a 50% subcut proportion in its updated base case. Note the proportion of subcut is likely to increase in the future especially since atezolizumab in the adjuvant setting is given as a monotherapy. Table 16 shows the requested scenario by the EAG, assuming 100% IV and 0% subcut. The ICER increases slightly from the company updated base case £3,233 per QALY gained to £4,453 per QALY gained (+£1,220) when comparing atezolizumab to BSC. Atezolizumab remains dominant over pembrolizumab.

Table 16: 100% IV infusions for atezolizumab

Technologies	Total costs	Total LYG	Total QALYs	Incremental costs	Incremental LYG	Incremental QALYs	ICER incremental (£/QALY)
Atezolizumab	[redacted]	[redacted]	[redacted]			[redacted]	
BSC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	4,543
Pembrolizumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	dominant

In addition, a scenario was explored, which assumed atezolizumab is administered every 4 weeks rather than every 3 weeks for the same amount of cycles and 100% of patients receive an atezolizumab IV infusion rather than a subcutaneous injection. The ICER increases slightly from the company updated base case £3,233 per QALY gained to £4,522 per QALY gained (+£1,289) when comparing atezolizumab to BSC. Atezolizumab remains dominant over pembrolizumab as can be seen in Table 17.

Table 17: Scenario analyses patients receive atezolizumab every 4 weeks and 100% of IV atezolizumab

Technologies	Total costs	Total LYG	Total QALYs	Incremental costs	Incremental LYG	Incremental QALYs	ICER incremental (£/QALY)
Atezolizumab	[redacted]	[redacted]	[redacted]			[redacted]	
BSC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	4,522
Pembrolizumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	dominant

B20. Clarify why Life Year Gained values are discounted. Where these values are reported as results, provide undiscounted values.

This correction has been applied to the CEM. The following changes in the CEM have been made:

1. The calculations in columns EI:EL of the ATZ and CMP tabs are no longer discounted by column EH.
2. The calculations in columns EN:EQ of the ATZ and CMP tabs are now directly discounted by column EH.

The resulting base case ICER when comparing atezolizumab to BSC is £3,233 per QALY gained and atezolizumab is dominant over pembrolizumab as can be seen in Table 18.

Table 18: Corrected company base case

Technologies	Total costs	Total LYG	Total QALYs	Incremental costs	Incremental LYG	Incremental QALYs	ICER incremental (£/QALY)
Atezolizumab	[redacted]	[redacted]	[redacted]			[redacted]	
BSC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	3,233
Pembrolizumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	dominant

B21. Typo in Table 31, should '1L progression free' be 'first line PD' which has a standard error and *p*-value in the Chouaid paper? Also confirm how the sentence immediately prior to Table 31 which lists values of 0.73, 0.74 and 0.66 relates to the utility values in the model for local recurrence (0.77) and metastatic disease (0.70). Clarify why the utilities associated with

the last 3 rows in Table 31 are not included in the modelling. If appropriate, perform a sensitivity analysis incorporating these values.

Firstly, the company can confirm that 1L progression free is a type and it should state first-line PD. Secondly, estimates on the effect of progression while on first-line metastatic treatment, and progression or stable disease (i.e. progression-free) while on second-line metastatic treatment on health state utility values were not considered. This is because it is shown in Chouaid et al. (2013) that the effects of these factors were not statistically significant at the 1%, 5% or 10% levels of significance and therefore not deemed appropriate to be included in the model.

B22. Please provide further details on how SACT data were used within the modelling. Provide an analysis where patient characteristics match those from the SACT dataset. Compare the OS results from the model in this scenario with OS from the SACT data if possible.

The company reviewed the SAC-T data report and included 2 of the patient characteristics from the report which were relevant to the IMpower010 cost-effectiveness model; age and gender. Table 19 below compares OS results using the median age of 67.00 years and the proportion of males (52.00%) from the SAC-T data report and compares it against the modelled OS survival using the IMpower010 mean age of 61.20 and the proportion of males (66.90%). Based on Table 19, you can see that the modelled OS (using the IMpower010 patient characteristics) results are similar to the modelled OS when using the patient characteristics from the SAC-T data further supporting the robustness and appropriateness of the model.

Table 19: OS at 6, 12, 18 and 24-month intervals

Time period	Overall survival SAC-T data (%)	Overall survival (model)
6 months	99% [95% CI: 98%, 100%]	99.0%
12 months	95% [95% CI: 92%, 98%]	97.0%
18 months	93% [95% CI: 88%, 97%]	94.5%
24 months	87% [95% CI: 78%, 96%]	91.6%

B23. For transparency, confirm whether there is a limitation in the methodology used for 'rechallenging' patients after progressing from local recurrence to metastatic recurrence. It is believed that the eligibility of patients for rechallenge is based on time since a DFS event from the initial treatment rather than related to the time to progression from durvalumab or

pembrolizumab. The EAG believes that if this is a limitation the impact would be negligible so is not requesting any changes to the model, just clarification that our understanding is correct.

The company can confirm that the EAG's understanding is correct. The company decided not to apply a rechallenge rule for local recurrence to metastatic recurrence, as it would overcomplicate the model and the scenario analyses. Applying an additional rechallenge rule would require additional tunnel states and significantly increase the complexity of the model whilst having a minimal impact on the ICER results as noted by the EAG.

B24. The costs for GP Home visits and Therapist visit (cells F60 and F61 in the 'Direct Costs' sheet) are set to zero. Clarify whether it is intentional. If not, please replace with appropriate costs. Clarify how the cost for a 10-minute GP appointment was estimated to be £50.50. Table 9.4.2 of Jones et al (Unit Costs of Health and Social Care 2023) reports a maximum cost of £49.

GP home visit and Therapist visit cost in the 2L metastatic setting

Cells F60 and F61 were set unintentionally to 0 and this has been corrected. The cost associated with these resources can be seen in Table 20 below.

Table 20: GP Home visits and therapist visit cost

Resource	Resource use reference	Unit cost reference (£)	Unit cost reference
GP home visit	UK clinical expert opinion	123.43	PSSRU 2016, p.145: Cost per home visit including 11.4 minutes for consultations and 12 minutes for travel (from TA531, inflated using the Bank of England inflation calculator)
Therapist visit	UK clinical expert opinion	52.00	PSSRU 2023, Community occupational therapist (local authority) with qualifications, page 77

GP visit cost in all health states

In addition, the EAG noted correctly that since the GP visit only lasts 10 minutes then the total GP visit cost should be divided by 6 (49/6) , which results in a GP visit cost of £8.17. Updating these resources costs results in the company's corrected base case. The resulting base case

ICER when comparing atezolizumab to BSC is £3,233 per QALY gained and atezolizumab is dominant over pembrolizumab as can be seen in Table 21

Table 21: Corrected company base case

Technologies	Total costs	Total LYG	Total QALYs	Incremental costs	Incremental LYG	Incremental QALYs	ICER incremental (£/QALY)
Atezolizumab	[redacted]	[redacted]	[redacted]			[redacted]	
BSC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	3,233
Pembrolizumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	dominant

Section C: Textual clarification and additional points

Typographical questions

C1. Table 36. Should the numbers in the PAS price column be CIC?

This is correct, CS Table 36 should have been marked as CIC as can be seen below in Table 22.

Table 22: Cost per month atezolizumab (PAS price)

Cycle	Cost per month, PAS price (£) (atezolizumab)	Cost per month, list price (£) (atezolizumab)
1	[redacted]	3,813.87
2	[redacted]	3,667.18
3	[redacted]	3,557.17
4	[redacted]	3,373.81
5	[redacted]	3,300.46
6	[redacted]	3,227.12
7	[redacted]	3,227.12
8	[redacted]	3,117.11
9	[redacted]	3,080.43
10	[redacted]	3,080.43

11	[redacted]	2,970.42
12	[redacted]	2,933.75
13	[redacted]	2,897.07
14	[redacted]	2,860.40
15	[redacted]	2,860.40
16	[redacted]	2,823.73
17	[redacted]	-
Total treatment cost per year	[redacted]	50,790.48

C2. The EAG believes there is a typographical error in Table 49 relating to utilities in the base case. We believe that the utility for BSC and atezolizumab off treatment should be 0.81, with atezolizumab on-treatment being 0.77 as used in the modelling.

Yes, this is correct. The correct utility values can be found in Table 23.

Table 23: Company base case utility values

Utilities – base case			
Disease-free survival			
On-treatment atezolizumab	0.77	Grutters at al. 2010	Section B.3.4.1
Off-treatment atezolizumab	0.81	Chouaid et al. 2013	
Off-treatment BSC	0.81	Chouaid et al. 2013	
On-treatment pembrolizumab	0.77	Grutters at al. 2010	
Off-treatment pembrolizumab	0.81	Chouaid et al. 2013	
Non-metastatic recurrence			
Intercept	0.77	Chouaid et al. 2013	Section B.3.4.2
First-line metastatic recurrence			
Stage IV	-0.07	Chouaid et al. 2013	Section B.3.4.2
Second-line metastatic recurrence			
Stage IV	-0.07	Chouaid et al. 2013	Section B.3.4.2

C3. The EAG believes there is a typographical error in cell BG13 of the ATZ workbook, which contains 'Ref#' and was probably intended to be BG12. This has no impact on the model results.

Yes, this is correct. This has been corrected in the updated model.

Appendix – Additional pembrolizumab analysis

B.2.8 Meta-analysis

As no further Phase III RCTs studying the efficacy and safety of atezolizumab for adjuvant treatment of resected NSCLC were found, no meta-analysis was conducted.

B.2.9 Indirect and mixed treatment comparisons

- **A Network Meta Analysis (NMA) was conducted to assess the comparative efficacy between pembrolizumab and atezolizumab**
- **3 relevant studies were identified for the NMA: IMpower010, PEARL and CANOPY-A.**
- **PEARLS / KEYNOTE-091 and its sample were similar to the reference trial IMpower010. CANOPY-A, in contrast, did evidence some information gaps. As a result, due to the similarity between PEARL and IMpower010, PEARL was included in the ITC network and CANOPY-A was excluded in the ITC.**
- **The Bayesian approach was chosen to model the NMA results**
- **Fixed-effects models were preferred over random-effects models since estimates of between-study heterogeneity (tau) were highly sensitive to the choice of prior distribution in the random-effects model due to the insufficient data points**
- **The mean posterior HR comparing atezolizumab to pembrolizumab for DFS is 0.63 (95% CrI: 0.35, 1.04)**

IMpower010 compared the efficacy and safety of atezolizumab and best supportive care. Randomised Phase III trial data comparing atezolizumab with pembrolizumab was not available at the time of submission. To inform this comparison and explore estimates of relative efficacy and safety, a network meta-analysis (NMA) was conducted to identify relevant studies for use in the indirect comparison with atezolizumab. The NMA results are used to assess the efficacy and safety of

atezolizumab versus pembrolizumab. Full details of the NMA results are presented in Appendix M.

B.2.9.1 Identification and selection of relevant studies

The following section reports on the results of the Feasibility Assessement (FA) and identification and selection of the relevant studies. Of the 67 trials identified in the SLR, 64 studies were excluded from the FA as seen in Table 24. Examination of these trials indicated that although platinum-based chemotherapy was among treatments investigated, these adjuvant chemotherapy trials compared to either observation only or to other adjuvant chemotherapy regimens (e.g., of different dosing schedules). No new investigational treatments and no additional connectivity were added to the master network. Finally, no information of PD-L1 expression was available in these trials.

Table 24: Summary of trials not considered (64 RCTs)

Treatment class	Investigational treatments	No. of trials	Rationale for no further consideration
Adjuvant chemotherapy regimens	platinum doublets, gemcitabine, S-1, UFT	38	Standard of care; however, all studies compare to observation only or to other chemotherapy regimens; no information on PD-L1 subgroups; no additional connectivity to network
Targeted therapies (TK/ALK inhibitors)	afatinib, alectinib, erlotinib, gefitinib, icotinib, pazopanib	18	Not standard therapy; interventions not of interest due to different drug class; no additional connectivity to network; no information on PD-L1 subgroups
Chemoradiotherapy	Post-operative radio therapy (PORT), post-operative concurrent radio chemotherapy (POCRT)	6	Not standard therapy; interventions not of interest; no additional connectivity to network; no information on PD-L1 subgroups
MAGE-A3 immunotherapy	MAGE-A3 immuno-therapeutic	2	Not standard therapy; intervention not of interest due to different drug class; no additional connectivity to network; no information on PD-L1 subgroups

The remainder of the trials investigated targeted therapies (including TK inhibitors), chemoradiotherapy, or MAGE-A3 antigen-specific cancer immunotherapy. Any studies related to these interventions were excluded as they are not considered

standard therapy or have been discontinued, belong to different drug classes, have differing proposed mechanisms of action, do not provide information on PD-L1 subgroups and/or do not provide any additional connectivity in the master network; therefore, they are not considered further.

Out of the 67 trials, three RCTs that investigate immunotherapies were deemed relevant for this NMA and were included in the FA as seen in Table 25. Particular attention has been given to pembrolizumab, as this comparator is in a similar treatment class of immune checkpoint inhibitors to atezolizumab.

Table 25: Trials included in master network (3 RCTS)

Trial	Intervention arm	Treatment class	Control arm	Definition of control arm	Timing of randomisation	Adjuvant chemotherapy received	Stratification factors
IMpower010	Atezolizumab	PDL-1 inhibitor	Best supportive care (BSC)	No treatment other than 16 cycles of best supportive care which included observation and regular scans for disease recurrence	Post adjuvant chemotherapy	All received as per eligibility criteria	Sex Tumour histology Disease stage PD-L1 expression
PEARLS / KEYNOTE-091	Pembrolizumab	PD-1 inhibitor	Placebo	Saline administered Q3W for 18 doses	Mixed (post-surgery and post adjuvant chemotherapy)	Optional; 86% received	Disease stage Adjuvant chemotherapy PD-L1 expression Geography
CANOPY-A	Canakinumab	Interleukin-1β inhibitor	Placebo	Matching placebo administered Q3W for ≤18 cycles (for	Post adjuvant chemotherapy	All received as per eligibility criteria	Disease stage Tumour histology

				approximately 54 weeks)			Geography

B.2.9.2 Feasibility assessment

Once the 3 relevant RCTs were identified, this section compares the three connected trials from the master network (IMpower010, PEARLS/KEYNOTE-091, and CANOPY-A) in terms of eligibility criteria, baseline characteristics, and endpoint definitions, with a focus on prognostic factors (PFs) and treatment-effect modifiers (TEMs).

Eligibility criteria

The key criteria for patient inclusion were examined and deemed consistent across the three trials. These are shown in Table 26.

Table 26: Comparison of eligibility criteria in early-stage NSCLC trials (3 RCTs)

Trial	Intervention	Disease stage	Surgery	Neoadjuvant chemotherapy	Age	ECOG performance status
IMpower010	Atezolizumab	IB-IIIB	Complete resection	Not allowed	18+	0-1
PEARLS / KEYNOTE-091 (full sample*)	Pembrolizumab	IB-IIIA	Complete resection	Not allowed	18+	0-1
CANOPY-A	Canakinumab	IB-IIIA	Complete resection	Not allowed	18+	0-1

*Note: *Baseline characteristics for the 86% subsample who received adjuvant chemotherapy were not available.*

Baseline characteristics

Reported baseline values with respect to the identified prognostic factors PFs/TEMs were examined. These are shown in Table 27 to Table 30. Notably, baseline characteristics in the pembrolizumab trial PEARLS/KEYNOTE-091 are only reported for the entire sample and the patient characteristic information specific to the 86% subsample who received adjuvant chemotherapy is not available. However, overall trial participants appeared similar in terms of age and sex. Table 8 shows that similar proportions of Stage IIIA patients were observed across trials. IMpower010 and PEARLS/KEYNOTE-091 patients appeared similar in squamous histology; CANOPY-A enrolled slightly fewer squamous cell carcinoma patients. Tumour stage was only

reported in IMpower010; therefore, no clear comparison could be drawn. The performance status across all RCTs was similar across trials as can be seen in Table 29.

PD-L1 levels, in terms of proportion of patients with ≥ 50% PD-L1 expression, was similar for IMpower010 and PEARLS/KEYNOTE-091 as seen in Table 30. However, there was a lack of information available (40–43%) in CANOPY-A, adding uncertainty to the comparability of this trial population to those in the other two studies.

Table 27: Comparison of baseline characteristics in early-stage NSCLC trials by age, sex, ethnicity, and smoking history (3 RCTs)

Trial	Intervention	N per arm	Age (Md years)	Sex (% male)	Ethnicity*	Smoking history*
IMpower010	Atezolizumab	507, 498	62.0, 62.0	66.5, 67.3	Not available	Not available
PEARLS / KEYNOTE-091 (full sample*)	Pembrolizumab	590, 587	65.0, 65.0	68.0, 68.7	Not available	Not available
CANOPY-A	Canakinumab	693, 689	63.0, 62.0	62.0. 62.7	Not available	Not available

*Note: * Baseline ethnicity and smoking history were not part of the list of baseline characteristics that were extracted for this SLR (consistent with the original grid for adjuvant SLR).*

Table 28: Comparison of baseline characteristics in early-stage NSCLC trials by disease stage, tumour stage, and histology (3 RCTs)

Trial	Intervention	N per arm	Disease stage	Tumour stage	Histology (squamous)
IMpower010	Atezolizumab	507, 498	IIA: 29%, 30% IIB: 18%, 17% IIIA: 40%, 42%	T2A: 50%, 38% T2B: 14%, 16% T3: 24%, 23% T4: 4%, 5%	35%, 34%
PEARLS / KEYNOTE-091 (full sample*)	Pembrolizumab	590, 587	II: 56%, 58% IIIA: 30%, 28%	Not available	33%, 38%
CANOPY-A	Canakinumab	693, 689	IIA: 17%, 17% IIB: 38%, 38% IIIA: 39%, 39%	Not available	25%, 26%

*Note: *Baseline characteristics for the 86% subsample who received adjuvant chemotherapy were not available*

Table 29: Comparison of baseline characteristics in early-stage NSCLC trials by performance status (3 RCTs)

Trial	Intervention	N per arm	Performance status	
			ECOG: 0	ECOG: 1
IMpower010	Atezolizumab	507, 498	54%, 57%	46%, 43%
PEARLS / KEYNOTE-091 (full sample*)	Pembrolizumab	590, 587	64%, 58%	36%, 42%
CANOPY-A	Canakinumab	693, 689	65%, 65%	36%, 35%

*Note: *Baseline characteristics for the 86% subsample who received adjuvant chemotherapy were not available*

Table 30: Comparison of baseline characteristics in early-stage NSCLC by PD-L1 expression (3 RCTs)

Trial	Intervention	N per arm	PD-L1 status				Missing
			<1%	≥1%	1-49%	≥50%	
IMpower010	Atezolizumab	507, 498	43%, 48%	52%, 57%	-	27%, 26%	Not reported
PEARLS / KEYNOTE-091 (full sample*)	Pembrolizumab	590, 587	Not reported**	Not reported	Not reported**	29%, 28%	Not reported
CANOPY-A	Canakinumab	693, 689	30%, 30%	-	14%, 17%	12%, 14%	43%, 40%

*Note: *Baseline characteristics for the 86% subsample who received adjuvant chemotherapy were not available.*
***Baseline data were not reported, however endpoint data (DFS) by this subgroup are available.*

Study design and DFS endpoint definitions

Other study design features as well as endpoint definitions for DFS across the three trials were compared and are shown in Table 31. The study designs are consistent except for blinding approach as IMpower010 was an open-label trial whilst PEARLS and CANOPY-A were blinded RCTs.

Table 31: Trials included in master network (3 RCTs)

Trial	Intervention arm	Phase	Blinding	Endpoint definition: DFS
IMpower010	Atezolizumab	III	Open label	Time from randomisation to date of first recurrence of NSCLC, occurrence of new primary NSCLC, or death from any cause, whichever occurs first
PEARLS	Pembrolizumab	III	Blinded	Time from randomisation to locoregional or metastatic recurrence assessed per

/ KEYNOTE-091				RECIST version 1.1 by investigator review, appearance of a second NSCLC primary or other malignancy, or death from any cause, whichever occurs first
CANOPY-A	Canakinumab	III	Blinded	Time from randomisation to the date of the first documented NSCLC disease recurrence as assessed by local investigator radiologically or of death due to any cause

Feasibility and eligibility criteria assessment summary

Overall, the three trials in the master network were similar in patient eligibility criteria and in most baseline characteristics. The closest comparison can be drawn between the PEARLS / KEYNOTE-091 and IMpower010 as the PEARLS trial population was similar to the reference trial IMpower010 in most respects except for the use of blinding. CANOPY-A, in contrast, did evidence some information gaps. For example, CANOPY-A did not stratify by PD-L1 expression, compared to the PEARL trial, and reported a lack of information (and therefore uncertainty) in a number of patient baseline characteristic, which poses a challenge to its inclusion in an ITC.

As a result, due to the similarity between PEARLS and IMpower010, PEARLS was included in the ITC network. CANOPY-A was excluded in the ITC due to information gaps such as the lack of PD-L1 expression stratification.

B.2.9.3 Network meta-analysis methodology

Statistical models

This section provides a summary of the statistical model used to produce the NMAs. Separate NMAs were conducted for the DFS and 3-year DFS endpoints in a commonly implemented Bayesian framework (Bayesian analysis using Markov chain Monte Carlo (MCMC) simulation) in accordance with the National Institute for Health and Care Excellence Decision Support Unit Technical Support Document 1. The Bayesian approach was chosen since it allows the inclusion of prior information, which can improve the accuracy of estimates, especially when dealing with sparse or

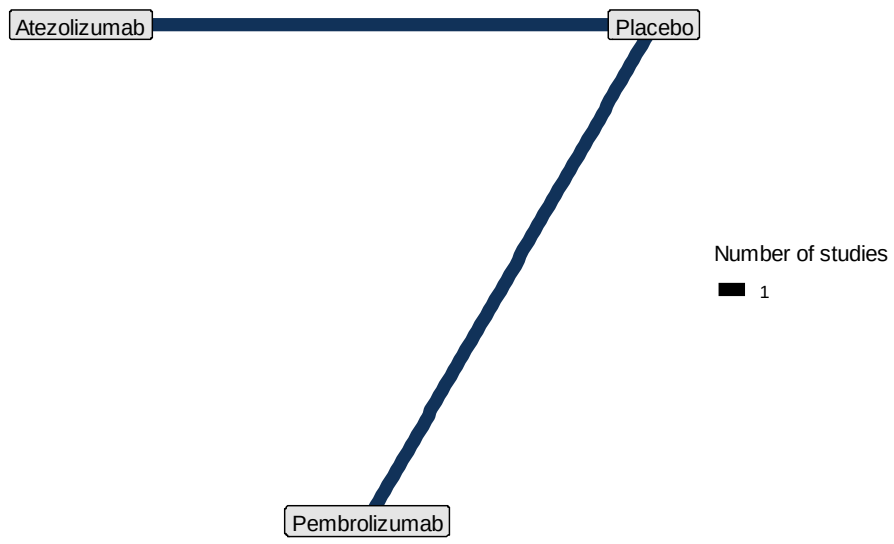
heterogeneous data. Further information on the NMA methodology can be found in the Appendix M.

B.2.9.4 NMA results

A total of 4 NMAs were conducted, which can be seen in Appendix M. For the purpose of this analysis only 2 (DFS PD-L1 high and DFS at 3 years PD-L1 high) out of the 4 NMA results were included in this ITC section as these were conducted in the target population for this appraisal. The evidence network for the 2 NMAs, as shown in .

Figure **20**, consists of two studies and three treatments connected through placebo as the common comparator.

Figure 20: Network diagram for DFS



DFS, in PD-L1 high patients

The reported DFS data for PD-L1 high (≥ 50%) patients from the two studies are listed in Table 32.

Table 32: Summary of included study characteristics for the DFS endpoint in PD-L1 high patients

Study	Treatment arm	N (patients)	HR (95% CI), placebo reference
Impower10	Placebo	114	0.503 (0.33, 0.76)

Impower10	Atezolizumab	115	
PEARLS/KEYNOTE-091	Placebo	165	0.83 (0.59, 1.16)
PEARLS/KEYNOTE-091	Pembrolizumab	168	

The results from the fixed and random-effects models (with informative prior), along with model fit statistics are shown in Table 33.

Table 33: Estimated treatment effects for DFS (PD-L1 high)

Treatment comparisons	Mean posterior HR (95% CrI)	
	Fixed effects model	Random effects model
Atezolizumab vs. Placebo	0.51 (0.33, 0.76)	0.52 (0.30, 0.81)
Pembrolizumab vs. Placebo	0.84 (0.59, 1.16)	0.86 (0.55, 1.27)
Atezolizumab vs Pembrolizumab	0.63 (0.35, 1.04)	0.64 (0.30, 1.14)
Residual deviance	2 (on 2 data points)	2 (on 2 data points)
DIC	4	4

CrI credible interval; DIC deviance information criteria; HR: Hazard ratio; Informative prior = log normal [-3.95, 1.742] from Turner 2015 (Table IV).

Both the fixed effects and random effects models produced a residual deviance of 2 based on two data points, indicating a similar good fit of the model to the observed data. However, estimates of between-study heterogeneity (tau) were highly sensitive to the choice of prior distribution in the random-effects model due to the insufficient data points, hence the fixed-effects model was favoured for statistical inference. Figure 21 displays the results from the fixed-effects model in a forest plot. The mean posterior HR comparing atezolizumab to pembrolizumab for DFS is 0.63 (95% CrI: 0.35, 1.04). This suggests that atezolizumab has a potential reduction in the risk of disease recurrence or death compared to pembrolizumab, but the credible interval including one indicates the effect is not statistically significant.

Figure 21: Forest plot of hazard ratio (95% CrI) of treatment effects from the fixed-effects model for disease-free survival, in PD-L1 high patients

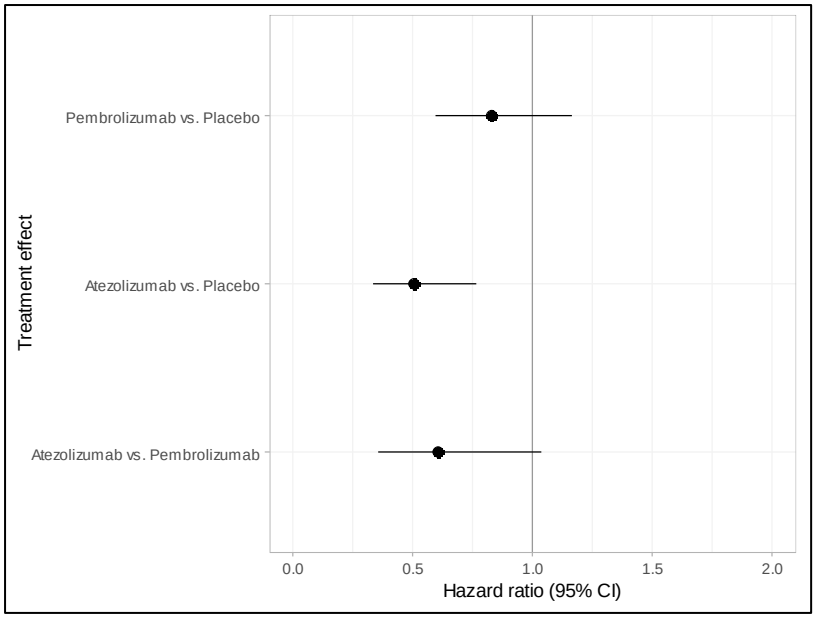
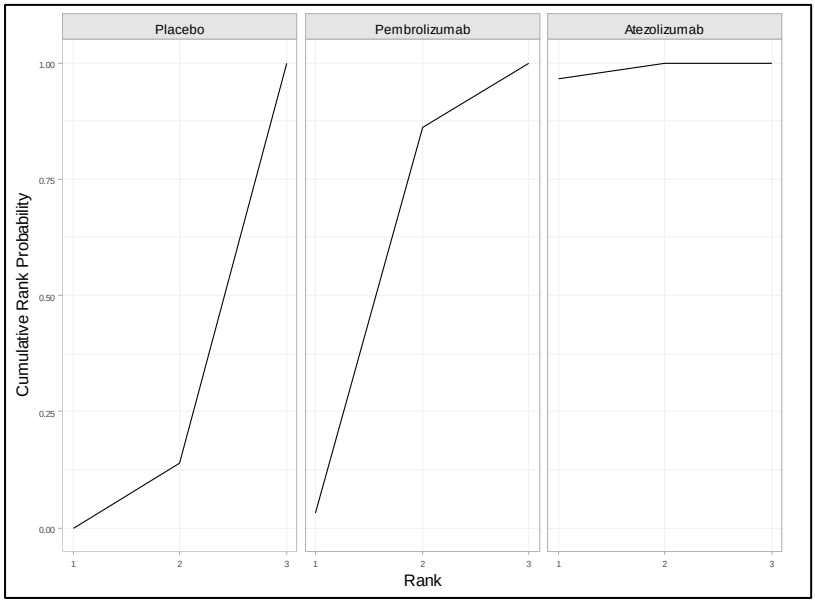


Figure **22** shows the cumulative treatment rankings for the 3 treatments. Atezolizumab had a 96% probability of being ranked first. It had the highest SUCRE score (0.98).

Figure 22: Cumulative rank probability plots for disease free survival (PD-L1 high, fixed-effects model)



3-year DFS, in PD-L1 high patients

The reported 3-year DFS data for PD-L1 high (≥ 50%) patients from the two studies are listed in Table 34.

Table 34: Summary of included study characteristics for the 3-year DFS endpoint in PD-L1 high patients

Study	Treatment arm	N (patients)	r (disease recurrence)
Impower10	Placebo	114	53
Impower10	Atezolizumab	115	29
PEARLS/KEYNOTE-091	Placebo	165	69
PEARLS/KEYNOTE-091	Pembrolizumab	168	57

The results from the fixed and random-effects models (with informative prior), along with model fit statistics are shown in Table 35.

Table 35: Estimated treatment effect for 3-year DFS (PD-L1 high)

Treatment comparisons	Mean posterior OR (95% CrI)	
	Fixed effects model	Random effects model
Atezolizumab vs. Placebo	0.40 (0.22, 0.67)	0.41 (0.21, 0.72)
Pembrolizumab vs. Placebo	0.73 (0.45, 1.11)	0.74 (0.43, 1.19)
Atezolizumab vs Pembrolizumab	0.58 (0.26, 1.10)	0.59 (0.24, 1.20)
Residual deviance	4 (on 4 data points)	4 (on 4 data points)
DIC	8.1	8

CrI credible interval; DIC deviance information criteria; HR: Hazard ratio; Informative prior = log normal [-3.95, 1.742] from Turner 2015 (Table IV).

Both the fixed effects and random effects models produced a residual deviance of 4 based on four data points, indicating a similar good fit of the model to the observed data. However, estimates of between-study heterogeneity (tau) were highly sensitive to the choice of prior distribution in the random-effects model due to the insufficient data points, hence the fixed-effects model was favoured for statistical inference. Figure 23 displays the results from the fixed-effects model in a forest plot. The mean posterior OR comparing atezolizumab to pembrolizumab for 3-year DFS is 0.58 (95% CrI: 0.26, 1.10). This suggests that atezolizumab has a potential reduction in the risk of disease recurrence or death compared to pembrolizumab, but the credible interval including one indicates the effect is not statistically significant.

Figure 23: Forest plot of odds ratio (95% CrI) of treatment effects from the fixed-effects model for 3-year disease-free survival, in PD-L1 high patients

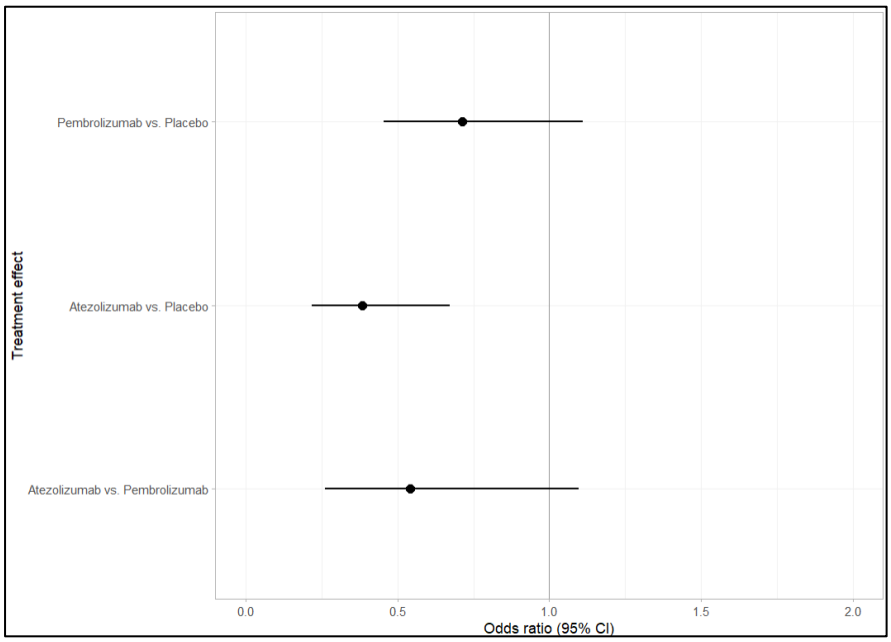
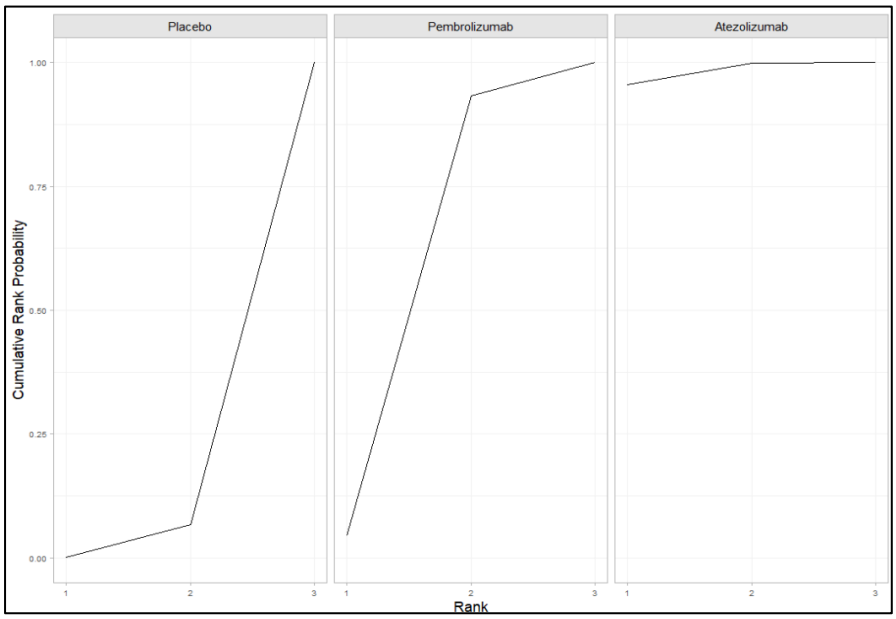


Figure **24** shows the cumulative treatment rankings for the 3 treatments. Atezolizumab had a 96% probability of being ranked first. It had the highest SUCRE score (0.98).

Figure 24: Cumulative rank probability plots for 3-year disease free survival (PD-L1 high, fixed-effects model)



B.2.9.5 Summary of results

In sum, for the first endpoint, DFS, atezolizumab was ranked first out of the three treatments, with a mean posterior HR of 0.63 [95% CrI (0.35, 1.04)] when compared to pembrolizumab. To further validate the NMA results a second endpoint was used. For 3-year DFS, atezolizumab was ranked first out of the three treatments, with a mean posterior odds ratio (OR) of 0.58 [95% CrI: 0.26, 1.10] relative to pembrolizumab. Therefore, after evaluating both endpoints, DFS and 3-year DFS, it can be concluded that atezolizumab consistently ranked higher than pembrolizumab in the network meta-analyses suggesting that atezolizumab results in better outcomes for PD-L1 high NSCLC patients in the adjuvant setting than pembrolizumab.

Fixed-effects models were preferred over random-effects models to generate these results since estimates of between-study heterogeneity (tau) were highly sensitive to the choice of prior distribution in the random-effects model due to the insufficient data points. Therefore, the fixed-effects model was chosen to establish comparative efficacy between pembrolizumab and atezolizumab.

B.2.9.6 Limitations in the indirect and mixed treatment comparisons

A key limitation of the NMAs was that the PEARLS/KEYNOTE-091 study reported DFS and 3-year DFS outcomes for the subgroup patients (PD-L1 high) only in the overall study population, which included patients who did not receive adjuvant chemotherapy. This necessitated an assumption of population equivalence between the overall population in PEARLS/KEYNOTE-091 and the IMpower010 study, based on similar eligibility criteria and comparable baseline characteristics for most patients. However, it is important to note that the studies differed in design, with IMpower010 being an open-label trial and PEARLS/KEYNOTE-091 employing a blinded design. Additionally, the assumption of population equivalence has not been validated by clinical expert consultation, which could strengthen the justification for this approach. As the IMpower010 study focused exclusively on patients who had received adjuvant chemotherapy, using data from a subsample of the 86% patients in PEARLS/KEYNOTE-09 that received adjuvant chemotherapy could have reduced variability and improved the comparability of the studies included in the NMA.

Our feasibility assessment found the trials to be similar in terms of eligibility criteria and baseline characteristics including prognostic factors and treatment effect modifiers. However, if there were differences in unreported treatment effect modifiers this could have introduced bias.

B.3 Cost effectiveness

B.3.1 Intervention technology and comparators

The intervention technology, atezolizumab (1825 mg every 21 days; 74% of patients completed 16 cycles).

The comparators, BSC (as per the trial protocol, patients will undergo randomised CT scans (assuming no recurrence at each timepoint (Year 1: every 4 months, Year 2: every 6 months, Year 3-5: every 6 months, after 5 years: once a year by X-ray)) and pembrolizumab (200 mg every 21 days; mean of 17 cycles) are consistent with what was included in the updated decision problem and discussed at the decision problem meeting as outlined in CS Section B.1.1. The intervention and comparators are listed in Table 36.

Table 36: Adjuvant treatment regimens and comparators

Intervention	Intervention arm	Control arm	
	Atezolizumab	**BSC**	**Pembrolizumab**
Administration	Fixed dose, subcutaneous injection/ IV	-	Fixed dose intravenous infusion (IV).
Dose size	1825 mg	-	200mg
Frequency	3 weeks	-	3 weeks
Duration	74% of patients completed 16 cycles	Until recurrence	Mean, 17 cycles

B.3.3 Clinical parameters and variables

- **The primary data source for the economic model was the IMpower010 trial**
- **Additional evidence came from published literature, clinical expert advice, and clinically validated assumptions**

- **DFS data was extrapolated over a lifetime time horizon of 40 years and the curves were adjusted to avoid overestimating patients who have recurrences in the longer term. This involved:**
  - **Fitted parametric curves to the IMpower010 patient-level data as per NICE Decision Support Unit methodology**
  - **Referred to literature identified on longer term survival and "cure" proportions, gathered in Section B.3.3.4**
  - **Adjusted curves with five-year "cure" assumption followed by 100% of patients are cured at 7 years.**
  - **Validated cure assumption survival outputs with identified literature and UK clinical expert opinion**
- **The model did not allow the estimates for the proportion of patients who transitioned to death to be greater than the probabilities from the literature or trial data, instead, it would switch to the use of age-adjusted probabilities of death from the general population**
- **To determine the treatments that patients received in the non-metastatic and metastatic health states, an Advisory board of 6 UK clinical oncologists (November 2024) was undertaken.**
- **Transition probabilities for non-metastatic and metastatic disease recurrences were extrapolated from published literature and NSCLC NICE appraisals**
- **Grade ≥ 3 treatment-related, AEs. 2% incidence in the IMpower010 trial were included in the economic model**
- **For the remaining health states, the following sources were used:**
  - **Non-metastatic recurrence – Antonia et al. 2017**
  - **First-line metastatic recurrence – Reck et al. 2014, Herbst et al. 2020, Ghandi et al. 2018**
  - **Second-line metastatic recurrence – OAK trial (TA520), Reck et al. 2014**

Pembrolizumab

An NMA was conducted to establish comparative efficacy between pembrolizumab and atezolizumab. A fixed effects model was chosen to establish this comparison. The fixed-effects models were preferred over random-effects models since estimates of between-study heterogeneity (tau) were highly sensitive to the choice of prior distribution in the random-effects model due to the insufficient data points.

The NMA results showed that for the PD-L1 high population, DFS, atezolizumab was ranked first out of the three treatments, with a mean posterior HR of 0.63 [95% CrI (0.35, 1.04)] when compared to pembrolizumab. For further information on the NMA analysis and results please refer to Section 2.9. To model and compare the long-term DFS curves for atezolizumab and pembrolizumab, the HR was applied to the extrapolated atezolizumab curve (Gompertz) at any given time point. As result a pembrolizumab arm is generated and a comparison can be drawn how long patients in the atezolizumab vs. pembrolizumab arm remain disease-free at any given timepoint.

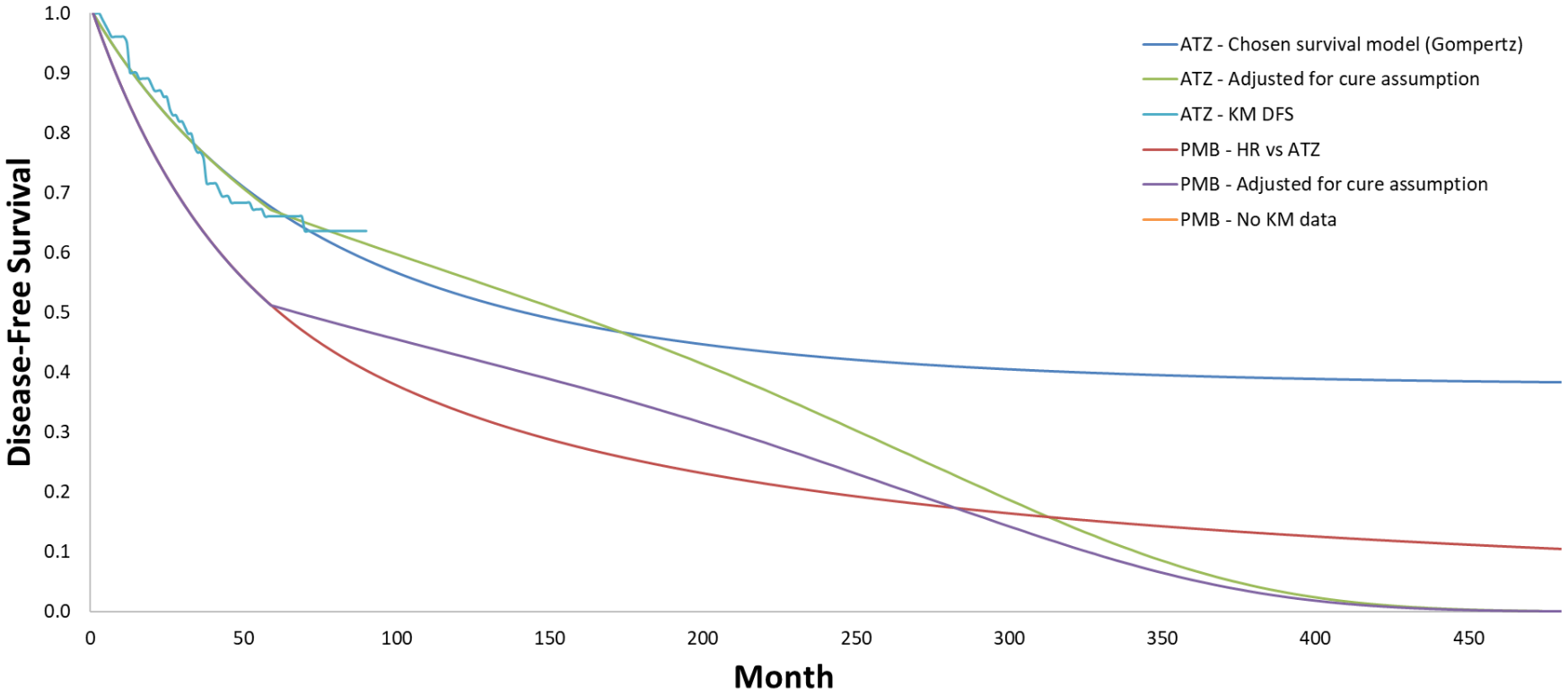
B.3.3.4 Adjusting the DFS curves

DFS curve adjustment and validation process:

1. **Fitted parametric curves to the IMpower010 patient-level data as per NICE Decision Support Unit methodology**
2. **Referred to literature identified on longer term survival and "cure" proportions, gathered in Section B.3.3.3.5**
3. **Adjusted curves with five-year "cure" assumption at 89% cure rate at 5 years, 100% at 7 years.**
4. **A mortality rate of 1.25 of "cure" patients is assumed**
5. **Treatment waning after 60 months is assumed.**
6. **Validated cure assumption survival outputs with identified literature and UK clinical expert opinion**

Cure adjustment: As written in the company's clarification questions response, the base case was updated to 89% of patients are cured at 5 years and 100% are cured at 7 years. Figure 25 shows that without all the adjustments, applying an SMR of 1.25, updating the cure assumption and applying the treatment waning effect , the proportion of patients in DFS is lower.

Figure 25: DFS curve extrapolations for pembrolizumab and atezolizumab – unadjusted and adjusted

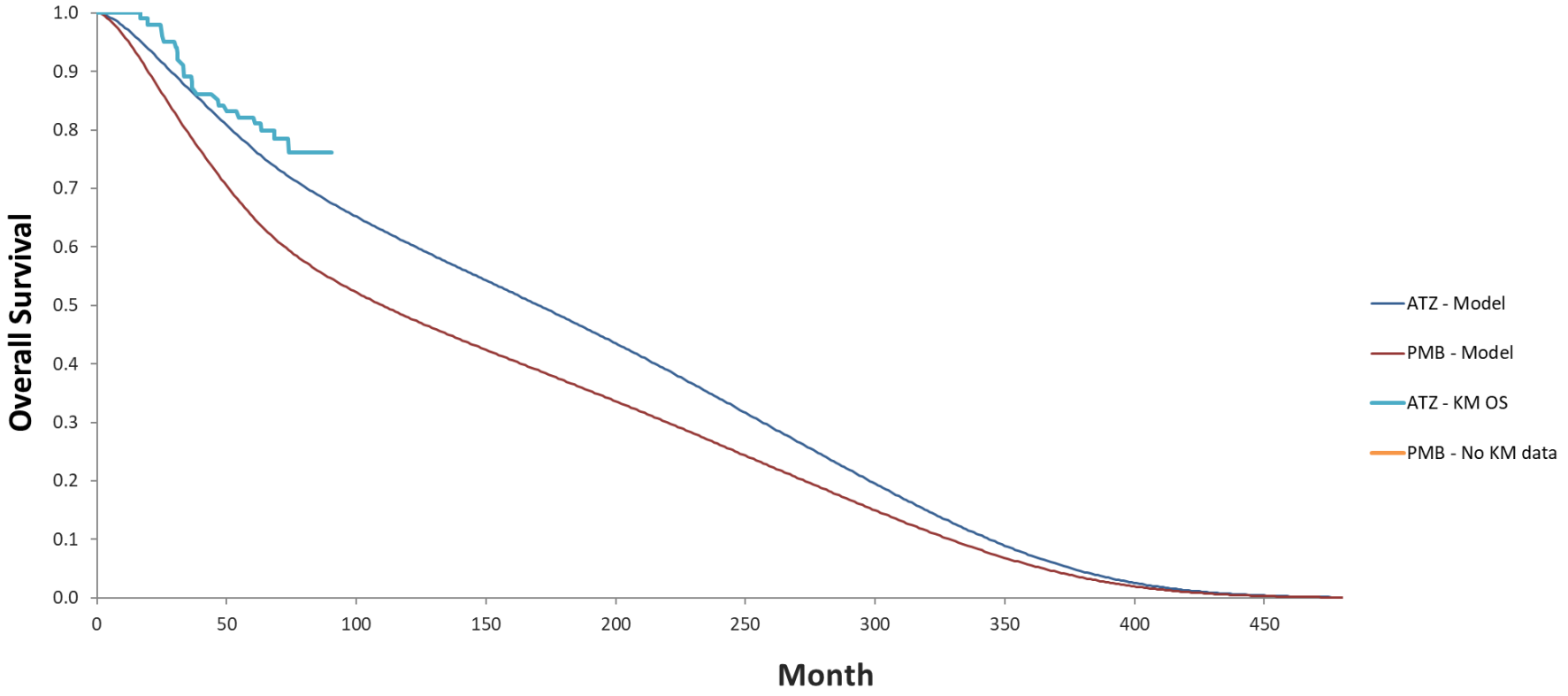


DFS, disease-free survival; BSC, best supportive care

B.3.3.5 Overall survival

OS was not captured as a primary endpoint in the IMpower010 and was analysed post-hoc in an exploratory analysis. As a result, OS was modelled and derived using DFS as a surrogate and literature was used to derive patients and their progression across different health states. OS was used to visually match the derived OS to the OS KM data. In addition, the curves were validated in the UK clinical ad board in November 2024 and were deemed appropriate. Clinicians validated the assumptions that significant improvements in DFS observed with atezolizumab are likely to translate into corresponding OS benefits (9). This perspective is informed by historical precedents in oncology where enhanced DFS has been shown to predict improved OS, particularly in treatments targeting specific cancer mechanisms, like NSCLC. Figure 26 shows the OS of atezolizumab vs. pembrolizumab.

Figure 26: Modelled and observed overall survival (IMpower010; Stage II–IIIA, PD-L1 ≥ 50% (excluding EGFR-positive and ALK-positive [CCOD 26 January 2024] – atezolizumab and pembrolizumab



PD-L1, Programmed Death-Ligand 1; EGFR, epidermal growth factor receptor; ALK, naplastic lymphoma kinase, CCOD, clinical cut-off date.

B.3.3.6 Treatment after recurrence

The following section will lay out the treatment patterns for patients after they progress from DFS to non-metastatic, metastatic or death. The model allows patients who experience non-metastatic recurrence and/or metastatic recurrence (separately for first- and second line) to either be treated or not. For those patients who are treated, four of the most common treatment options in the UK are included. The model also accounts for treatment choices whether patients have been treated with adjuvant immunotherapy within or after 18 months (1 year of treatment with atezolizumab plus the 6 month rechallenge period according to the Blueteq form) or with best supportive care. Clincians at the advisory board on 4th November 2024 confirmed that patients who were treated with adjuvant immunotherapy and relapsed within 18 months of treatment initiation would be treated differently to patients who were treated with adjuvant immunotherapy and relapsed after 18 months of treatment initiation or had only received best supportive care after adjuvant chemotherapy (9).

The same advisory board on 4th November 2024 informed what treatments patients within each of the different health states would receive and their respective proportions (9). In addition, the treatment patterns were supplemented by NICE guidelines as described in Section B.3.3.7 (10).

B.3.3.7 Types of disease recurrences in the DFS setting

To inform the relative split in disease-free events, the model uses evidence from IMpower010 as seen in Table 37. It can leverage two sets of estimates to inform the proportions. The first set was derived separately for each study arm while the second set was derived from the pooled sample of patients from both study arms. The base case uses the pooled sample estimates in the base case, which differs to the original approach that was in the IMpower010 2022 submission. While this approach restricts the type of events that patients experience across all treatment arms, the ERG stated during the NICE technical appraisal of NICE that using separate estimates is not appropriate. This is because it was not clinically plausible to assume that there would be difference in the split of these events (11).

Based on this rationale, the model also uses this evidence to inform the relative split in the type of disease-free events for patients who are treated with pembrolizumab.

Table 37: Type of disease-free survival events (IMpower010; Stage II–IIIA, PD-L1 ≥ 50% (excluding EGFR-positive and ALK-positive) [CCOD 26 Jan 24]

DFS event	Adjuvant atezolizumab	Best supportive care	Adjuvant atezolizumab and best supportive care
Total events	**33**	**52**	**85**
Death	6 (18.2%)	8 (15.4%)	14 (16.5%)
Non-Metastatic recurrence	16 (48.5%)	16 (30.8%)	32 (37.6%)
Metastatic recurrence	11 (33.3%)	28 (53.8%)	39 (45.9%)

In the adjuvant atezolizumab and best supportive care arms of IMpower010, 1 and 3 patients experienced a new primary lung cancer in this population.

Types of disease-free events

The model uses the results from external sources to inform the progression-free survival (PFS) and OS of patients who are treated and not treated after experiencing recurrence for the intervention and all comparators. Refer to Doc B for further information

B.3.3.9 Treatment discontinuation

The study allows patients to discontinue adjuvant treatment, and treatment received after recurrence, if they experience recurrence, disease progression, death, or cannot tolerate the treatment (e.g. toxicity).

B.3.3.9.1 Adjuvant treatment

In the base case, treatment duration for atezolizumab is based on time-to-off treatment (TTOT) from IMpower010. Table 38 provides an overview of the proportion of patients who discontinue treatment during each treatment cycle.

To inform treatment discontinuation for pembrolizumab, the model uses O'Brien et al. (2022), which shows that in KEYNOTE-091, the median number of adjuvant cycles completed was 17 as opposed to a minimum of 18 cycles.

Table 38: Treatment discontinuation - adjuvant atezolizumab (IMpower010; Stage II–IIIA, PD-L1 ≥ 50% (excluding EGFR-positive and ALK-positive) [CCOD 26 Jan 24]

Cycle	Proportion	Cycle	Proportion	Cycle	Proportion

1	3.8%	7	2.9%	13	1.0%
2	2.9%	8	1.0%	14	0.0%
3	4.8%	9	0.0%	15	1.0%
4	1.9%	10	2.9%	16	74.0%
5	1.9%	11	1.0%		
6	0.0%	12	1.0%		

No unexpected results were observed in the treatment discontinuation rates. 74% of patients completed their treatment (patients receive 16 cycles of atezolizumab). 18.2% of patients discontinued their treatment due to atezolizumab related adverse events, however, no unexpected adverse events were recorded that led to a disproportionate number of patients not completing their treatment. Clinicians confirmed that no unexpected adverse events were observed in the 26th January 2024 data cut.

B.3.3.10 Adverse events

B.3.3.10.1 Safety

Based on the number of occurrences per adverse event (AE) for a given period and across treatment options, the study calculates a probability of experiencing an AE. The calculation is performed using this formula:

$$P(adverse\ event_x) = 1 - e^{-occurence_x / follow-up}$$

where x is the AE, $occurence$ is the number of times it occurred, and $follow-up$ is follow-up in months. The model does not consider grade 1-2 AEs as these are events that are defined by mild to moderate symptoms which may not require any medical attention. It attempts to only considers Grade 3–5 treatment emergent AEs as these events that are treatment related and produce severe to life threatening symptoms that may require invasive and/or immediate emergency intervention. However, this is not entirely possible due to the different definitions used by the different sources when publishing evidence on adverse events.

B.3.3.10.2 Adjuvant treatment

In order to determine which AEs should be included in the model, the AE event rates should be Grade >3 treatment-related AEs with an incidence of >2%. Previous appraisals within this therapy area have utilised the criteria of all Grade >3 treatment

related AEs with an incidence of > 2% – > 5% in either treatment arm to include in the economic model (TA531 (12), TA428 (13), TA520 (14), TA584 (15)). The treatment-related AEs are presented in CS Section B.2.10.

Using this cut-off criteria, no AEs from the IMpower010 trial were included in the economic model for the DFS health state, as the proportion of patients experiencing treatment-related AEs/SAEs of Grade 3 and above were all below 2% (in the atezolizumab arm, as BSC arm was active monitoring only).

B.3.4 Measurement and valuation of health effects

- **The IMpower010 trial did not collect patient-reported outcome data**
- **The model sourced health state utility values from published literature**
- **Disutilities associated with AEs were not included to avoid double-counting**
- **The HRQoL SLR identified 4 full publications which had utility values which were deemed appropriate to be used for the DFS health state in the model. Grutters et al. (2010) (16-19) was used in the base case as it gave the most clinically plausible utility values**
- **For the remaining health states, the following sources were used:**
  - **Non-metastatic recurrence, treatment – Chouaid et al. 2013**
  - **First-line metastatic recurrence, treatment – Chouaid et al. 2013 (20)**
  - **Second-line metastatic recurrence, treatment – Chouaid et al. 2013 (20)**

B.3.4.3 Health state utilities used in the economic analysis

Once the appropriate studies had been identified the appropriate utility values were allocated for each health state. In the DFS health state, HSUV for patients were differentiated between atezolizumab on-treatment and off-treatment, informed by Grutters et al. (2010). To inform the HSUV of patients in the non-metastatic and metastatic setting, the values from the regression analysis by Chouaid et al. 2013 were used. The non-metastatic patients are assumed to have a HSUV of 0.77. Patients who

are in the 1st line or 2nd line metastatic setting are assumed to have a HSUV of 0.70 (Intercept + Stage IV = metastatic HSUV).

Table 39: Utility values for each health state

Health state		Utility value	Reference
Disease-free survival	Atezolizumab, on-treatment	0.77	Grutters et al. (2010)
	Atezolizumab, off-treatment	0.81	Grutters et al. (2010)
Disease-free survival	Pembrolizumab, on-treatment	0.77	Grutters et al. (2010)
	Pembrolizumab, off-treatment	0.81	Grutters et al. (2010)
Disease-free survival (BSC)		0.81	Grutters et al. (2010)
Locoregional (non-metastatic)		0.77	Chouaid et al. 2013
1st line metastatic (Stage IV)		0.70	Chouaid et al. 2013
2nd line metastatic (Stage IV)		0.70	Chouaid et al. 2013

Disutilities associated with AEs were not included to avoid double counting, as impact on utilities from AEs may have already been accounted for in the identified utility sources. Not including disutilities in the model is expected to only have a minor impact as adverse events were only included for progressed states. B12 provides a scenario analysis when applying disutilities.

B.3.4.4 Adjusting utility values

The sourced utility values in Section B.3.4.2.1 and B.3.4.2.2 were based on a static period. As these utility values are used over a long time horizon within the model, it was appropriate to adjust the values so that they did not exceed general population values, given that HRQoL and utility were expected to decline due to the NSCLC population age increase and comorbidities (21).

$$HSUV\ x\ (\frac{\big(General\ Population\ Utility\ Value(age-adjusted)\big)}{(General\ Population\ Utility\ Value\ (Age-average\ age\ cohort))}$$

This approach multiplies the HSUV by the general population utility value (equal to age of cohort in cycle X), and then divides this value by the general population utility value equal to the age of the cohort at the beginning (i.e. average age of the cohort when entering the model). This approach has been used in other submissions and

was deemed appropriate such as TA1014 (21). As result, the model uses an approach that allows the utility values to be converted to time-variant values by multiplying them by age/sex-adjusted general population utility values.

B.3.5 Cost and healthcare resource use identification, measurement and valuation

- **An SLR was conducted to identify cost and resource use data for early NSCLC**
- **The studies identified in the SLR showed that costs increase as the disease progresses and in the early stages of disease, surgery was the predominant cost driver**
- **Estimation of subsequent treatment use was obtained from a survey of 6 UK clinical oncologists during the 4th November 2024 advisory board**

B.3.5.1 Intervention and comparator costs and resource use

B.3.5.1.1 Drug acquisition costs

Drug acquisition costs for the treatment regimens included in the economic model are summarised in Table 40. Prices for generic medicines were taken from the 2024 electronic market information tool (eMIT), which reports the average price paid by the NHS for a generic medicine for the last period. For medicines only available to the NHS as proprietary medicines, prices were taken as the list price stated in the 2024 British National Formulary (BNF). Health care resource use costs were taken from NHS Reference Costs 2022-2023 and the Personal Social Services Research Unit 2023. Note that for the atezolizumab treatment cost only the subcutaneous (subcut) injection cost is presented as the subcut formulation is used in the base case.

Atezolizumab has a patient access scheme (PAS) which offers a discount of [redacted]. All other treatments are assumed to be list price. Although it should be noted that pembrolizumab, durvalumab and nivolumab have confidential PAS discounts within the UK.

The average weight (kg) and BSA (m^2 using the Dubois formula) from the IMpower010 study (74.03 kg and 1.84 m^2) were used to estimate the average cost per dose per patient for the treatments with dosing according to weight or BSA.

Table 40: Drug acquisition unit costs

Drug	Dose per vial/pack (large vial, mg)	Cost per vial/pack (£)	Source
Atezolizumab	1875	£3,807.69 (list price) [redacted] (PAS price)	BNF
Cisplatin	50	£19.69	eMIT
	100	£37.34	
Vinorelbine	10	£76.45	eMIT
	50	£181.95	
Gemcitabine	1200	£18.17	eMIT
	2200	£45.96	
Pembrolizumab	100	£2,630	BNF
Pemetrexed	100	£18.34	eMIT
	500	£28.76	
Carboplatin	50	£6.71	eMIT
	600	£38.93	
Docetaxel	20	£4.49	eMIT
	160	£19.70	
Nintedanib	60	£2,151.00	BNF
Nivolumab	40	£439.00	BNF
	240	£2,633.00	
Durvalumab	120	£592.00	BNF
	500	£2,466.00	

B.3.5.1.2 Administration costs

The administration costs for all therapies across all health states, apart from atezolizumab and nintedanib, are sourced from the NHS reference costs 22-23 and patients are assumed to receive SB12Z, simple parenteral chemotherapy at first attendance (NHSE reference costs 2022-2023, Day case/ Reg night). Any subsequent

treatment cycles were costed by using SB15Z (NHSE reference costs 2022-2023, Day case/ reg night).

In the model it is assumed that atezolizumab is administered as a subcutaneous injection (subcut) in 50% of patients and 50% of patients will receive IV, although the proportion of subcut is expected to increase in the future. The IV/subcut 50/50 split assumption is expected to be in-line with real world practice should atezolizumab receive a positive recommendation in this indication. In terms of administration cost for the injection, it was assumed that a qualified nurse (band 5) can administer the injection in 7 minutes. According to the PSSRU 2023 cost report, qualified Band 5 nurses earn £53 per hour, therefore, administering subcut for 7 minutes costs £6.18 per administration.

Nintedanib is an oral therapy and in line with TA1014, it was assumed that it would take a pharmacist (Band 6) 12 minutes to administer the drug, which costs £10 per administration (8).

Table 41: Drug administration costs

Drug	Type of administration		NHS reference code	Cost per administration	Source
Atezolizumab	Subcutaneous formulation		-	£6.18	Qualified nurse Band 5, 1 hour salary (£53), subcut administation (7 minutes), PSSRU 2023
All therapies (apart from nintedanib and atezolizumab subcut)	Deliver simple parenteral chemotherapy at first attendance	Daycase and Reg day/night	SB12Z	£431.16	NHSE reference costs 2022-2023, Day case/ reg night
All therapies (apart from nintedanib and atezolizumab subcut)	Deliver Subsequent Elements of a Chemotherapy Cycle	Daycase and Reg day/night	SB15Z	£392.61	NHSE reference costs 2022-2023, Day case/ reg night
Nintedanib	Oral		-	£10.00	PSSRU 2023, 12 minutes pharmacist time every 4

				weeks, hospital pharmacist (band 6)

B.3.5.1.3 PD-L1 testing

The model assumes that patients who receive either atezolizumab, BSC or pembrolizumab have an associated cost of a PD-L1 test. **Table *42*** shows the cost of a PD-L1 test.

Table 42: PD-L1 testing

PD-L1 test cost	£42.61

B.3.5.2 Health-state unit costs and resource use

B.3.5.2.1 Disease-free survival

Patients in the atezolizumab arm of the model started on treatment in the DFS health state. Treatment duration was limited to 16 cycles (three weeks per cycle) as per trial protocol. Patients could discontinue treatment before this point due to disease progression or death. Table 43 shows the cost of atezolizumab each month (list and PAS price) and pembrolizumab each month (list price) over one year. There are no treatment acquisition costs associated for BSC, only resource use costs, which will be discussed in the *Follow-up costs* sections.

Table 43: Treatment acquisition costs per cycle – DFS health state – atezolizumab and pembrolizumab

Cycle	Cost per month, PAS price (£) (atezolizumab)	Cost per month, list price (£) (atezolizumab)	Cost per month, list price (£) (pembrolizumab)
1	[redacted]	3,813.87	5,573.91
2	[redacted]	3,667.18	5,573.91
3	[redacted]	3,557.17	5,573.91
4	[redacted]	3,373.81	5,573.91
5	[redacted]	3,300.46	5,573.91
6	[redacted]	3,227.12	5,573.91
7	[redacted]	3,227.12	5,573.91
8	[redacted]	3,117.11	5,573.91
9	[redacted]	3,080.43	5,573.91
10	[redacted]	3,080.43	5,573.91
11	[redacted]	2,970.42	5,573.91
12	[redacted]	2,933.75	5,573.91
13	[redacted]	2,897.07	5,573.91
14	[redacted]	2,860.40	5,573.91
15	[redacted]	2,860.40	5,573.91
16	[redacted]	2,823.73	5,573.91
17	[redacted]	-	5,573.91
Total treatment cost per year	[redacted]	50,790.48	94,756.47

Follow-up costs

Patients in all arms of the model received the same follow-up healthcare. The current standard of care after surgery plus adjuvant chemotherapy for NSCLC consists of active monitoring. The resource use associated with active monitoring was informed by UK clinical oncologists. Based on feedback, it was assumed that follow-up care is restricted to 5 years, however a scenario was provided in B16 if patients who receive atezolizumab and pembrolizumab were to be followed for 6 years. Note that the same resource use is assumed for treatment and no treatment. Refer to Doc B for a breakdown of all the costs in the recurrence health states.

B.3.5.3 Adverse reaction unit costs and resource use

AEs for adjuvant atezolizumab and subsequent therapies in progressive health states have been outlined in Section B.3.3.10. Adverse event management costs and resource use are presented below in Sections B.3.5.3.1.

B.3.5.3.1 Adjuvant Atezolizumab and non-metastatic recurrence

Since no adverse events in the adjuvant and non-metastatic setting met the AE definition, Grade >3 treatment-related AEs with an incidence of >2%, no adverse events costs were attributed to the adjuvant and non-metastatic setting.

B.3.5.4 Miscellaneous unit costs and resource use

An end of life/terminal care cost was included in the model and applied to patients who enter the death state as a one-off cost, in line with NICE appraisal TA705, atezolizumab monotherapy for untreated advanced NSCLC (22).

The model differentiated end-of-life cost based on whether the death was all-cause or disease related. Patients in the DFS health state who died incurred the all-cause death related end-of-life cost, while patients in the post-DFS health states incurred the disease-related death end-of-life cost. A scenario will be provided attributing a cost to all-cause mortality as seen in B17 of the clarification questions.

Table 44: End of life cost

Death	AE management cost
All-cause	£0
Disease related (8)	£19,943 per episode

B.3.6 Summary of base-case analysis inputs and assumptions

B.3.6.1 Summary of base-case analysis inputs

Table 45 summarises all key variable applied in the base case of the economic model.

Table 45: Summary of variables applied in the base case setting of the economic model

Variable	Value	Measurement of uncertainty and distribution: CI (distribution)	Reference to section in submission
General model parameters			
Time horizon	40 years	Fixed	Section B.3.2
Discount rate – efficacy	3.5%	Fixed	
Discount – costs	3.5%	Fixed	
Population parameters			
Age	61.20 years	Fixed	Baseline characteristics section
Body weight	74.03 kg	Fixed	
Height	168.82 cm	Fixed	
Body surface area	1.84 m^2	Fixed	
Proportion of males (%)	66.90%	Fixed	
Population in Analysis	PD-L1 high Stage II–IIIA, no ALK- and EGFR-positive mutation	Fixed	
Efficacy inputs			
Disease-free survival			
Parametric distribution – atezolizumab arm	Gompertz	Fixed	Section B.3.3.3
Parametric distribution – BSC arm	Log-normal	Fixed	
First event occurrence by type – trial data to use to inform recurrence type split	Pooled	Fixed	
First event occurrence by type – Atezo arm: proportion of patients with non-metastatic recurrence	37.6% (pooled)	Fixed	
First event occurrence by type – Atezo arm: proportion of patients with first line metastatic recurrence	45.9% (pooled)	Fixed	
First event occurrence by type – BSC arm: proportion of patients with non-metastatic recurrence	37.6% (pooled)	Fixed	

First event occurrence by type – Atezo arm: proportion of patients with first line metastatic recurrence	45.9% (pooled)	Fixed	
Treatment effect – Duration of atezo treatment effect	Limited to 60 months	Fixed	
Cured patients – maximum proportion of cured patients	89% (5 years), 100% (7 years)	Fixed	Section B.3.3.4
Cure point	5 years and 7 years	Fixed	
Excess mortality of long-term survivors – standardised mortality ratio	1.25	Fixed	
Non-metastatic recurrence			
Treatment setting - % of patients treated	70%	UK clinical expert opinion	Section B.3.3.7
Treatment setting - % of patients not treated	30%	UK clinical expert opinion	
Treatment setting - treatment regimen: treatment regimen drug 1	Cisplatin	Fixed	
Treatment setting - treatment regimen: treatment regimen drug 2	Vinorelbine	Fixed	
Treatment setting - treatment regimen: treatment regimen drug 3	Durvalumab	Fixed	
Treatment setting - treatment regimen: treatment regimen drug 4	Pembrolizumab	Fixed	
Efficacy by treatment intent - use result from survival analysis or calculation (based on median)	Exponential extrapolation	Fixed	
First-line metastatic recurrence			
Treatment setting - % of patients treated	60%	UK clinical expert opinion	Section B.3.3.7
Treatment setting - % of patients not treated	40%	UK clinical expert opinion	
Treatment setting – Treatment option 1	Pembrolizumab	Fixed	
Treatment setting – Treatment option 2	Atezolizumab	Fixed	

Treatment setting – Treatment option 3	Pembrolizumab + Pemetrexed + Carboplatin	Fixed	
Treatment setting – Treatment option 4	Pemetrexed + Carboplatin	Fixed	
Treatment setting – Re-challenging with immunotherapy allowed after treatment initiation	6 months	Fixed	
Efficacy by treatment intent – Use result from survival analysis or calculation (based on median)	Exponential extrapolation	Fixed	
Second-line metastatic setting			
Treatment setting - % of patients treated	60%	UK clinical expert opinion	Section B.3.3.7
Treatment setting - % of patients not treated	40%	UK clinical expert opinion	
Treatment setting – Treatment option 1	Nintendanib + Docetaxel	Fixed	
Treatment setting – Treatment option 2	Gemcitabine + Carboplatin	Fixed	
Treatment setting – Treatment option 3	Docetaxel	Fixed	
Efficacy by treatment intent – Use result from survival analysis or calculation (based on median)	Exponential extrapolation	Fixed	
Cost inputs			
Drug costs			
Drug costs – Atezolizumab: Composition (mg) subcutaneous injection = 1825 mg – List Price (PAS price)	£3,807.69 [redacted]	Fixed	
Administration costs			
Subcut administration cost	£6.18	Fixed	Section B.3.5.1
Admininstration cost, first attendance	£431.16	Fixed	Section B.3.5.1
Administration cost, subsequent attendance	£392.61	Fixed	Section B.3.5.1
Disease-free survival cost and resource use			
Estimated monthly cost, resource use	£63.24	Fixed	Section B.3.5.2

Non-metastatic recurrence cost and resource use			
Estimated monthly cost, resource use, treatment	£188.23	Fixed	Section B.3.5.2
Estimated monthly cost, resource use, no treatment	£188.23	Fixed	
First-line metastatic recurrence cost and resource use			
Estimated monthly cost, resource use, treatment	£411.21	Fixed	Section B.3.5.2
Estimated monthly cost, resource use, no treatment	£411.21	Fixed	
Estimated monthly cost, adverse events (Pembrolizumab)	£38.16	Fixed	Section B.3.5.3
Estimated monthly cost, adverse events (Atezolizumab)	£23.17	Fixed	
Estimated monthly cost, adverse events (Pembrolizumab + Pemetrexed + Carboplatin)	£6.96	Fixed	
Estimated monthly cost, adverse events (Pemetrexed + Carboplatin)	£45.14	Fixed	
Second-line metastatic recurrence cost and resource use			
Estimated monthly cost, resource use, treatment	£327.38	Fixed	Section B.3.5.2
Estimated monthly cost, resource use, no treatment	£327.38	Fixed	
Estimated monthly cost, adverse events (Nintendanib + Docetaxel)	£46.46	Fixed	Section B.3.5.3
Estimated monthly cost, adverse events (Gemcitabine + Carboplatin)	£46.46	Fixed	
Estimated monthly cost, adverse events (Docetaxel)	£5.13	Fixed	
End of life costs			
Disease-related death	£19,943	Fixed	Section B.3.5.4
Utilities – base case			
Disease-free survival			
On-treatment atezolizumab	0.77	Grutters at al. 2010	Section B.3.4.1
Off-treatment atezolizumab	0.81	Chouaid et al. 2013	

Off-treatment BSC	0.81	Chouaid et al. 2013	
On-treatment pembrolizumab	0.77	Grutters at al. 2010	
Off-treatment pembrolizumab	0.81	Chouaid et al. 2013	
Non-metastatic recurrence			
Intercept	0.77	Chouaid et al. 2013	Section B.3.4.2
First-line metastatic recurrence			
Stage IV	-0.07	Chouaid et al. 2013	Section B.3.4.2
Second-line metastatic recurrence			
Stage IV	-0.07	Chouaid et al. 2013	Section B.3.4.2

B.3.7 Base-case results

B.3.7.1 Base-case incremental cost effectiveness analysis results

Base case results of the economic model are presented in **Table *46*** (PAS price; [redacted] discount) for the Stage II–IIIA patients with completely resected NSCLC which expressed PD-L1 on 50% or more of tumour cells, who do not have EGFR-positive or ALK-positive NSCLC and has not progressed after platinum based chemotherapy In these comparisons, all comparators (and therapies included in the treatment pathway) are at list price.

Table 46: Base case cost effectiveness results – Stage II–IIIA population, PD-L1 on 50% or more of tumour cells, who do not have EGFR-positive or ALK-positive NSCLC and has not progressed after platinum based chemotherapy – PAS price

Technologies	Total costs	Total LYG	Total QALYs	Incremental costs	Incremental LYG	Incremental QALYs	ICER incremental (£/QALY)
Atezolizumab	[redacted]	[redacted]	[redacted]	[redacted]			
Pembrolizumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	dominant

At PAS price, pembrolizumab vs. atezolizumab provided [redacted] QALYs and [redacted] life years at a total overall cost of [redacted]. In contrast, pembrolizumab provided [redacted] QALYs and [redacted] life years, at a total cost of [redacted]. The resulting base ICER is dominant over pembrolizumab.

It should be noted that the with-PAS analysis does not account for confidential discounts of therapies used in the treatment pathway, such as pembrolizumab, durvalumab and nivolumab.

B.3.8 Sensitivity analyses

B.3.8.1 Probabilistic sensitivity analysis

To assess the uncertainty surrounding the variables included in the cost effectiveness model, a PSA was undertaken using 1,000 iterations to ensure results had converged. Results of the PSA compared to deterministic results at list price are in **Table *47***. Deterministic and probabilistic results are similar, therefore not indicating any signs of non-linearity in the model.

Table 47: PSA results compared to base-case (with PAS)

	Incremental Costs		Incremental QALYs		ICERs	
	Deterministic base case	PSA	Deterministic base case	PSA	Deterministic base case	PSA
Atezolizumab	-	-	-	-	-	-
Pembrolizumab	[redacted]	[redacted]	[redacted]	[redacted]	dominant	dominant

The incremental cost effectiveness planes in Figure 27 show the individual PSA iterations for the comparisons of atezolizumab and pembrolizumab at PAS price, respectively. For pembrolizumab, at PAS price, atezolizumab was 100% dominant in all simulations further supporting the view that atezolizumab is a cost-effective option.

Figure 27: Incremental cost effectiveness plane – atezolizumab vs pembrolizumab, PAS price

Cost effectiveness acceptability curves (CEAC) for the comparisons of atezolizumab and pembrolizumab at PAS price are presented in Figure 28. For pembrolizumab at PAS price, There is a 100% willingness to pay for atezolizumab due to atezolizumab being dominant compared to pembrolizumab.

Figure 28: Cost effectiveness acceptability curve – atezolizumab vs pembrolizumab, PAS price

B.3.8.2 Deterministic sensitivity analysis

Scenario analyses were conducted to assess uncertainty around parameter inputs and structural assumptions in the model.

Due to atezolizumab being dominant over pembrolizumab, the Net Monetary Benefit (NMB) was calculated to ensure the dominant ICERs indicate that atezolizumab is less costly and more effective than pembrolizumab. Table 48 shows a NMB of £121,696 at PAS price, with a positive incremental NMB indicating that atezolizumab is cost-effective compared to pembrolizumab at the £30,000 willingness-to-pay threshold.

The results of the deterministic sensitivity analyses were as expected due to the number of parameters included within the model and number of progressive states – no individual input would be expected to have a significantly large impact.

Table 48: Net monetary benefit, atezolizumab vs. pembrolizumab (PAS price)

Net monetary benefit (NMB)	£121,696

B.3.8.3 Scenario analysis

No scenario analyses results were tabulated as atezolizumab is consistently dominant against pembrolizumab in all scenario analyses.

B.3.9 Validation

The modelling approach and structure in ID6324 (this appraisal) is broadly consistent with the modelling approach that was taken in TA823 and in 2022 the original approach was deemed suitable to recommend adjuvant atezolizumab (through the CDF). In addition, the modelling approach and structure is consistent with the other NICE appraisal looking at a similar population: alectinib for untreated ALK-positive advanced non-small-cell lung cancer (TA1014) (recommended), osimertinib for adjuvant treatment of EGFR mutation-positive NSCLC after complete tumour resection [ID5120] (4) and pembrolizumab for adjuvant treatment of resected non-small-cell lung cancer [ID3907] (6). The methodology described above has adhered to the NICE Guide to the methods of technology appraisal 2013 and any instances where Roche has deviated from this guide has been highlighted and justified.

The modelling approach and inputs were cross-referenced with previous technology appraisals and subsequently validated by UK clinical oncologists. Early 1:1 discussions with UK clinical oncologists and with UK health economists provided valuable insights on the model's validity (i.e. model structure, assumptions, and inputs

values) (23, 24). The feedback provided confirmed that the structure of the model accurately represents the disease and treatment pathways of early NSCLC. In addition, a recent advisory board in November 2024 with 6 clinical oncologists was held to validate key assumptions in the model (9). These validations ensured that the model was robust and reflective of current UK clinical practice.

Clinical data for the DFS health state have been incorporated into the model from the IMpower010 trial and the methodology is described in Sections B.3.3.2 and B.3.3.3. The clinical outcomes in in all treatment arms of the model have been compared with published evidence and clinical expert opinion.

This cost effectiveness analysis was from the perspective of the UK NHS. The health states included in the model are similar to those in TA1014, ID5120 and ID3907. Roche uses the BNF, eMIT and NHS reference costs, the PSSRU, clinical expert to inform the cost and resource use inputs.

B.3.10 Interpretation and conclusions of economic evidence

Conclusions of economic results evidence

- **The cost effectiveness analysis used the best available evidence and methods to inform the model, as well as extensive scenario and sensitivity analyses**
- **There are uncertainties in the extrapolation of DFS and heterogeneity literature and utility sources for the different health states, however, extensive scenario and sensitivity analyses have been provided, showing that atezolizumab is cost-effective in all scenarios (PAS and list price)**
- **In a potentially curative setting, preventing early lung cancer recurrence or progression to metastatic disease has significant benefits for both patients and society**

B.3.10.1 Relevance of the economic evaluation for decision problem

The populations included in the economic evaluation are consistent with the population in the IMpower010 trial and the UK NSCLC population.

The analysis is applicable to clinical practice in England since:

- The patient population in IMpower010 trial and the economic evaluation are reflective of patients following resection and platinum-based chemotherapy with NSCLC whose tumours have PD-L1 expression on $\geqslant$ 50% of tumour cells excluding patients with an EGFR-positive and ALK-positive mutation. Advice from clinical experts suggest that the IMpower010 trial is broadly consistent with UK patients treated in clinical practice. Therefore, the outcomes observed in the trial are expected in UK patients.
- The economic structure is consistent with the model structure TA1014, ID5120 and ID390 in a similar indication.
- The resource utilisation and unit costs are reflective of UK clinical practice and were mainly derived from the NHS reference costs, PSSRU, BNF and eMIT and previous NICE submissions in NSCLC, as well as from clinical expert opinion.
- Extensive scenario and sensitivity analyses were conducted in the economic model, considering alternative approaches to the extrapolation of DFS, alternative parameter inputs and data sources.
- The outputs of the model were validated against available published sources and UK clinical expert opinion to ensure the clinical plausibility of the model and its applicability to the UK.

B.3.10.2 Strengths and weaknesses of the evaluation

The key strengths associated with the cost effectiveness analysis are related to the use of the best available evidence and methods to inform the model, as well as extensive scenario and sensitivity analyses as mentioned in Section B.3.8.

- IMpower010 RCT: IMpower010 is a randomised, multicentre, open-label, Phase III trial, with the comparator being current standard of care in the UK. As

a result, the data used in this cost-effectiveness analysis is a reliable source to inform decision-making.

- Modelling and validation: The modelling approach and structure was extensively validated in 2022 and in 2024 to ensure the validated of our assumptions through literature and leading UK oncologists during multiple Advisory boards.

- DFS curve adjustment: Numerous assumptions have been made to address any uncertainty in DFS and a conservative approach was taken to resolve this uncertainty such as the treatment waning effect was applied, the cure proportion (79% literature vs. 95% UK clinical opinion), SMR 1.25.

- SLRs and evidence: Numerous SLRs, such as cost-effectiveness, clinical, costs SLRs, were run within the appropriate time-frame to inform key parameters and inputs of the model.

- Scenario and sensitivity analysis: Extensive sensitivity and scenario analyses were conducted at PAS price and list price to test the sensitivity of atezolizumab and atezolizumab remains cost-effective or dominant in all scenarios.

The economic evaluation is also associated with some limitations. These are considered below:

- Extrapolation – Best efforts were made to ensure the methods were statistically sound, clinically plausible, and reflective of real-world clinical practice. More flexible models such as mixture-cure models were not considered as the follow-up period of the trial is not sufficiently long enough to have meaningful data to assess the extent of long-term survivorship. However, as expected, choice of parametric fit is not as important as cure assumption as this has the biggest impact on the ICER. Extensive sensitivity and scenario analyses were conducted to inform the impact of alternative extrapolation models and assess the long-term plausibility and appropriateness of each scenario.

- PRO data – No PRO data was collected as part of IMpower010. The systematic literature review (Appendix J showed that there is a lack of published literature

capturing long-term QoL data relevant for the model health states of interest. The published literature used to provide the health state utility values could impact the results given the heterogeneity of the different sources, however, Roche has provided extensive scenario analyses to show the minor impact on the ICER when varying the values and where possible, the same source was used for multiple progressive states.

- DFS as a surrogate for OS – In the absence of long-term OS data (the 'gold standard' in terms of outcomes for oncology), DFS is used in the model. We validated this with UK clinical oncologists who considered that the adjuvant setting means measurable disease and recurrence which could correlate well with OS.
- Subsequent therapies – Based on UK clinical oncologists' opinion, subsequent treatments in the non-metastatic, first-line and second-line metastatic were derived. Efficacy and safety for these subsequent treatments were informed by literature, NICE TAs and RCTs.

Roche have aimed to address limitations by adopting conservative assumptions and following robust methodology where possible, testing the impact on the ICER, providing thorough sensitivity and scenario analyses, and ultimately providing an appropriate cost effectiveness analysis to assist decision-making.

B.3.10.3 Conclusions

Currently there is a high unmet need for NSCLC patients in the adjuvant setting. Atezolizumab offers an innovative approach to adjuvant therapy through targeting a different mechanism of action versus currently used conventional therapies.

There were no new safety signals demonstrated in IMpower010 latest data cut (26th January 2024) and the safety profile for adjuvant atezolizumab is consistent with that established for atezolizumab monotherapy across multiple indications and lines of therapy and also showed no new safety signals. These positive findings suggest that atezolizumab after adjuvant chemotherapy might offer a promising treatment option that extends DFS in patients with completely resected NSCLC which expressed PD-L1 on 50% or more of tumour cells, without ALK- positive and EGFR-positive mutation,

and has not progressed after platinum based chemotherapy, even beyond the treatment period.

In the economic analysis, the results show that atezolizumab offers a new highly cost-effective treatment option for adjuvant patients at PAS and list price. The analysis demonstrates that earlier intervention with atezolizumab could both delay and prevent disease progression, which is associated with a reduction in both the costs and clinical burden of NSCLC, whilst also delivering less progression to the metastatic setting.

Atezolizumab in the adjuvant setting offers an incremental QALY gain at an increased cost to the healthcare system with ICERs significantly below the cost effectiveness threshold at PAS price vs BSC and pembrolizumab despite taking an overall conservative approach to the modelling (treatment waning at 60 months, 79% vs. 95% cure proportion, 1.25 = SMR). These results are further quantified in addressing uncertainty in the analysis through sensitivity and scenario analyses, evidencing further the cost-effective potential of atezolizumab in the adjuvant setting.

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Additional clarification questions related to the NMA that was submitted as part of the company's response to the initial clarification question.

1. Note, the EAG has already made multiple changes to the model supplied at clarification stage. It believes it will be quicker to change any parameter values in the EAG-adapted model rather than to make these changes in a new model. Can the company make sure it details all changes (if any) made to parameters within a new model, so that these can be replicated?

   Please refer to Question 3 to replicate the only change the company is making to the model.

2. The EAG believes it likely in the appraisal of pembrolizumab that the committee used the fully-licensed population for the HR for pembrolizumab for all PD-L1 groups, rather than the subgroup specific HRs. Could the company provide additional NMAs using the PD-L1 high population from the IMpower010 trial and the full licenced population (post-chemo, irrespective of PD-L1) from the PEARLS trial, using the most recent data cut-off for PEARLS as is shown in the most recent NICE committee slides (3rd October 2024)? Please update the model to include the mean from the CODA samples as the point estimate, and the CODA samples themselves for probabilistic analyses.

   The request above involves comparing different patient populations with respect to tumour characteristics and biomarker status, and the company would like to highlight that such a comparison would not be in line with the existing methods of population adjustment. Specifically, Chapter 11 of the Cochrane Handbook: "A valid network meta-analysis relies on the assumption that the different sets of studies included in the analysis are similar, on average, in all important factors that may affect the relative effects" (1).

   From a methodological perspective, comparing treatments for PD-L1 high versus mixed populations in non-small cell lung cancer (NSCLC) presents several significant challenges. A major issue here is heterogeneity. The PD-L1 high population and the mixed PD-L1 population have distinct biological characteristics and display varying responses to cancer immunotherapy (CIT). This heterogeneity will likely introduce bias, as the baseline characteristics and treatment responses of these two groups are not directly comparable.

Additionally, the outcomes measured in studies involving PD-L1 high populations may differ significantly from those measured in mixed populations, complicating the synthesis and comparison of results. These differences make it nearly impossible to draw accurate and reliable comparisons between the two populations.

Lastly, from a clinical perspective, PD-L1 status is a key biomarker for guiding treatment and influencing disease progression in NSCLC. Any method applied to compare the treatment effect without considering the specific population's PD-L1 status is likely to lead to implausible results and biased conclusions.

In summary, for these methodological and clinical reasons, the company finds this analysis unsuitable especially as adjuvant atezolizumab is only licenced in the PD-L1 high population (≥50%). Consequently, the company has not provided the requested analysis in this response as this could lead to potentially misleading conclusions.

3. Please could the company provide results on the ln(HR) scale and clarify how these relate to the point estimates (cells F30 and G30 in the Network Meta-Analysis Results worksheet) and CODA samples (cells F15064:G20063 Network Meta-Analysis Results worksheet) used within the economic model.

   The results of the comparisons on the ln(HR) scale are presented Table 1. The CEM uses the ln(HR) of the pembrolizumab versus atezolizumab comparison to account for the treatment effect of pembrolizumab when evaluating the cost-effectiveness of atezolizumab versus pembrolizumab.

Table 1: Estimated treatment effects (log hazard ratio scale) for DFS (PD-L1 high)

Treatment comparisons	Mean posterior ln(HR) (95% CI)		
	Fixed effects model	Random effects model	
		Log-normal (-3.95, 1.792) prior for tau	Half-normal (0.1) for tau
Atezolizumab vs. Placebo	[redacted]	[redacted]	[redacted]

Pembrolizumab vs. Placebo	[redacted]	[redacted]	[redacted]
Atezolizumab vs Pembrolizumab	[redacted]	[redacted]	[redacted]
Pembrolizumab vs Atezolizumab	[redacted]	[redacted]	[redacted]
Residual deviance	[redacted]	[redacted]	[redacted]
DIC	[redacted]	[redacted]	[redacted]

Crl: credible interval; DIC: deviance information criteria; HR: Hazard ratio;
Informative prior: log normal [-3.95, 1.79^2] from Turner 2015 (Table IV) (2), Half-normal (0.1) from Lilienthal 2024 (3).
For log-normal prior RE model: tau on the logHR scale is 0.06 (95% Crl: 0.00 to 0.42)
For half-normal prior RE model: tau on the logHR scale is 0.08 (95% Crl: 0.00 to 0.22)

The point estimates in cells F30 and G30 in the Network Meta-Analysis Results worksheet should, thus, equal 0.5 (fixed effects model) and either 0.51 or 0.50 (random effects model). In the CEM that was previously sent, the estimates 0.54 (fixed effects model) and 0.56 (random effects model) are incorrectly used which were calculated by manually log transforming the hazard ratios presented in Table 2 for the comparison. The impact of this discrepancy on the ICER is minimal with the deterministic results continuing to show atezolizumab as dominant at atezolizumab PAS price.

Table 2: Estimated treatment effects for DFS (PD-L1 high)

Treatment comparisons	Mean posterior HR (95% Crl)	
	Fixed effects model	Random effects model
Atezolizumab vs. Placebo	[redacted]	[redacted]
Pembrolizumab vs. Placebo	[redacted]	[redacted]
Atezolizumab vs Pembrolizumab	[redacted]	[redacted]
Pembrolizumab vs Atezolizumab	[redacted]	[redacted]
Residual deviance	[redacted]	[redacted]
DIC	[redacted]	[redacted]

Crl: credible interval; DIC: deviance information criteria; HR: Hazard ratio; Informative prior = log normal [-3.95, 1.792] from Turner 2015 (Table IV) (2).

The CODA samples in use are already on the ln(HR) scale and are drawn from the posterior distribution on the treatment effect of pembrolizumab versus atezolizumab that is generated by the analysis.

4. Please provide the posterior mean and 95% credible intervals of tau for all random effects analyses.

   The NMA results on the ln(HR) or ln(OR) scale from the fixed and two random-effects models (with log-normal and half-normal informative priors) are presented in the tables below. The posterior mean and 95% credible intervals of tau for all random effects analyses are also provided in the table footnotes.

   Table 3 shows the estimated treatment effects (log hazard ratio scale) for DFS (PD-L1 high).

Table 3: Estimated treatment effects (log hazard ratio scale) for DFS (PD-L1 high)

Treatment comparisons	Mean posterior ln(HR) (95% CrI)		
	Fixed effects model	Random effects model	
		Log-normal (-3.95, 1.792) prior for tau	Half-normal (0.1) for tau
Atezolizumab vs. Placebo	[redacted]	[redacted]	[redacted]
Pembrolizumab vs. Placebo	[redacted]	[redacted]	[redacted]
Atezolizumab vs Pembrolizumab	[redacted]	[redacted]	[redacted]
Pembrolizumab vs Atezolizumab	[redacted]	[redacted]	[redacted]
Residual deviance	[redacted]	[redacted]	[redacted]
DIC	[redacted]	[redacted]	[redacted]

CrI: credible interval; DIC: deviance information criteria; HR: Hazard ratio;
Informative prior: log normal [-3.95, 1.792] from Turner 2015 (Table IV) (2), Half-normal (0.1) from Lilienthal 2024 (3).
For log-normal prior RE model: tau on the logHR scale is 0.06 (95% CrI: 0.00 to 0.42)
For half-normal prior RE model: tau on the logHR scale is 0.08 (95% CrI: 0.00 to 0.22)

Table 4 shows the estimated treatment effects (log odds ratio scale) for 3-year DFS (PD-L1 high).

Table 4: Estimated treatment effects (log odds ratio scale) for 3-year DFS (PD-L1 high)

Treatment comparisons	Mean posterior ln(OR) (95% CrI)		
	Fixed effects model	Random effects model	
		Log-normal (-3.95, 1.792) prior for tau	Half-normal (0.2) for tau
Atezolizumab vs. Placebo	[redacted]	[redacted]	[redacted]
Pembrolizumab vs. Placebo	[redacted]	[redacted]	[redacted]
Atezolizumab vs Pembrolizumab	[redacted]	[redacted]	[redacted]
Pembrolizumab vs Atezolizumab	[redacted]	[redacted]	[redacted]
Residual deviance	[redacted]	[redacted]	[redacted]
DIC	[redacted]	[redacted]	[redacted]

CrI credible interval; DIC deviance information criteria; HR: Hazard ratio;
Informative prior: log normal [-3.95, 1.792] from Turner 2015 (Table IV) (2), Half-normal (0.2) from Lilienthal 2024 (3).
For log-normal prior RE model: tau on the logHR scale is 0.06 (95% CrI: 0.00 to 0.40)
For half-normal prior RE model: tau on the logHR scale is 0.16 (95% CrI: 0.01 to 0.45)

5. In Tables 2, 4, 6 and 8 of the NMA report, the input data to the NMA is presented, please could the company clarify the source of the data within each of these tables, highlighting the populations for which these values correspond (including the stage, PD-L1 status, chemo status, ALK/EGFR status, data cut-off for both trials).

   The company has updated tables and provided the relevant tables below, which now include the source of data within each table and the patient characteristics. The reported DFS data for PD-L1 high (≥50%) patients from the two studies are listed in Table 7.

Table 7: Summary of included study characteristics for the DFS endpoint in PD-L1 high patients

Study	Treatment arm	N (patients)	Patient characteristics	HR (95% CI), placebo reference
Impower10	Placebo	114	Disease stage: Stage II-IIIA PD-L1 status: PD-L1 ≥50% Chemo status: Cisplatin-based chemotherapy given to both groups post-enrolment but pre-randomization ALK status: Positive (2.6%); Negative (54.1%); Unknown (42.3%) EGFR status: Positive (6.1%); Negative (54.1%); Unknown (39.7%) Cut-off date: Jan 2024	0.503 (0.33, 0.76)
Impower10	Atezolizumab	115		
PEARLS/KEYNOTE-091	Placebo	165	Disease stage: IB-IIIA PD-L1 status: PD-L1 ≥50% Chemo status: 143 (85%) patients received adjuvant chemotherapy, rest 15% have not received adjuvant chemotherapy ALK status: Positive (2%); Negative (33.9); Unknown (64.1%) EGFR status: Positive (3.3%); Negative (37.2); Unknown (59.5%) Cut-off date: Jan 2023	0.83 (0.59, 1.16)
PEARLS/KEYNOTE-091	Pembrolizum	168		

Table 8 shows a summary of included study characteristics for the 3-year DFS endpoint in PD-L1 high patients.

Table 8: Summary of included study characteristics for the 3-year DFS endpoint in PD-L1 high patients

Study	Treatment arm	N (patients)	Patient characteristics	r (disease recurrence)
Impower10	Placebo	114	Disease stage: Stage II-IIIA PD-L1 status: PD-L1 ≥50% Chemo status: Cisplatin-based chemotherapy given to both groups post-enrolment but pre-randomization ALK status: Positive (2.6%); Negative (54.1%); Unknown (42.3%) EGFR status: Positive (6.1%); Negative (54.1%); Unknown (39.7%) Cut-off date: Jan 2024	53
Impower10	Atezolizumab	115		29
PEARLS/KEYNOTE-091	Placebo	165	Disease stage: IB-IIIA PD-L1 status: PD-L1 ≥50% Chemo status: 143 (85%) patients received adjuvant chemotherapy, rest 15% have not received adjuvant chemotherapy ALK status: Positive (2%); Negative (33.9); Unknown (64.1%) EGFR status: Positive (3.3%); Negative (37.2); Unknown (59.5%) Cut-off date: Sept 2021	69
PEARLS/KEYNOTE-091	Pembrolizumab	168		57

The reported DFS data for PD-L1 positive (≥1%) patients from the two studies are listed in Table 9.

Table 9: Summary of included study characteristics for the DFS endpoint in PD-L1 positive patients

Study	Treatment arm	N (patients)	Patient characteristics	HR (95% CI), placebo reference	r (disease recurrence)
Impower10	Placebo	228	Disease stage: Stage II-IIIA PD-L1 status: PD-L1 ≥1% Chemo status: Cisplatin-based chemotherapy given to both groups post-enrolment but pre-randomization ALK status: Positive (4.8%); Negative (53.4%); Unknown (41.8%) EGFR status: Positive (9.0%); Negative (52.1%); Unknown (38.9%) Cut-off date: Jan 2024	0.7 (0.55, 0.91)	127
Impower10	Atezolizumab	248			113

PEARLS/KEYNOTE-091	Placebo	355	Disease stage: IB-IIIA PD-L1 status: PD-L1 ≥1% Chemo status: NR ALK status: NR EGFR status: NR Cut-off date: Sept 2021	n/r	154
PEARLS/KEYNOTE-091	Pembrolizumab	357			123

n/r = not reported

The reported 3-year DFS data for PD-L1 positive (≥1%) patients from the two studies are listed in Table 10.

Table 10: Summary of included study characteristics for the 3-year DFS endpoint in PD-L1 positive patients

Study	Treatment arm	N (patients)	Patient characteristics	r (disease recurrence)
Impower10	Placebo	228	Disease stage: Stage II-IIIA PD-L1 status: PD-L1 ≥1% Chemo status: Cisplatin-based chemotherapy given to both groups post-enrolment but pre-randomization ALK status: Positive (4.8%); Negative (53.4%); Unknown (41.8%) EGFR status: Positive (9.0%); Negative (52.1%); Unknown (38.9%) Cut-off date: Jan 2024	109
Impower10	Atezolizumab	248		93

PEARLS/KEYNOTE-091	Placebo	355	Disease stage: IB-IIIA PD-L1 status: PD-L1 ≥1% Chemo status: NR ALK status: NR EGFR status: NR Cut-off date: Sept 2021	174
PEARLS/KEYNOTE-091	Pembrolizumab	357		143

6. The company uses Schoenfeld residuals to assess the proportional hazard assumption in Section 7.2 of the Feasibility Assessment, please could it also provide log-log plots to further support this assumption of proportional hazards.

   Figure 1 shows the log cumulative hazards against time for DFS in IMpower010.

Figure 1: Log cumulative hazards plot for DFS in Impower010

Figure 2 shows the log cumulative hazards against time for OS in IMpower010.

Figure 2: Log cumulative hazards plot for OS in Impower010

Figure 3 shows the log cumulative hazards against log time for DFS in PEARLS/KEYNOTE-091.

Figure 3: Log cumulative hazards plot for DFS in PEARLS/KEYNOTE-091

Figure 4 shows the log cumulative hazards against log time for DFS in PEARLS/KEYNOTE-091.

Figure 4: Log cumulative hazards plot for OS in PEARLS/KEYNOTE-091

Figure 5 shows the log cumulative hazards against log time for DFS in CANOPY-A.

Figure 5: Log cumulative hazards plot for DFS in CANOPY-A

Figure 6 shows the log cumulative hazards against log time for DFS in CANOPY-A.

Figure 6: Log cumulative hazards plot for OS in CANOPY-A

7. Please could the company provide further justification to that in Section 3.1.1 for the assumption of equivalence of BSC in the IMpower010 trial and the placebo arm in the PEARLS trial. The current text is not sufficient.

The assumption of equivalence between the BSC arm in the IMpower010 trial and the placebo arms in the PEARLS/KEYNOTE-091 trial is compellingly supported by both trial design and treatment regimens, as detailed in Table 11. In the IMpower010 trial, patients received 1 - 4 cycles of adjuvant platinum-based chemotherapy and then were randomised to receive adjuvant atezolizumab or best supportive care (best supportive care is defined as observation and regular scans for disease recurrence only). In the PEARSL/KEYNOTE-091 trial, a maximum of 4 platinum-based adjuvant chemotherapy was considered for stage IB disease and strongly recommended for Stage II and IIIA disease according to national and local guidelines. Patients were then randomised to receive adjuvant pembrolizumab or placebo (saline solution). The best supportive care received in IMpower010 and placebo received in PEARLS/KEYNOTE-091 involved no active treatments, only

observation, scans & saline solution, hence justifying the assumption of equivalence between the two arms

Despite IMpower010 being an open-label trial and PEARLS being double-blind, this difference is inconsequential regarding control arm outcomes since no active treatment was administered in any groups. Given the parallel post-surgical management protocols and absence of additional therapy in both trials, assuming equivalence between Best Support Care and placebo is reasonable.

Table 11: Trials included in master network (2 RCTS)

Trial	Intervention arm	Treatment class	Control arm	Definition of control arm	Timing of randomisation	Adjuvant chemotherapy received	Stratification factors

IMpower 010	Atezolizumab	PDL-1 inhibitor	Best supportive care (BSC)	No treatment other than 16 cycles of best supportive care which included observation and regular scans for disease recurrence	Post adjuvant chemotherapy	All received as per eligibility criteria	Sex Tumour histology Disease stage PD-L1 expression
PEARLS / KEYNOTE-091	Pembrolizumab	PD-1 inhibitor	Placebo	Saline administered Q3W for 18 doses	Mixed (post-surgery and post adjuvant chemotherapy)	Optional; 86% received	Disease stage Adjuvant chemotherapy PD-L1 expression Geography

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NICE National Institute for Health and Care Excellence

Single Technology Appraisal

Atezolizumab for adjuvant treatment of resected non-small-cell lung cancer (MA review of TA823) [ID6324]

Professional organisation submission

Thank you for agreeing to give us your organisation's views on this technology and its possible use in the NHS.

You can provide a unique perspective on the technology in the context of current clinical practice that is not typically available from the published literature.

To help you give your views, please use this questionnaire. You do not have to answer every question – they are prompts to guide you. The text boxes will expand as you type.

Information on completing this submission

- Please do not embed documents (such as a PDF) in a submission because this may lead to the information being mislaid or make the submission unreadable
- We are committed to meeting the requirements of copyright legislation. If you intend to include **journal articles** in your submission you must have copyright clearance for these articles. We can accept journal articles in NICE Docs.
- Your response should not be longer than 13 pages.

NICE National Institute for Health and Care Excellence

About you

1. Your name	[redacted]/ Jason Adhikaree
2. Name of organisation	British Thoracic Oncology Group
3. Job title or position	[redacted]/ Consultant Medical Oncologist/BTOG Steering Committee Member
4. Are you (please select Yes or No):	An employee or representative of a healthcare professional organisation that represents clinicians? Yes A specialist in the treatment of people with this condition? Yes A specialist in the clinical evidence base for this condition or technology? Yes Other (please specify):
5a. Brief description of the organisation (including who funds it).	The British Thoracic Oncology Group (BTOG) is the multi-disciplinary group for healthcare professionals involved with thoracic malignancies throughout the UK. BTOG is funded by registration fees for the annual conference and sponsorship
5b. Has the organisation received any funding from the manufacturer(s) of the technology and/or comparator products in the last 12 months? [Relevant manufacturers are listed in the appraisal matrix.] **If so, please state the name of manufacturer, amount, and purpose of funding.**	Yes Sponsorship BTOG 2024 annual conference £60,000+ VAT
5c. Do you have any direct or indirect links with, or funding from, the tobacco industry?	no

The aim of treatment for this condition

6. What is the main aim of treatment? (For example, to stop progression, to improve mobility, to cure the condition, or prevent progression or disability.)	The main aim is to increase the chance of cure and overall survival from lung cancer, reasonably surrogate as 5 yr-survival in the case of non-small cell lung cancer
7. What do you consider a clinically significant treatment response? (For example, a reduction in tumour size by x cm, or a reduction in disease activity by a certain amount.)	Clinically significant responses include disease free survival and overall survival at 5 years – likely constituting cure
8. In your view, is there an unmet need for patients and healthcare professionals in this condition?	Yes. Resectable NSCLC has a very poor prognosis. Prior to the Impower 10 trial the comparator (as in the trial) was best supportive care. 5-year survival in this patient cohort for stage II-IIIA NSCLC (AJCC v8) is 58%-31% with adjuvant chemotherapy alone after 'curative surgery'.

What is the expected place of the technology in current practice?

9. How is the condition currently treated in the NHS?	Since adjuvant Atezolizumab has been available for patients on the Cancer Drug Fund (CDF) for this indication, peri-operative including neoadjuvant chemo-immunotherapy has become available including Nivolumab and chemotherapy (TA876) and this month perioperative Pembrolizumab and chemotherapy (final NICE draft guidance approved). Hence a number of patients may have received PD-1/PDL1 blocking antibodies pre-op. However, there are still a significant proportion of patients whom are upstaged at surgery, mainly those whom

	the primary did not meet size criteria for neo-adjuvant, but have lymph node spread at surgery not seen on imaging/EBUS. There are also a small number of patients with large obstructing primary tumours with co-existing infection where surgical removal upfront may be safer than neoadjuvant chemo-imuunotherapy. This group of patients can then be offered sequential adjuvant chemotherapy and Atezolizumab if they meet the licenced indication criteria.
9a. Are any clinical guidelines used in the treatment of the condition, and if so, which?	NICE guidelines (NG122) specifically combination treatment for early stage disease (section 1.7), at the time of writing is out of date and does not reflect current practice. For example it does not cover the neo-adjuvant chemo-immunotherapy approach widely recommended for stage II and III disease. European Society of Medical Oncology (ESMO) likewise has not been updated The National Comprehensive Cancer Network (NCCN) recommends peri-operative approach although significant differences in licenced treatment options and hence not used widely in the UK.
9b. Is the pathway of care well defined? Does it vary or are there differences of opinion between professionals across the NHS? (Please state if your experience is from outside England.)	The UK current consensus is uniform that patients should be offered neo-adjuvant Nivolumab and chemotherapy where patient meet the criteria. If patient have not received a neo-adjuvant approach, adjuvant chemotherapy followed by Atezolizumab is offered to patients where they meet the criteria. What is yet to be defined internationally is which patients need a purely neoadjuvant chemo-immunotherapy approach or a peri-operative treatment (neo-adjuvant chemo-immunotherapy followed by adjuvant immunotherapy). Given the formal guidance is yet to be published on the latter (although peri-operative Pembrolizumab has been approved in draft guidance) this has not been a problem in the UK at the time of writing. This is not the scope of this appraisal however.
9c. What impact would the technology have on the current pathway of care?	Adjuvant Atezolizumab remains an important treatment option to patients whom have received upfront surgery and meet the criteria. It prolongs disease free survival and overall survival for select groups defined on the CDF.
10. Will the technology be used (or is it already used) in the same way as current care in NHS clinical practice?	If the current review is using the same indication criteria as TA823 then this is available on the CDF and in routine use throughout the NHS
10a. How does healthcare resource use differ	There will be no difference given this is used in routine NHS practice via the CDF

between the technology and current care?	
10b. In what clinical setting should the technology be used? (For example, primary or secondary care, specialist clinics.)	Secondary care in Oncology specialist clinic as is established throughout the UK
10c. What investment is needed to introduce the technology? (For example, for facilities, equipment, or training.)	No investment is required. Currently used as routine care and accessed via the CDF.
11. Do you expect the technology to provide clinically meaningful benefits compared with current care?	Yes. The comparator being best supportive care following chemotherapy.
11a. Do you expect the technology to increase length of life more than current care?	For those with PDL1 expression over 50% both disease free survival and overall survival was significantly increased.
11b. Do you expect the technology to increase health-related quality of life more than current care?	I have not seen trial data from Impower 10 published on QoL. One can extrapolate increase disease free survival would result in improved quality of life
12. Are there any groups of people for whom the technology would be more or less effective (or appropriate) than the general population?	Atezolizumab is licenced on the CDF for patient with tumours ≥40mm or any size tumour with lymph node involvement within a surgical field and PDL1 expression greater than 50%. We would not recommend Atezolizumab to the EGFR or ALK mutated population where there is low efficacy. Although Impower 10 did include this subgroup we would not usually recommend this based on efficacy in advanced disease and availability of adjuvant Osimertinib (TA761) and adjuvant Alectinib for ALK mutations in the future (approved in final draft guidance October 2024)

The use of the technology

13. Will the technology be easier or more difficult to use for patients or healthcare professionals than current care? Are there any practical implications for its use (for example, any concomitant treatments needed, additional clinical requirements, factors affecting patient acceptability or ease of use or additional tests or monitoring needed.)	The technology is currently in routine use within the NHS and hence there should be no resource issue. Since the initial CDF listing of Atezolizumab, this is available in a 4 weekly intravenous administration and 3 weekly subcutaneous dosing in addition to the trial 3 weekly intravenous regime. These having different dosing but similar bioavailability and have been appraised and currently available to NHS users.
14. Will any rules (informal or formal) be used to start or stop treatment with the technology? Do these include any additional testing?	The only rule of note now may be to exclude prior neo-adjuvant immunotherapy in combination with chemotherapy (TA816) and the forthcoming perioperative Pembrolizumab, which was not available when Atezolizumab was initially listed on the CDF.
15. Do you consider that the use of the technology will result in any substantial health-related benefits that are unlikely to be included in the quality-adjusted life year (QALY) calculation?	By increasing cure, there will be less patient requiring treatments on relapse such as chemo-radiotherapy followed by 1 year of Durvalumab for local disease or 2 years of Pembrolizumab either as a single agent (or indefinite Atezolizumab until progression/toxicity) or in combination with chemotherapy for stage palliative intent disease. Hence the cost of the immunotherapy can be higher (due to duration) on relapse. More than 50% relapse within 2years with chemotherapy treatment alone as adjuvant treatment.

16. Do you consider the technology to be innovative in its potential to make a significant and substantial impact on health-related benefits and how might it improve the way that current need is met?	Yes with chemotherapy alone the benefit to survival is only 5% increase to 5 year-survival. The overall survival published by Felip, E. et al. (Annals of Oncology, Volume 34, Issue 10, 907 – 919) showed in PDL1≥50% subgroup was 84.8% vs 70.0% in favour of Atezolizumab vs best supportive care were alive at 4 years.
16a. Is the technology a 'step-change' in the management of the condition?	Yes. This was the first immunotherapy drug licenced in the adjuvant setting, where the comparator was best supportive care. Prior to this only adjuvant chemotherapy alone was available with only small gain in survival (5% addition to 5year survival). The five year
16b. Does the use of the technology address any particular unmet need of the patient population?	Yes without this licence patients whom had upfront surgery only have adjuvant chemotherapy still as an adjuvant option
17. How do any side effects or adverse effects of the technology affect the management of the condition and the patient's quality of life?	Patient receiving adjuvant Atezolizumab can get immune related adverse events which are generally manageable and include fatigue, itching, arthralgia. In the trial 10.5% had to stop the treatment due to Atezolizumab related toxicity. Most severe toxicity do respond to prednisolone with 6-8weeks. A small proportion (<5%) may require longterm endocrine replacement therapy such as levothyroxine or hydrocortisone.

Sources of evidence

18. Do the clinical trials on the technology reflect current UK clinical practice?	Impower 010 reflected the UK practice at the time and is reflective for patient with upfront surgery and the CDF listed indication. The introduction of neo-adjuvant Nivolumab and chemotherapy has only been available within the NHS since March 2024 hence some patients meeting staging criteria will now have neo-adjuvant approach. Adjuvant Atezolizumab remains the only approved immunotherapy in the purely adjuvant phase for patients whom had upfront surgery.
18a. If not, how could the results be extrapolated to the UK setting?	Within the adjuvant licence without any prior neo-adjuvant treatment, this would fully extrapolated to the UK setting
18b. What, in your view, are the most important outcomes, and were they measured in the trials?	The most important outcome is both disease free survival and overall survival. Secondly, toxicity are also important. These are all recorded in the clinical trial. Quality of life data has not been published but it important.
18c. If surrogate outcome measures were used, do they adequately predict long-term clinical outcomes?	No surrogate outcomes were used. Overall survival has been reported. This data is following 4 year follow-up was published in October 2023. This is adequate since most relapsed are occur by 2-3 years of surgery.
18d. Are there any adverse effects that were not apparent in clinical	No

trials but have come to light subsequently?	
19. Are you aware of any relevant evidence that might not be found by a systematic review of the trial evidence?	No
20. How do data on real-world experience compare with the trial data?	A small 36 patient single institute experience suggested real world data was similar to published Impower 10 trial data (Zheng et al.2024 EP.08A.03 Real World Outcomes of Adjuvant Atezolizumab in NSCLC: A Single Institution Study, Journal of Thoracic Oncology (19), 10, S564-S565) A poster presented by Lee et al shows United states real world experience is comparable to Impower 10 trial including 155 patients (Real-world treatment patterns among resected NSCLC patients treated with adjuvant atezolizumab - IASLC-NACLC-2023-poster-albarmawi-real-world-treatment-patterns-among-resected-NSCLC-patients.pdf)

Equality

21a. Are there any potential equality issues that should be taken into account when considering this treatment?	No equality issues idenified
21b. Consider whether these issues are different from issues with current care and why.	Not applicable

Key messages

22. In up to 5 bullet points, please summarise the key messages of your submission.	• Atezolizumab improves overall survival and cure for early stage lung cancer • Atezolizumab improves disease free survival after surgery • This therapeutic option remains an important treatment for patients whom had upfront surgery • Relapse is high with adjuvant chemotherapy alone • The financial cost of relapse is higher given immunotherapy for up to 2 years (or beyond with Atezolizumab TA705) with palliative intent or 1 year immunotherapy with chemoradiotherapy with radical intent and justifies cost of 1year Atezolizumab compared to best supportive care

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Single Technology Appraisal

Atezolizumab for adjuvant treatment of resected non-small-cell lung cancer (MA review of TA823) [ID6324]

Clinical expert statement

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Part 1: Treating non-small-cell lung cancer and current treatment options

Table 1 About you, aim of treatment, place and use of technology, sources of evidence and equality

1. Your name	Dr Adam Januszewski
2. Name of organisation	British Thoracic Oncology Group
3. Job title or position	Consultant Thoracic Oncologist
4. Are you (please tick all that apply)	☒ An employee or representative of a healthcare professional organisation that represents clinicians? ☒ A specialist in the treatment of people with non-small-cell lung cancer? ☐ A specialist in the clinical evidence base for non-small-cell lung cancer or technology? ☐ Other (please specify):
5. Do you wish to agree with your nominating organisation's submission? (We would encourage you to complete this form even if you agree with your nominating organisation's submission)	☒ Yes, I agree with it ☐ No, I disagree with it ☐ I agree with some of it, but disagree with some of it ☐ Other (they did not submit one, I do not know if they submitted one etc.)
6. If you wrote the organisation submission and/or do not have anything to add, tick here. (If you tick this box, the rest of this form will be deleted after submission)	☐ Yes
7. Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	None.
8. What is the main aim of treatment for non-small-cell lung cancer? (For example, to stop progression, to improve mobility, to cure the condition, or prevent progression or disability)	To delay time to relapse and improve overall survival for patients with NSCLC

9. What do you consider a clinically significant treatment response? (For example, a reduction in tumour size by x cm, or a reduction in disease activity by a certain amount)	A reduction in risk of death from lung cancer by an absolute value of 10%
10. In your view, is there an unmet need for patients and healthcare professionals in non-small-cell lung cancer?	Yes
11. How is non-small-cell lung cancer currently treated in the NHS? • Are any clinical guidelines used in the treatment of the condition, and if so, which? • Is the pathway of care well defined? Does it vary or are there differences of opinion between professionals across the NHS? (Please state if your experience is from outside England.) • What impact would the technology have on the current pathway of care?	Current treatment is complex with a rapidly evolving field. Early-stage lung cancer cab treated with: 1. Neo-adjuvant chemo-immunotherapy vs. 2. Up front surgery followed by adjuvant chemotherapy +/- immunotherapy vs. 3. Peri-operative (ie pre and post surgery) chemotherapy and immunotherapy There are differences of expert opinion whether immunotherapy should be used before / after or sandwiched between surgery. Trial cross comparison is challenging and it is likely patient dependent (stage vs. PDL1 status in the context of performance status, frailty and co-morbidities). The pathways are complex and varied across England and the recent option of neo-adjuvant therapies means that patients sometimes see oncolgoists and surgeons prior to embarking on a treatment programme. This has largely been adopted across England, but there is some variation in implantation of pathways and challenges regarding access to molecular testing. England has been slower adopting the use of neo-adjuvant therapies compared to the US. This technology has already widespread adoption through the CDF.

	TA 1037: Pembrolizumab for adjuvant treatment for of resected non-small cell lung cancer (05-Feb-2025) TA1030: **Durvalumab with chemotherapy before surgery (neoadjuvant) then alone after surgery (adjuvant) for treating resectable non-small-cell lung cancer: Jan 2025** TA 1017: **Pembrolizumab with chemotherapy before surgery (neoadjuvant) then alone after surgery (adjuvant) for treating resectable non-small-cell lung cancer, 20-Nov 2024** **TA1014: Alectinib for adjuvant treatment of ALK-positive non-small-cell lung cancer, 13-Nov 2024** **TA876: Nivolumab with chemotherapy for neoadjuvant treatment of resectable non-small-cell lung cancer, 22-Mar-2023** **TA 761: Osimertinib for adjuvant treatment of EGFR mutation-positive non-small-cell lung cancer after complete tumour resection: 19-Jan 2022**
12. Will the technology be used (or is it already used) in the same way as current care in NHS clinical practice? • How does healthcare resource use differ between the technology and current care? • What treatment(s) are currently used for this population and therefore would consider appropriate comparator(s)? • In what clinical setting should the technology be used? (for example, primary or secondary care, specialist clinic) • What investment is needed to introduce the technology? (for example, for facilities, equipment, or training)	It is currently in use under Cancer Drugs Fund The same patient population could also be treated with: 1. Neo-adjuvant chemo-io: TA 876 2. Peri-operative Chemo-io: TA 1030 and TA 1017 3. Adjuvant Pembrolizumab: TA 1037 Direct comparator for adjuvant therapy would be in the form of NICE licenced Pembrolizumab TA 1037. This can be given 3 or 6 weekly for total of 1 year post-operatively. Atezolizumab could be given iv (4 weekly) or S/C (3 weekly) for PDL1 high population. Resource implications for clinical appointments with oncology and chemotherapy day unit treatment chairs. These would be used in secondary / tertiary oncology care

13. Do you expect the technology to provide clinically meaningful benefits compared with current care? • Do you expect the technology to increase length of life more than current care? • Do you expect the technology to increase health-related quality of life more than current care?	When compared to observation, atezolizumab provides a clinically meaningful and statistically significant improvement in progression free survival with expectation that utilisation of this treatment would increase number of patients who are cured of their lung cancer and in other delay time to progression.
14. Are there any groups of people for whom the technology would be more or less effective (or appropriate) than the general population? (For example, use of the technology in different PD-L1 groups or any other sub-groups)	PDL1 high sub-group (ie >50%) are expected to derive increased benefit
15. Will the technology be easier or more difficult to use for patients or healthcare professionals than current care? Are there any practical implications for its use? (For example, any concomitant treatments needed, additional clinical requirements, factors affecting patient acceptability or ease of use or additional tests or monitoring needed)	Already utilised as CDF with widespread adoption in England. Therefore this would not change. The alternative (adjuvant pembrolizumab) TA1037 is delivered iv every 6 weeks. The use of subcutaneous formulation of atezolizumab would see the potential for an innovative delivery modes in clinics / home that are more convenient for patients.
16. Will any rules (informal or formal) be used to start or stop treatment with the technology? Do these include any additional testing?	Started adjuvant platinum-doublet chemotherapy. No progression after platinum doublet chemotherapy (as determined by cross sectional imaging) No progression on treatment through imaging
17. Do you consider that the use of the technology will result in any substantial health-related benefits that are unlikely to be included in the quality-adjusted life year (QALY) calculation? • Do the instruments that measure quality of life fully capture all the benefits of the technology or have some been missed? For example, the treatment regimen	The use of subcutaneous atezolizumab would be an important consideration that allows easier administration with reduction in use of chemotherapy chair time and potential for delivery at home / mobile in certain services.

may be more easily administered (such as an oral tablet or home treatment) than current standard of care	
18. Do you consider the technology to be innovative in its potential to make a significant and substantial impact on health-related benefits and how might it improve the way that current need is met? • Is the technology a 'step-change' in the management of the condition? • Does the use of the technology address any particular unmet need of the patient population?	It is / was a step change when the standard of care / comparator was observation only. This is now a complex treatment pathway with many patients receiving neo-adjuvant or peri-operative immunotherapy. The requirement for post-operative adjuvant immunotherapy will remain for more frail individuals not suitable for upfront chemo-io or those found to have unexpected to be upstaged at surgery and therefore require adjuvant chemo + immunotherapy (that may not be part of the original treatment plan) There is still much debate regarding how much immunotherapy is enough for patients. Whether upfront (neoadjuvant) vs. Post-op (adjuvant) vs. peri-operative immunotherapy is the correct treatment. It is without a doubt that immunotherapy is required in this cohort of patients. There are no direct head to head trials to understand which paradigm is optimal. I suspect that it will be individual based on the patient, fitness and comorbidities.
19. How do any side effects or adverse effects of the technology affect the management of the condition and the patient's quality of life?	Immune-related adverse events, should they develop, would require management which can require increased clinic appointments, time in hospital and use of steroids / immunosuppressants to control the toxicities. These can be temporary or long-term sequelae. Sometimes referrals to other specialties are required to control / diagnose these adverse events.
20. Do the clinical trials on the technology reflect current UK clinical practice? • If not, how could the results be extrapolated to the UK setting? • What, in your view, are the most important outcomes, and were they measured in the trials?	Yes

• If surrogate outcome measures were used, do they adequately predict long-term clinical outcomes? • Are there any adverse effects that were not apparent in clinical trials but have come to light subsequently?	
21. Are you aware of any relevant evidence that might not be found by a systematic review of the trial evidence?	No
22. Are you aware of any new evidence for the comparator treatment(s) since the publication of NICE technology appraisal guidance [TA1017]?	No
23. How do data on real-world experience compare with the trial data?	Real world data and experience is that adjuvant atezolizumab is well tolerated and appears to mirror that observed in the Impower010 trial. It is important to note that not all patients are eligible due to fitness for any adjuvant therapy. In fact, a significant number of patients are simply not well enough post-operatively (20 – 40% according to different case series). Therefore caution needs to be exhibited in any indirect comparisons between neo-adjuvant, peri-operative and adjuvant immunotherapy.
24. NICE considers whether there are any equalities issues at each stage of an evaluation. Are there any potential equality issues that should be taken into account when considering this condition and this treatment? Please explain if you think any groups of people with this condition are particularly disadvantaged. Equality legislation includes people of a particular age, disability, gender reassignment, marriage and civil partnership, pregnancy and maternity, race, religion or belief, sex, and sexual orientation or people with any other shared characteristics.	Lung cancer is associated with age and deprivation who are a more frail patient population. As with most trials, patients are only eligible for treatment if they have a good performance status. Mandating that excludes some patients that may benefit. This is of importance in this radical setting. Access to pre-habilitation in order to provide optimisation and rehabilitation is critical to opening access to treatments.

Please state if you think this evaluation could • exclude any people for which this treatment is or will be licensed but who are protected by the equality legislation • lead to recommendations that have a different impact on people protected by the equality legislation than on the wider population • lead to recommendations that have an adverse impact on disabled people. Please consider whether these issues are different from issues with current care and why. More information on how NICE deals with equalities issues can be found in the NICE equality scheme. Find more general information about the Equality Act and equalities issues here.	

Part 2: Key messages

In up to 5 sentences, please summarise the key messages of your statement:

Adjuvant atezolizumab has provided a clinically meaningful stepwise improvement in care of patients with resected PDL1 high NSCLC

This technology has been utilised through the CDF with widespread adoption and real-world experience that mirrors the trial outcomes and toxicity profile

Since the publication of this data, immunotherapy in early stage lung cancer has been shown to be fundamental to improving outcomes (in what otherwise still has poor long term outcomes)

The options for treatment in the early-stage setting has become significantly more complex with indirect trial comparison complicated. There are differences of expert opinion whether immunotherapy should be best delivered pre-op, post-op or peri-operatively and ultimately an individualised patient approach is what will be required based on fitness, co-morbidities in the context of tumour characteristics (ie stage, PDL1 status)

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Atezolizumab for adjuvant treatment of resected non-small-cell lung cancer (MA review of TA823) [ID6324].

A Single Technology Appraisal

Produced by Sheffield Centre for Health and Related Research (SCHARR), The University of Sheffield

Authors Matt Stevenson, Professor of Health Technology Assessment, SCHARR, University of Sheffield, Sheffield, UK
Jessica E. Forsyth, Research Associate, SCHARR, University of Sheffield, Sheffield, UK
Katy Cooper, Senior Research Fellow, SCHARR, University of Sheffield, Sheffield, UK
Andrew Rawdin, Research Assistant, SCHARR, University of Sheffield, Sheffield, UK
Ruth Wong, Information Specialist, SCHARR, University of Sheffield, Sheffield, UK
Nicole Dorey, Consultant Clinical Oncologist and Clinical Lead for Radiotherapy, Torbay and South Devon NHS Foundation Trust, UK
Robin Young, Consultant Medical Oncologist, Weston Park Cancer Centre, Sheffield, UK

Correspondence Author Matt Stevenson, Professor of Health Technology Assessment, SCHARR, University of Sheffield, Sheffield, UK

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Rider on responsibility for report

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Contributions of authors

Matt Stevenson led the project and he, and Andrew Rawdin, were responsible for critiquing the company's model and running the EAG's exploratory analyses. Jessica Forsyth critiqued the company's statistical analyses and ran the EAG's network meta-analysis. Katy Cooper critiqued the company's systematic review and Ruth Wong critiqued the company's search strategy. Nicole Dorey and Robin Young provided clinical advice to the EAG.

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ABBREVIATIONS

ADAs	Anti-drug antibodies
AEs	Adverse events
AESIs	Adverse events of special interest
ALK	Anaplastic lymphoma kinase
AM	Active monitoring
ATA	Anti-therapeutic antibodies
BSC	Best supportive care
CI	Confidence interval
CIT	Cancer immunotherapy
CODA	Convergence diagnosis and output
cPAS	Comparator patient access schemes
CrI	Credible interval
CS	Company submission
DIC	Deviance information criterion
DFS	Disease-free survival
DPP	Decision problem population
EA	Exploratory analysis
EAG	External assessment group
EGFR	Epidermal growth factor receptor
eMIT	Electronic market information tool
EORTC QLQ-C30	European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire core quality of life questionnaire,
EORTC QLQ-LC13	European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire lung cancer specific
EQ-5D	EuroQol 5-Dimensions
EQ-5D-3L	EuroQol 5-Dimensions (3 level)
FLP	Full licensed population
HCRU	Health care resource use
HRQoL	Health-related quality of life
ICER	Incremental cost effectiveness ratio
ITC	Indirect treatment comparison
IV	Intravenous
MHRA	Medicines and Healthcare products Regulatory Agency
NHS	National Health Service
NICE	National Institute for Health and Care Excellence

NMA	Network meta-analysis
NSCLC	Non-small-cell lung cancer
OR	Odds ratio
OS	Overall survival
PD-L1	Programmed death-ligand 1
PRO	Patient reported outcome
PSS	Personal social services
Q2W	Every 2 weeks
Q3W	Every 3 weeks
Q4W	Every 4 weeks
QALY	Quality-adjusted life years
SA	Sensitivity analysis
SACT	Systemic anti-cancer therapy
SC	Subcutaneous
SLR	Systematic literature review
SMC	Scottish Medicines Consortium
SMR	Standardised mortality rate

1. EXECUTIVE SUMMARY

1.1 Overview of the EAG's key issues

The EAG had no key issues. Minor issues were noted but the cumulative impact on the incremental cost-effectiveness ratio (ICER) was low, changing the company's base case estimate of £3233 to £3453 when adjuvant atezolizumab was compared to active monitoring (AM). Atezolizumab dominated pembrolizumab in both the company's and the EAG's base cases, although the patient access scheme price for pembrolizumab was not considered.

1.2 Overview of key model outcomes

NICE technology appraisals estimate how much a new technology changes the length of life and the quality of life using the change in QALYs.

The company's model assumes that atezolizumab, compared with both AM and pembrolizumab, affects QALYs by:

- Maintaining patients in the disease-free survival (DFS) health state for longer and therefore increasing the quality of, and extending the length of, life.

The company's model assumes that atezolizumab affects costs by:

- The patient access scheme price for atezolizumab being less than the list price for pembrolizumab (therefore saving costs in this comparison)
- Increasing costs compared with AM due to the acquisition price of atezolizumab
- Reducing the time spent in more expensive health states due to the longer time spent in DFS
- Reducing the number of non-small cell lung cancer deaths which were assumed to be relatively expensive compared with other causes of death.

1.3 The decision problem: summary of the EAG's key issues

The EAG identified no key issues.

1.4 The clinical effectiveness evidence: summary of the EAG's key issues

The EAG identified no key issues; however, did believe there were limitations within the company's NMA comparing the relative efficacy of atezolizumab and pembrolizumab. When using the EAG's preferred NMA, the incremental cost-effectiveness ratio (ICER) did not noticeably change.

1.5 The cost-effectiveness evidence: summary of the EAG's key issues

The EAG identified no key issues but identified multiple minor limitations which were amended in the EAG's exploratory analyses (EA). However, these did not markedly change the ICER.

1.6 Other key issues: summary of the EAG's key issues

No other key issues were identified.

1.7 Summary of EAG's preferred exploratory analyses

Table 1 provides the results from the EAG's exploratory analyses.

Table 1 Results of the EAG's exploratory analyses

	Costs (£)	QALYs	Incremental Cost (£)	Incremental QALYs	Cost per QALY gained (£)*
The company's deterministic base case					
AM	[redacted]	[redacted]	-	-	-
Atezolizumab	[redacted]	[redacted]	[redacted]	[redacted]	3233
Pembrolizumab	[redacted]	[redacted]	[redacted]	[redacted]	Dominated
EA1 (amending the indirect treatment comparison with pembrolizumab)					
AM	[redacted]	[redacted]	-	-	-
Atezolizumab	[redacted]	[redacted]	[redacted]	[redacted]	3233
Pembrolizumab	[redacted]	[redacted]	[redacted]	[redacted]	Dominated
EA2 (amending the cure proportion at 5 years)					
AM	[redacted]	[redacted]	-	-	-
Atezolizumab	[redacted]	[redacted]	[redacted]	[redacted]	2642
Pembrolizumab	[redacted]	[redacted]	[redacted]	[redacted]	Dominated
EA3 (increasing the administration costs in cycle 1 for atezolizumab)					
AM	[redacted]	[redacted]	-	-	-
Atezolizumab	[redacted]	[redacted]	[redacted]	[redacted]	3354
Pembrolizumab	[redacted]	[redacted]	[redacted]	[redacted]	Dominated
EA4 (increasing the follow up times for atezolizumab and pembrolizumab to 6 years)					
AM	[redacted]	[redacted]	-	-	-
Atezolizumab	[redacted]	[redacted]	[redacted]	[redacted]	3347
Pembrolizumab	[redacted]	[redacted]	[redacted]	[redacted]	Dominated
EA5 (increasing the cost of GP appointments to £49)					
AM	[redacted]	[redacted]	-	-	-
Atezolizumab	[redacted]	[redacted]	[redacted]	[redacted]	3214
Pembrolizumab	[redacted]	[redacted]	[redacted]	[redacted]	Dominated
EA6 (increasing the cost of non-lung cancer deaths to £12,726)					
AM	[redacted]	[redacted]	-	-	-

	Costs (£)	QALYs	Incremental Cost (£)	Incremental QALYs	Cost per QALY gained (£)*
Atezolizumab	[redacted]	[redacted]	[redacted]	[redacted]	3748
Pembrolizumab	[redacted]	[redacted]	[redacted]	[redacted]	Dominated
EA7 (increasing the utility decrement of metastatic disease)					
AM	[redacted]	[redacted]	-	-	-
Atezolizumab	[redacted]	[redacted]	[redacted]	[redacted]	3162
Pembrolizumab	[redacted]	[redacted]	[redacted]	[redacted]	Dominated
EAG base case (EA1 – EA7)					
AM	[redacted]	[redacted]	-	-	-
Atezolizumab	[redacted]	[redacted]	[redacted]	[redacted]	3453
Pembrolizumab	[redacted]	[redacted]	[redacted]	[redacted]	Dominated
Probabilistic EAG base case (vs AM)					
AM	[redacted]	[redacted]	-	-	-
Atezolizumab	[redacted]	[redacted]	[redacted]	[redacted]	3462
Probabilistic EAG base case (vs pembrolizumab)					
Atezolizumab	[redacted]	[redacted]	-	-	-
Pembrolizumab	[redacted]	[redacted]	[redacted]	[redacted]	Dominated

AM: active monitoring; EA: exploratory analysis QALY: quality-adjusted life year

*full incremental analysis

2 BACKGROUND

2.1 Critique of company's description of underlying health problem

The underlying health problem is described in Section B1.3 of the company submission (CS).[1] The external assessment group (EAG) has no concerns with the general description of early non-small-cell lung cancer (NSCLC) and with data relating to the prognosis and treatment of NSCLC.

2.2 Critique of company's overview of current service provision

In the CS,[1] the company provides a detailed account of potential treatment options for early NSCLC. These include the use of surgery, platinum-based chemotherapy, cancer immunotherapy (CIT) and "*novel adjuvant treatments*".

The positioning of atezolizumab is as an adjuvant treatment following complete resection for adult patients with NSCLC with a programmed death-ligand 1 (PD-L1) expression in 50% or more of tumour cells, who do not have an epidermal growth factor receptor (EGFR) mutation or anaplastic lymphoma kinase (ALK)-positive NSCLC, who have not progressed after platinum-based doublet chemotherapy and who are at a high risk of recurrence.

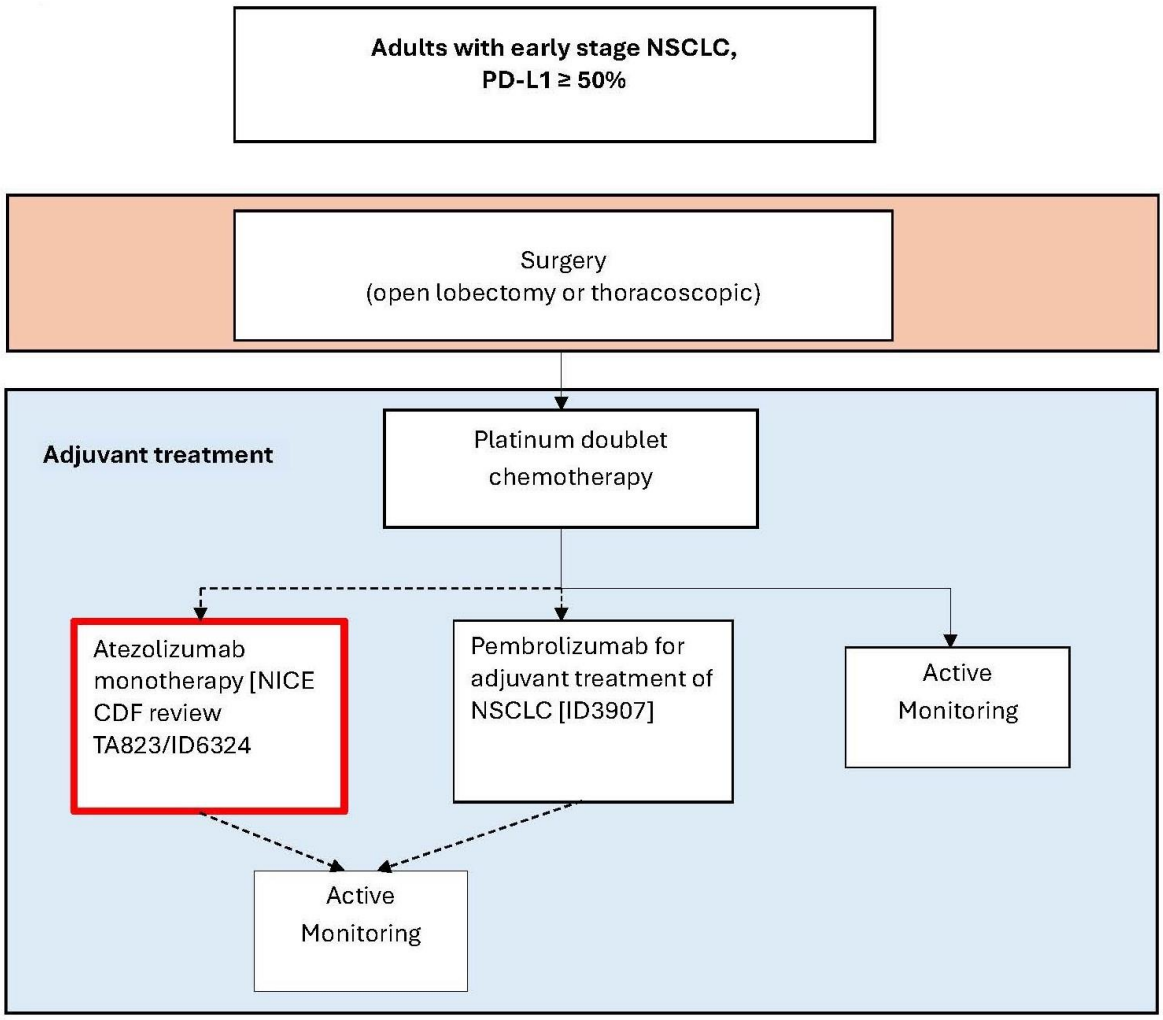
Following the clarification process the company responded to question A2[2] with "*The term "high risk of recurrence" is equivalent to disease stage II–IIIA, as defined by the 7th edition of the TNM staging system, and selected Stage II–IIIB disease based on the 8th edition. For further clarity, patient population defined by the "high risk of recurrence" in accordance with the relevant staging system aforementioned are:*

- *Tumour size ≥ 5 cm, or;*
- *Tumours of any size that are either accompanied by N1 or N2 status, or;*
- *Tumours that are invasive of thoracic structures (directly invade the parietal pleura, chest wall, diaphragm, phrenic nerve, mediastinal pleura, parietal pericardium, mediastinum, heart, great vessels, trachea, recurrent laryngeal nerve, oesophagus, vertebral body, carina), or;*
- *Tumours that involve the main bronchus < 2 cm distal to the carina but without involvement of the carina, or;*
- *Tumours that are associated with atelectasis or obstructive pneumonitis of the entire lung, or;*
- *Tumours with separate nodule(s) in the same lobe or different ipsilateral lobe as the primary.*"

For brevity, the group of patients described in the previous two paragraphs will be henceforth known as the decision problem population (DPP) and "adjuvant atezolizumab" is replaced with "atezolizumab", unless the full term is needed for clarity.

A depiction of the positioning of adjuvant atezolizumab is shown in Figure 1. The EAG has adapted the company's figure as this did not include pembrolizumab, which was included by the company as a comparator during the clarification process.

Figure 1: The company's proposed positioning of adjuvant atezolizumab (adapted from Figure 11 in the company's response to clarification)



2.3 Company's definition of the decision problem

The following sections provide a summary of the company's definition of the decision problem which was provided in Table 1 of the CS.[1] Where deemed appropriate, the EAG has commented on the company's definition of the decision problem.

2.3.1 Population

The company's population is the DPP. This differs from that population in the National Institute for Health and Care Excellence (NICE) final scope[3] as patients with an EGFR mutation or who have ALK-positive NSCLC are excluded as the company is not seeking reimbursement in these subgroups. The EAG is comfortable with these omissions.

2.3.2 Intervention

The intervention is atezolizumab as in NICE's final scope. Atezolizumab is a humanised IgG monoclonal antibody which directly and selectively binds to PD-L1, which is an immune checkpoint protein. The approved Medicines and Healthcare products Regulatory Agency (MHRA) licence was updated on 11th of November 2024, as part of the Windsor Framework, which positions atezolizumab as a monotherapy adjuvant treatment following complete resection and platinum-based chemotherapy for adult patients with NSCLC with a high risk of recurrence whose tumours have PD-L1 expression on ≥ 50% of tumour cells and who do not have EGFR mutant or ALK-positive NSCLC. The approval covers both intravenous (IV) infusion (in an 840mg or 1200mg solution) or via subcutaneous (SC) injection (1875mg solution). Treatment with atezolizumab will be given for a maximum of 16 cycles, unless disease recurrence or unmanageable toxicity occurred sooner.

The company states that the recommended dose of atezolizumab for NSCLC for patients receiving an IV infusion have a choice of schedules which are: 840mg administered every 2 weeks (Q2W); 1200mg administered every 3 weeks (Q3W) or 1680mg administered every 4 weeks (Q4W), although the CS states that only the first two doses are currently approved by the MHRA. Patients receiving a SC injection receive 1875mg Q3W.

2.3.3 Comparators

The NICE scope listed four comparators: active monitoring (AM); adjuvant pembrolizumab (subject to NICE appraisal); adjuvant osimertinib (for adults with an EGFR mutation and subject to NICE appraisal); and adjuvant alectinib (for adults with ALK-positive NSCLC and subject to NICE appraisal). In the CS, the company only included AM as a comparator, although it was termed 'best supportive care [BSC]'; the EAG has used the term AM as the decision choice is between active treatment and AM. Adjuvant osimertinib and adjuvant alectinib were excluded from the decision problem as the company is not seeking reimbursement for patients with an EGFR mutation or with ALK-positive

NSCLC. Adjuvant pembrolizumab was initially excluded as it was not reimbursed at the time of the CS; however, the final draft guidance for adjuvant pembrolizumab in early NSCLC was published on the 20th of December 2024 (with final guidance released on the 5th of February 2025) which recommended pembrolizumab for the DPP. Therefore, the company added adjuvant pembrolizumab as a comparator at the clarification stage.

2.3.4 Outcomes

The company included all of the outcome measures listed in NICE's final scope, which were: disease-free survival (DFS); overall survival (OS), adverse effects (AEs) of treatment, and health-related quality of life (HRQoL).

2.3.5 Economic analysis

The company has undertaken its analysis in line with NICE's reference case.[4]

2.3.6 Subgroups

The NICE scope stated two subgroups to be considered: disease stage; and the presence of biological or genetic markers. The company has not undertaken any subgroup analysis. The CS states that "*The Company will not provide a disease stage subgroup analysis because the trial was not designed to compare these subgroups. In addition, the patient population within each subgroup is too small to conduct any meaningful statistical analysis (Stage II n = 58, Stage IIIA n= 48)*" The clinical advisors to the EAG stated that there was not a large difference between Stage II and Stage IIIa patients and they would not expect the treatment effect to differ, although the EAG notes that the sizes of the population in each group cited above is misleading as this is just for the atezolizumab arm; for the full study the numbers of patients in Stage II and Stage IIIa were n=106 and n=103 respectively. The company did not undertake analyses based on biological or genetic markers as the company is not seeking reimbursement for patients with an EGFR mutation or with ALK-positive NSCLC, which the EAG deems appropriate.

2.3.7 Special considerations

Neither the NICE scope nor the company raised any special consideration relating to equity or equality.

3 CLINICAL EFFECTIVENESS

The clinical evidence contained in the CS[1] is comprised of:

- A systematic literature review (SLR)
- Effectiveness and safety of adjuvant atezolizumab based on the IMpower010[5] trial.
- A network meta-analysis (NMA) comparing adjuvant atezolizumab based on the IMpower010[5] trial versus adjuvant pembrolizumab based on the PEARLS/KEYNOTE-091[6, 7] trial (provided during clarification).

This chapter summarises and critiques the company's review methods and clinical effectiveness and safety data. Full details are presented in the CS[1] Section B.2, Appendix D of the CS[1], the clarification response (plus supporting documents) and the additional clarification response.

3.1 Critique of the methods of review

3.1.1 Searches

Appendix D of the CS[1] reports an SLR to identify evidence on the clinical effectiveness, safety and HRQoL associated with adjuvant treatments for completely resected stage I-III NSCLC. An initial search was conducted in March 2020 followed by four search updates carried out between April 2021 and July 2024. The company's database searches are comprehensive, using a combination of population terms for NSCLC combined with an RCT search filter. Overall, the EAG considers that the company search was comprehensive, and that there were no observable and/or consequential errors in the search strategies.

3.1.2 Inclusion criteria for the SLR

The company's SLR aimed to identify RCTs of atezolizumab and other treatments in the adjuvant, neoadjuvant or perioperative setting for adults with resectable or locally advanced (stage I-III) NSCLC, reporting efficacy, safety or HRQoL outcomes. Full inclusion criteria are described in Appendix D.1.3 of the CS[1]. The EAG considers the inclusion criteria to be appropriate to identify relevant studies of adjuvant atezolizumab and relevant comparators.

3.1.3 Critique of study selection, data extraction, quality assessment and evidence synthesis

Two reviewers screened all title/abstracts and relevant full texts (Appendix D of the CS[1]). Extracted data were checked by a second reviewer. Study quality for RCTs was assessed using the NICE quality assessment tool.[8] Due to the lack of head-to-head studies, the company undertook an NMA to evaluate the comparative efficacy of atezolizumab with adjuvant pembrolizumab, which was provided to the EAG during clarification. Overall, the EAG considers these methods to be appropriate.

3.1.4 Overall EAG view on company's review methods

Overall, the EAG considers that the company's review methods were appropriate.

3.2 Characteristics of IMpower010 study of adjuvant atezolizumab

3.2.1 Results of the company's SLR

The company's clinical SLR identified 67 trials of NSCLC treatments in the adjuvant setting (CS[1] Appendix D.1.4 Table 6).

One RCT of adjuvant atezolizumab (IMpower010[5]) was identified in the company SLR (as noted in clarification response A6). Data are available from the Systemic Anti-Cancer Therapy (SACT) dataset for atezolizumab, as noted in the NICE Managed Access Agreement for atezolizumab;[9] however, SACT data are not mentioned in the clinical evidence section of the CS.[1]

In terms of the NMA, one RCT of adjuvant pembrolizumab (PEARLS/KEYNOTE-091[6, 7]) was identified in the company SLR. This is discussed in Section 3.5 of this EAG report.

3.2.2 Ongoing studies

The CS[1] (Section B.2.11) lists the following ongoing studies of atezolizumab in NSCLC:

- IMpower010[5] is ongoing, though all patients have completed treatment, with [redacted].
- IMpower030[10] is a phase III RCT assessing neoadjuvant atezolizumab plus platinum-based chemotherapy for resectable early-stage NSCLC.
- IMscin002[11] is a phase III RCT investigating the non-inferiority of subcutaneous atezolizumab in two patient cohorts: resected Stage IIB-IIIB (T3-N2) early-stage NSCLC and chemotherapy-naïve Stage IV NSCLC. The study assesses whether subcutaneous administration is as effective and safe as intravenous administration in managing disease progression in these populations.

3.2.3 Study design for IMpower010 study of adjuvant atezolizumab

The clinical section of the CS[1] (Section B.2) focusses on the global IMpower010[5] phase III RCT of adjuvant atezolizumab versus AM. An overview of IMpower010 is provided in Table 2 (full details in CS Section B.2).

Table 2 Design of IMpower010 study of adjuvant atezolizumab (adapted from CS, Table 3)

Study	IMpower010
Key references	Roche 2024: IMpower010 Clinical Study Report (CSR)[5] Felip *et al*., 2021[12] (3-year DFS) Felip *et al*., 2023[13] (4-year OS) Felip *et al*., 2024[14] (5-year subgroup analyses; conference poster) Wakelee *et al*., 2024[15] (5-year DFS and OS; conference poster)
Study design	• Phase III multi-centre open-label RCT
Location	• Global
Population	• Adults with completely resected Stage IB to IIIA NSCLC (stage IB tumours were ≥4cm) • Eastern Cooperative Oncology Group performance status of 0 or 1 • Received cisplatin-based adjuvant chemotherapy (up to 4 cycles) • No restriction by PD-L1 status or EGFR/ALK mutation status
Intervention(s)	• Atezolizumab 1200mg intravenous every 3 weeks for up to 16 cycles (i.e., a maximum of 48 weeks of treatment)
Comparator(s)	• Active monitoring
Stratification factors	• Sex (male vs. female) • Tumour histology (squamous vs. non-squamous) • Extent of disease (Stage IB vs. II vs. IIIA) • PD-L1 tumour expression by IHC (TC2/3 and any IC vs. TC0/1 and IC2/3 vs. TC0/1 and IC0/1 via SP142 IHC assay)
Used in marketing authorisation	• Yes
Reported outcomes in decision problem	• Disease-free survival (DFS) • Overall survival (OS) • Adverse events (AEs)
Duration of follow-up	• Median follow-up 65 months; minimum follow-up 60 months; represents additional 36 months over the data in the previous NICE appraisal (Technology Assessment 823[16])
Data cut-off in CS	• 26 January 2024 (final DFS and second interim OS analysis)

AE: adverse event; ALK: anaplastic lymphoma kinase; CS: company submission; DFS: disease-free survival; EGFR: epidermal growth factor receptor; IC: tumour-infiltrating immune cells; IHC: immunohistochemistry; NSCLC: non-small cell lung cancer; OS: overall survival; PD-L1: programmed death-ligand 1; RCT: randomised controlled trial; TC: tumour cells.

Population and subgroups in IMpower010

The IMpower010[5] trial population consists of adults with completely resected Stage IB to IIIA NSCLC (stage IB tumours were ≥4cm), with an Eastern Cooperative Oncology Group performance status of 0 or 1, having received up to 4 cycles of cisplatin-based adjuvant chemotherapy. No patients had received neoadjuvant therapies (as confirmed in clarification response A7). In the full trial population, there was no restriction by PD-L1 status or EGFR/ALK mutation status, though all participants were tested for PD-L1 expression by immunohistochemistry (IHC). The analysed sub-populations are described below, including the DPP which aligns with the company's intended population and the MHRA licence.

Intervention in IMpower010

The intervention in IMpower010[5] is adjuvant atezolizumab, given as 1,200mg intravenous infusion every 3 weeks for up to 16 cycles (i.e. approximately 1 year). The EAG notes that atezolizumab can

also be administered as 840mg every 2 weeks intravenously, as 1,680mg every 4 weeks intravenously, or as 1,875mg every 3 weeks via subcutaneous injection (all doses for 1 year unless disease recurrence or unacceptable toxicity occurs). Information on non-inferiority of subcutaneous versus intravenous atezolizumab is summarised in Section 3.3.7 of this report.

Comparator in IMpower010

The comparator in IMpower010[5] is AM (described in the CS as BSC). Clinical advisors to the EAG considered AM to be a relevant comparator consistent with the decision problem. Adjuvant pembrolizumab is also listed as a comparator in the NICE final scope, and the company provided an NMA of adjuvant atezolizumab vs. adjuvant pembrolizumab during clarification (discussed in Section 3.5 of this EAG report).

Outcomes in IMpower010

The following outcomes specified in the decision problem were reported in IMpower010[5]:

- Overall survival (OS)
- Disease-free survival (DFS)
- Adverse events (AEs)

IMpower010[5] did not assess HRQoL or patient-reported outcomes (PROs).

3.2.4 Analysis populations and participant flow in IMpower010

Analysis populations in IMpower010

The CS[1] presents data for a number of trial sub-populations (summarised in

Table 3). The ITT population (Stage IB-IIIA) included 1,005 participants. The DPP (PD-L1 TC ≥ 50%, Stage II–IIIA, excluding EGFR and ALK alterations) included 209 participants (106 atezolizumab, 103 AM). The EAG notes that the DPP was not pre-specified in the statistical testing plan (CS Section B.2.4). The DPP corresponds to the company's intended population and is consistent with the MHRA licence. Therefore, this report focusses mainly on the DPP when presenting the clinical effectiveness data.

The safety population (all randomised participants who received ≥1 dose atezolizumab, or ≥1 post-baseline safety assessment in the AM arm) included 990 participants (495 atezolizumab, 495 AM).

Table 3 IMpower010 sub-populations

Sub-populations	Atezolizumab (N)	Active monitoring (N)	Total (N)
• **ITT:** Stage IB-IIIA	507	498	1,005
• All randomised Stage II–IIIA	442	440	882
• PD-L1 TC ≥ 1%, Stage II–IIIA	248	228	476
• PD-L1 TC ≥ 50%, Stage II–IIIA	115	114	229
• **Decision problem population (DPP):** PD-L1 TC ≥ 50%, Stage II–IIIA, excluding EGFR and ALK alterations	**106**	**103**	**209**
• **Safety population:** randomised and received ≥1 dose atezolizumab, or ≥1 post-baseline safety assessment in active monitoring arm	**495**	**495**	**990**

ALK: anaplastic lymphoma kinase; DPP: decision problem population; EGFR: epidermal growth factor receptor; ITT: intention-to-treat; PD-L1: programmed death-ligand 1; TC: tumour cells.

Data cut-offs and follow-up duration in IMpower010

The IMpower010[5] data in the CS[1] is based on a data cut-off of the 26th of January 2024, which was the final DFS analysis and the second interim OS analysis. Patients had a median follow-up of 65 months (minimum follow-up of 60 months) and this data cut represents an additional 36 months over the data presented in the previous NICE appraisal (TA823[16]).

Participant flow in IMpower010

All patients had completed treatment by the January 2021 data cut-off, and were either in follow-up, had withdrawn consent or had died. Patient disposition at the January 2024 cut-off is shown in Table 4 (the CS only reports this for the ITT population; data for the DPP were requested in clarification response A11 but were not provided). The proportions remaining in the study were 59% and 57% (for the atezolizumab and AM arms), while 30% and 31% respectively had died, and 11% and 12% respectively had discontinued the study for other reasons.

Table 4 Patient disposition in IMpower010 (ITT population) (adapted from CS Table 5)

Patient disposition	Atezolizumab (n=507)	Active monitoring (n=498)	All patients (N=1005)
Received treatment	495 (98%)	495 (99%)	990 (99%)
On study status			
Ongoing	301 (59%)	282 (57%)	583 (58%)
Discontinued	206 (41%)	216 (43%)	422 (42%)
Reasons for discontinuing study			
Death	154 (30%)	155 (31%)	309 (31%)
Disease relapse	1 (0.2%)	0	1 (<0.1%)
Lost to follow-up	5 (1%)	11 (2%)	16 (2%)
Physician decision	0	3 (0.6%)	3 (0.3%)

Patient disposition	Atezolizumab (n=507)	Active monitoring (n=498)	All patients (N=1005)
Protocol deviation	2 (0.4%)	0	2 (0.2%)
Withdrawal by subject	44 (9%)	47 (9%)	91 (9%)

ITT: intention-to-treat.
Includes study disposition events occurring on or after the randomisation date.
Data cut-off January 2024.

3.2.5 Study quality of IMpower010

Results of a critical appraisal of IMpower010[5] are presented in the CS[1] (Section B.2.5) using the NICE checklist.[8] All items scored low risk of bias, except that the study was not blinded (due to the lack of an active comparator). The EAG agrees that the study is of low risk of bias overall.

3.2.6 Baseline characteristics in IMpower010

Baseline characteristics for IMpower010[5] are shown in Table 5 for the PD-L1 TC ≥ 50% Stage II–IIIA population (other sub-populations are shown in CS[1] Table 4). Baseline characteristics were not available for the DPP (confirmed in clarification response A8), but the CS[1] notes that these were similar to the latter population. In the PD-L1 ≥ 50% Stage II–IIIA population, the median age was 62 years across both groups, and the majority of patients were male (atezolizumab 77%, AM 68%) and White (atezolizumab 65%, AM 75%). Disease stages included Stage II (atezolizumab 54%, AM 50%) and Stage IIIA (atezolizumab 46%, AM 50%). Most patients had non-squamous histology (atezolizumab 59%, AM 61%). Eastern Cooperative Oncology Group performance status was reported to be either 0 (atezolizumab 62%, AM 53%) or 1 (atezolizumab 38%, AM 46%). The majority of patients had current or previous tobacco use (atezolizumab 86%, AM 87%). Overall, clinical advisors to the EAG considered that the participants in IMpower010 were representative of clinical practice.

The CS[1] states (footnote to Table 5) that patients with squamous NSCLC were not required to undergo EGFR/ALK testing. A proportion of patients had unknown EGFR/ALK status; the majority of these had squamous NSCLC but a smaller proportion had non-squamous. Clarification responses A9 and A10 note that the IMpower010 study was initiated in 2015 before testing for EGFR/ALK status became standard practice, and that testing for these alterations in squamous NSCLC is typically not mandatory. Clinical advisors to the EAG noted that UK centres differ in terms of whether patients with squamous NSCLC are routinely tested for EGFR/ALK status, since squamous disease has a lower prevalence of EGFR/ALK alterations and considered that atezolizumab would be indicated for squamous NSCLC in the absence of EGFR/ALK testing.

The CS[1] states that baseline characteristics and stratification factors were generally well-balanced between treatment arms. Clinical advisors to the EAG agreed that there were no major differences between arms likely to impact the efficacy of atezolizumab.

Table 5 Baseline characteristics in IMpower010 (adapted from CS Table 4)

Characteristics	PD-L1 TC ≥ 50% (Stage II–IIIA) population[a]	
	Atezolizumab (n=115)	Active monitoring (n=114)
Median age, years (range)	62 (34-77)	62 (36-84)
Age ≥ 65 years, n (%)	45 (39)	46 (40)
Sex, male, n (%)	89 (77)	78 (68)
Race, n (%)		
White	75 (65)	86 (75)
Asian	36 (31)	26 (23)
Other	4 (3)	2 (2)
ECOG PS, n (%)		
0	71 (62)	60 (53)
1	44 (38)	53 (46)
Histology, non-squamous, n (%)	68 (59)	69 (61)
Stage, n (%)		
IB	NA	NA
IIA	62 (54)	57 (50)
IIB		
IIIA	53 (46)	57 (50)
Type of surgery, n (%)[b]		
Lobectomy[c]	87 (76)	86 (75)
Pneumonectomy	20 (17)	20 (18)
Bilobectomy	7 (6)	7 (6)
Chemotherapy treatment, n (%)		
Cisplatin-docetaxel	13 (11)	20 (18)
Cisplatin-gemcitabine	22 (19)	17 (15)
Cisplatin-vinorelbine	45 (39)	40 (35)
Cisplatin-pemetrexed	35 (30)	37 (32)
Tobacco use history, n (%)		
Never	16 (14)	15 (13)
Current/previous	99 (86)	99 (87)
EGFR mutation status, n (%)[d]		
Positive	6 (5)	8 (7)
Negative	60 (52)	64 (56)
Unknown	49 (43)	42 (37)
ALK rearrangement status, n (%)[d]		
Positive	3 (3)	3 (3)
Negative	62 (54)	62 (54)
Unknown	50 (43)	49 (43)

ALK: anaplastic lymphoma kinase; CS: company submission; ECOG: Eastern Cooperative Oncology Group; EGFR: epidermal growth factor receptor; PD-L1: programmed death-ligand 1; PS: performance status; TC: tumour cells.

[a] Baseline characteristics were similar in the PD-L1 ≥ 50% population excluding EGFR/ALK+ patients.

[b] Subgroups with ≤10 patients are not shown.

[c] Includes patients who had lobectomy and sleeve lobectomy.

[d] For patients with non-squamous NSCLC, EGFR/ALK status was assessed locally or centrally. Patients with squamous NSCLC were not required to undergo EGFR/ALK testing, and the majority of patients with unknown EGFR or ALK status had squamous NSCLC (in the ITT population, 89.2% with unknown EGFR status and 80.7% with unknown ALK status had squamous NSCLC).

3.3 Clinical effectiveness of adjuvant atezolizumab

3.3.1 Overview of effectiveness data from IMpower010

Clinical effectiveness data from IMpower010[5] are summarised in the following sections. Only data for the DPP and for the January 2024 data cut-off (where available) are presented in this EAG report; data for other populations and cut-offs are provided in the CS[1] (Section B.2.6).

3.3.2 Disease-free survival (DFS)

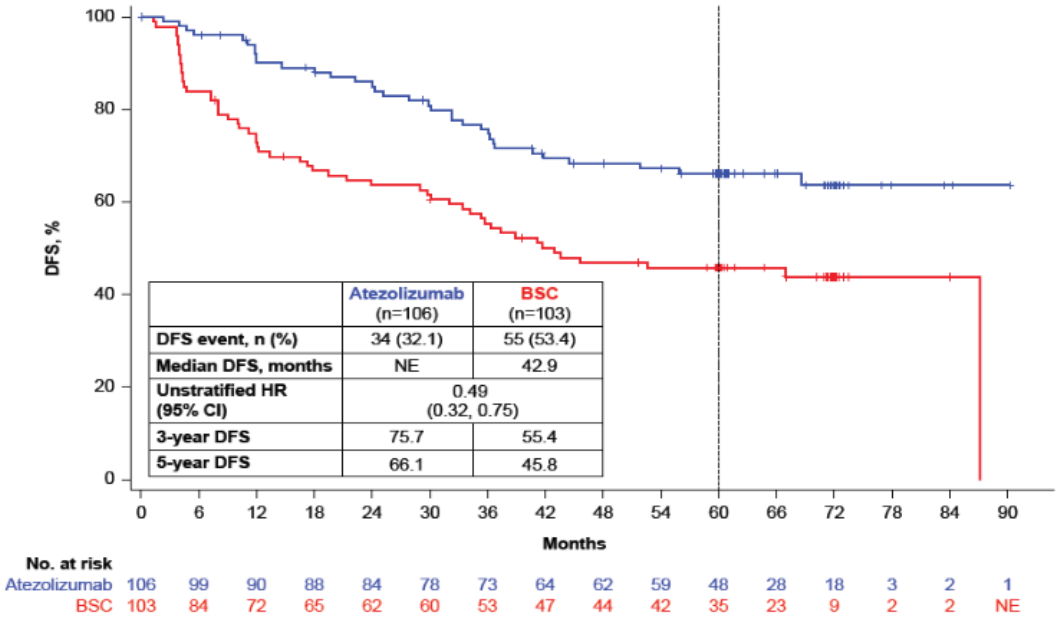
DFS in the DPP population is shown in Table 6 and Figure 2. DFS was statistically significantly longer in the atezolizumab arm compared to the AM arm. Median DFS was not reached for atezolizumab vs. 43 months for AM, with a HR of 0.49 (95% CI: 0.32, 0.75). A higher proportion of patients in the AM group (53%) experienced disease recurrence or death compared to those in the atezolizumab group (32%).

Table 6 DFS (decision problem population) (adapted from CS Table 8)

DFS	Atezolizumab (n=106)	Active monitoring (n=103)	Unstratified HR (95% CI)
Median DFS (months)	NE	43	0.49 (0.32, 0.75)
No. (%) of events	34 (32%)	55 (53%)	
3-year DFS rate (%)	76	55	
5-year DFS rate (%)	66	46	

CI: confidence interval; CS: company submission; DFS: disease-free survival; HR: hazard ratio; NE: not estimable.
Data cut-off January 2024.

Figure 2 DFS (decision problem population) (reproduced from CS Figure 12)



BSC: best supportive care (active monitoring); CI: confidence interval; CS: company submission; DFS: disease-free survival; HR: hazard ratio; NE: not estimable.
Data cut-off January 2024.

3.3.3 Overall survival (OS)

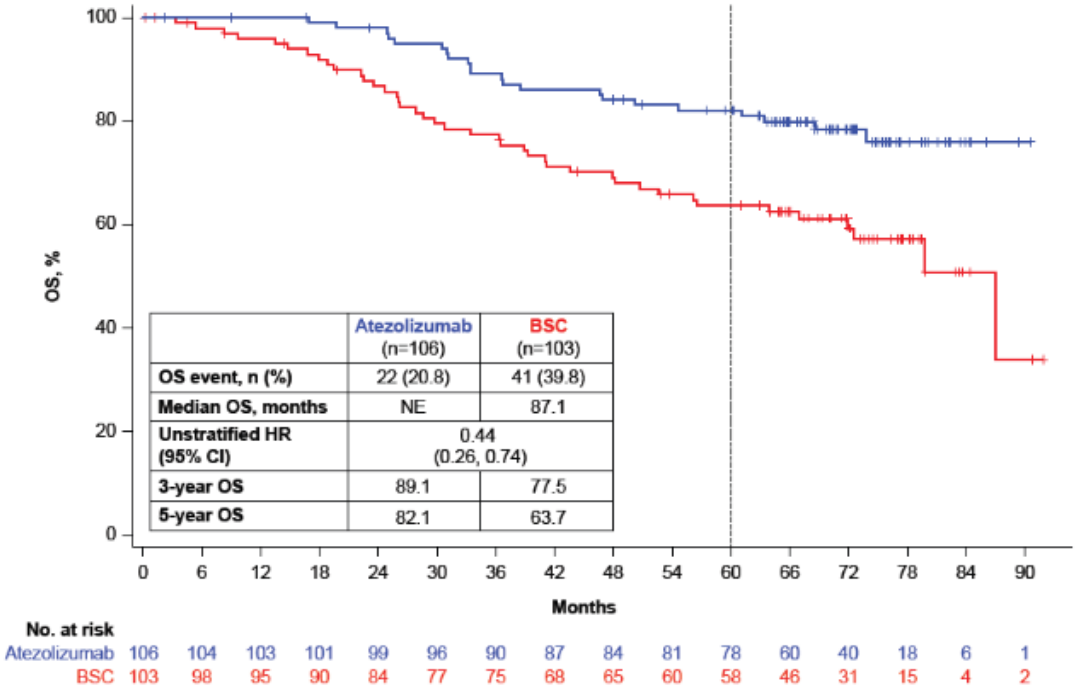
OS in the DPP population is shown in Table 7 and Figure 3. OS was statistically significantly longer in the atezolizumab arm compared to the AM arm. Median OS was not reached for atezolizumab vs. 87 months for AM, with a HR of 0.44 (95% CI: 0.26, 0.74). A higher proportion of patients in the AM group (40%) died, compared to those in the atezolizumab group (21%).

Table 7 OS (decision problem population) (adapted from CS Table 8)

OS	Atezolizumab (n=106)	Active monitoring (n=103)	Unstratified HR (95% CI)
Median OS (months)	NE	87	0.44 (0.26, 0.74)
No. (%) of events	22 (21%)	41 (40%)	
3-year OS rate (%)	89	78	
5-year OS rate (%)	82	64	

CI: confidence interval; CS: company submission; HR: hazard ratio; NE: not estimable; OS: overall survival.
Data cut-off January 2024.
The OS HR is unstratified; this was incorrectly labelled as stratified in CS Table 8 (clarified in clarification response A16).

Figure 3 OS (decision problem population) (reproduced from CS Figure 13)



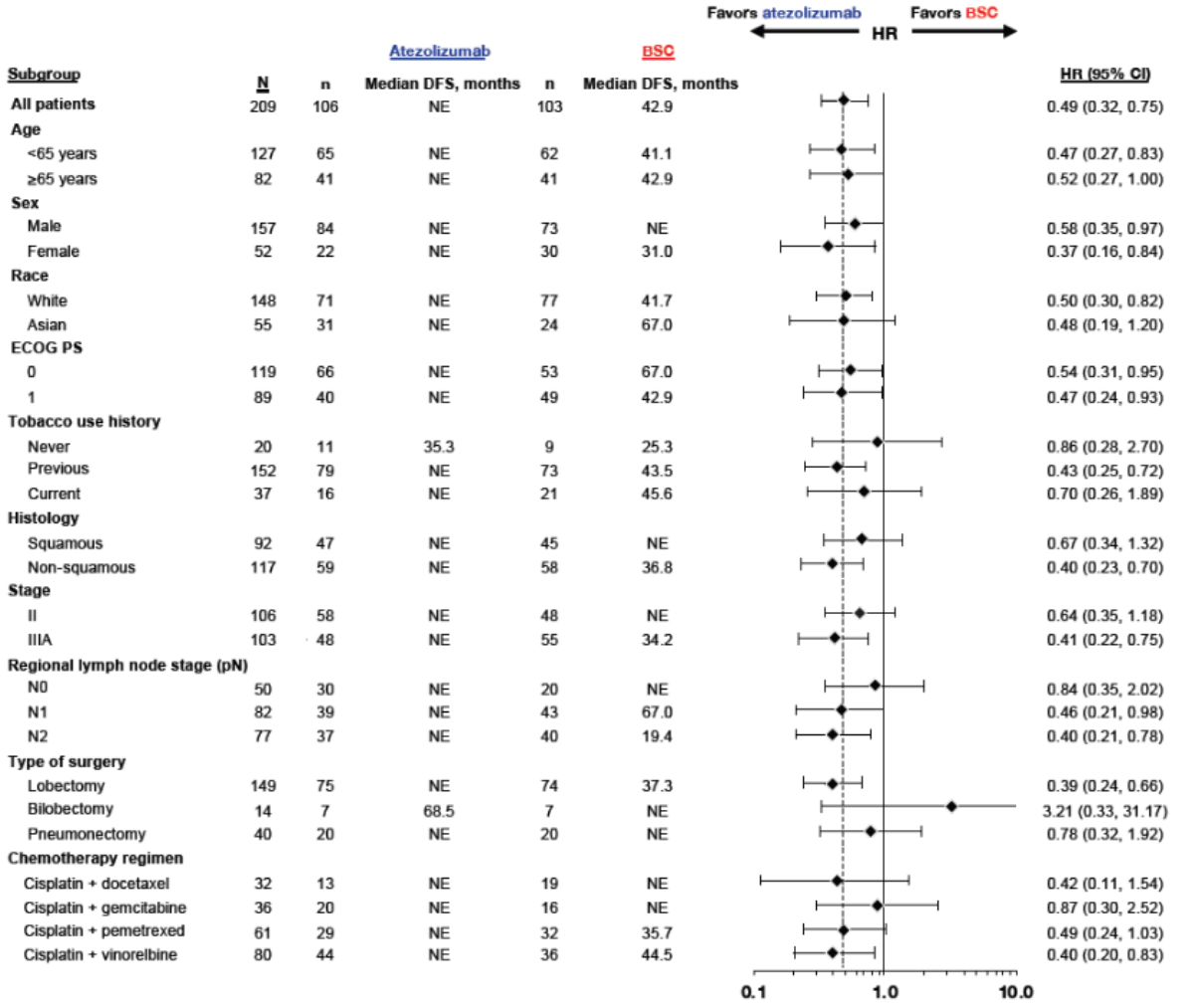
BSC: best supportive care (active monitoring); CI: confidence interval; CS: company submission; HR: hazard ratio; NE: not estimable; OS: overall survival.
Data cut-off January 2024.

3.3.4 Subgroup analyses for DFS and OS

Subgroup analyses for the DPP are shown in Figure 4 for DFS and in Figure 5 for OS (reported in CS[1] Section 2.7). The CS[1] states that the DFS benefit of atezolizumab was consistent across most pre-defined subgroups. The EAG notes that (omitting subgroups with very low numbers) the DFS benefit

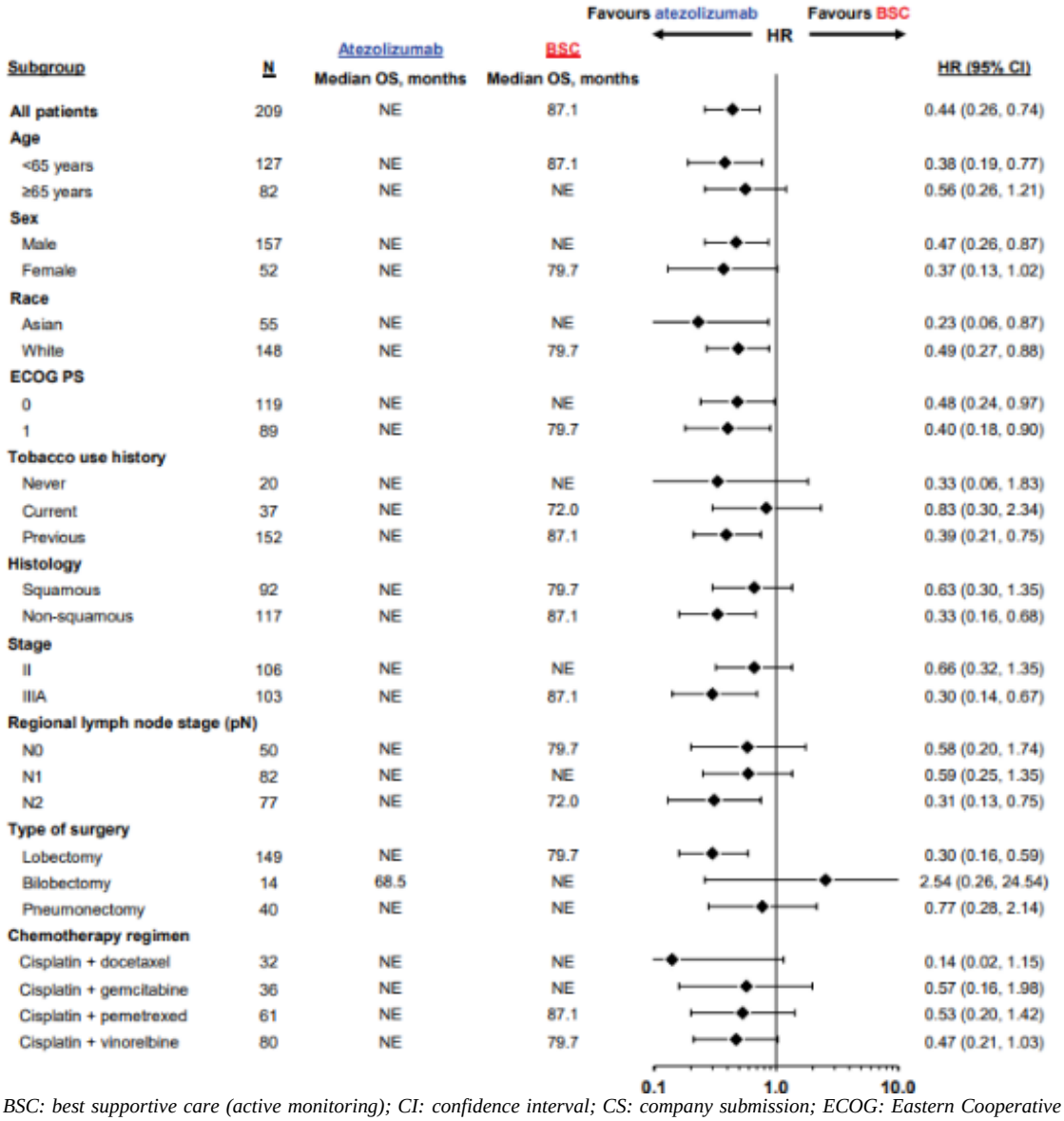
was not statistically significant in subgroups with squamous NSCLC and those with stage II disease but notes that this could be due to the relatively small numbers analysed. Clinical advisors to the EAG did not have any major concerns that the subgroup analyses represented a genuine difference in effectiveness in any assessed subgroup.

Figure 4 Subgroup analysis of DFS (decision problem population) (reproduced from CS Figure 14)



BSC: best supportive care (active monitoring); CI: confidence interval; CS: company submission; DFS: disease-free survival; ECOG: Eastern Cooperative Oncology Group; HR: hazard ratio; PS: performance status.
Data cut-off January 2024.

Figure 5 Subgroup analysis of OS (decision problem population) (reproduced from CS Figure 15)



Subgroup	N	Atezolizumab Median OS, months	BSC Median OS, months	HR (95% CI)
All patients	209	NE	87.1	0.44 (0.26, 0.74)
Age				
<65 years	127	NE	87.1	0.38 (0.19, 0.77)
≥65 years	82	NE	NE	0.56 (0.26, 1.21)
Sex				
Male	157	NE	NE	0.47 (0.26, 0.87)
Female	52	NE	79.7	0.37 (0.13, 1.02)
Race				
Asian	55	NE	NE	0.23 (0.06, 0.87)
White	148	NE	79.7	0.49 (0.27, 0.88)
ECOG PS				
0	119	NE	NE	0.48 (0.24, 0.97)
1	89	NE	79.7	0.40 (0.18, 0.90)
Tobacco use history				
Never	20	NE	NE	0.33 (0.06, 1.83)
Current	37	NE	72.0	0.83 (0.30, 2.34)
Previous	152	NE	87.1	0.39 (0.21, 0.75)
Histology				
Squamous	92	NE	79.7	0.63 (0.30, 1.35)
Non-squamous	117	NE	87.1	0.33 (0.16, 0.68)
Stage				
II	106	NE	NE	0.66 (0.32, 1.35)
IIIA	103	NE	87.1	0.30 (0.14, 0.67)
Regional lymph node stage (pN)				
N0	50	NE	79.7	0.58 (0.20, 1.74)
N1	82	NE	NE	0.59 (0.25, 1.35)
N2	77	NE	72.0	0.31 (0.13, 0.75)
Type of surgery				
Lobectomy	149	NE	79.7	0.30 (0.16, 0.59)
Bilobectomy	14	68.5	NE	2.54 (0.26, 24.54)
Pneumonectomy	40	NE	NE	0.77 (0.28, 2.14)
Chemotherapy regimen				
Cisplatin + docetaxel	32	NE	NE	0.14 (0.02, 1.15)
Cisplatin + gemcitabine	36	NE	NE	0.57 (0.16, 1.98)
Cisplatin + pemetrexed	61	NE	87.1	0.53 (0.20, 1.42)
Cisplatin + vinorelbine	80	NE	79.7	0.47 (0.21, 1.03)

BSC: best supportive care (active monitoring); CI: confidence interval; CS: company submission; ECOG: Eastern Cooperative Oncology Group; HR: hazard ratio; OS: overall survival; PS: performance status.
Data cut-off January 2024.

3.3.5 Post-relapse non-protocol anticancer therapy

Post-relapse therapies for the DPP are shown in Table 8; the EAG notes that these are based on small numbers of patients. Of those patients with relapse (n=28 in the atezolizumab arm and n=47 in the AM arm), more patients in the atezolizumab arm received any systemic non-protocol anticancer therapy (71%) than in the AM arm (57%). More patients in the atezolizumab arm received chemotherapy (68%) than in the AM arm (32%), while more patients in the AM arm received cancer immunotherapy (40%) than in the atezolizumab arm (18%). Surgery was slightly more frequent in the AM arm (19%) than in the atezolizumab arm (11%); other therapies were used similarly in both groups. Clinical advisors to the EAG considered that the proportions of post-relapse therapies per group appeared broadly representative of clinical practice.

Table 8 Post-relapse therapies (decision problem population) (adapted from CS Table 9 and Figure 16)

Patients receiving each therapy, n (%)	Atezolizumab (n = 28)	Active monitoring (n = 47)
Any systemic non-protocol anticancer therapy	20 (71)	27 (57)
Chemotherapy	19 (68)	15 (32)
Cancer immunotherapy	5 (18)	19 (40)
Targeted TKI	3 (11)	4 (9)
Targeted mAb	2 (7)	4 (9)
Radiation therapy	13 (46)	23 (49)
Surgery	3 (11)	9 (19)

CS: company submission; mAb: monoclonal antibody; TKI: tyrosine kinase inhibitor.
The denominators for post-relapse treatments are based on number of patients with relapse.
Data cut-off January 2024.

3.3.6 Health-related quality of life (HRQoL) and patient-reported outcomes (PROs)

The IMpower010[5] trial did not collect data on HRQoL or PROs (as noted in CS Section B.3.4.1).

3.3.7 Non-inferiority of subcutaneous versus intravenous atezolizumab

In August 2023, the MHRA approved subcutaneous (SC) atezolizumab for all indications in which the intravenous (IV) formulation is authorised, supported by findings from the IMscin001[17] study. Access to atezolizumab SC has also been granted in the UK. Clinical advisors to the EAG noted that some UK centres were using IV atezolizumab while others had moved to the SC formulation.

Non-inferiority of SC vs. IV atezolizumab was demonstrated in the IMscin001[17] and IMscin002[11] studies; information on these studies is provided in clarification response A14 and summarised here. IMscin001 is a two-part study to evaluate the pharmacokinetics (PK), safety, and efficacy of SC vs. IV atezolizumab in locally advanced or metastatic NSCLC. Part 1 determined that SC atezolizumab 1800mg every 3 weeks provided similar serum concentration (C_{trough}) and area under the curve (AUC) values to IV atezolizumab 1200 mg every 2 weeks, with a similar safety profile.[18] Part 2 was a randomised phase III non-inferiority study which demonstrated non-inferiority in terms of drug exposure, efficacy and safety of atezolizumab SC vs. atezolizumab IV.[17] IMscin002 was a Phase II randomised cross-over trial investigating patient- and clinician-reported preferences and safety of atezolizumab SC vs. IV.[11] The study demonstrated non-inferior drug exposure with SC vs. IV atezolizumab, and that efficacy, safety, and immunogenicity were similar between arms and consistent with data for atezolizumab IV. In terms of preference, most patients (79%) chose atezolizumab SC for the continuation period, and 86% of patients were very satisfied or satisfied with atezolizumab SC vs 75% of patients with IV.

3.4 Safety of adjuvant atezolizumab

3.4.1 Source of safety data

Safety data in the CS[1] (Section B.2.10) is based on the IMpower010[5] study safety population, i.e. those who received at least one dose of atezolizumab treatment, or (for the AM arm) had at least one post-baseline safety measurement. This consisted of 495 participants per arm. The EAG considered it was appropriate to use this wider population for safety analyses. This EAG report includes safety data for the January 2024 cut-off of IMpower010.

The EAG notes that no safety data were provided for pembrolizumab in the CS or in the company's NMA.

3.4.2 Overview of safety of atezolizumab

A summary of safety data is provided in Table 9. More patients in the atezolizumab arm than the AM arm experienced at least 1 AE (93% vs. 71%), grade 3-4 AEs (22% vs. 12%), serious AEs (18% vs. 8%) deaths due to AEs (1.8% vs. 0.6%), and adverse events of special interest (AESIs) (52% vs. 10%). In the atezolizumab arm, 29% experienced AEs leading to dose interruption and 18% experienced AEs leading to discontinuation. Treatment-related AEs and AESIs are summarised in Table 9.

Table 9 Safety summary (safety population) (adapted from CS Table 10)

AE grouping	All AEs		Treatment-related AEs	
	Atezo (n=495)	AM (n=495)	Atezo (n=495)	AM (n=495)
AEs				
Total number of patients with at least one AE	458 (92.5%)	351 (70.9%)	336 (67.9%)	0
Total number of events	2776	1258	NR	NR
Total number of patients with at least one:				
AE with fatal outcome (Grade 5)	9 (1.8%)	3 (0.6%)	4 (0.8%)	0
Serious AE	88 (17.8%)	42 (8.5%)	37 (7.5%)	0
Grade 3-4 AE	109 (22.0%)	57 (11.5%)	53 (10.7%)	0
AE leading to dose interruption of atezolizumab	143 (28.9%)	0	NR	NR
AE leading to atezolizumab discontinuation	90 (18.2%)	0	NR	NR
AESIs				
Total number of patients with at least one AESI	258 (52.1%)	48 (9.7%)	227 (46%)	0
Total number of events	520	71		
Total number of patients with at least one:				
AESI with fatal outcome (Grade 5)	2 (0.4%)	1 (0.2%)	2 (0.4%)	0
Serious AESI	21 (4.2%)	4 (0.8%)	20 (4.0%)	0
Grade 3–4 AESI	39 (7.9%)	4 (0.8%)	31 (6.3%)	0
AESI leading to dose interruption of atezolizumab	59 (11.9%)	0	NR	NR
AESI leading to atezolizumab discontinuation	52 (10.5%)	0	NR	NR

AE: adverse event; AESI: adverse event of special interest; AM: active monitoring; atezo: atezolizumab; NR: not reported.
Data cut-off January 2024.

3.4.3 Deaths due to AEs

Deaths due to AEs are shown in Table 10, and occurred in 9 patients (1.8%) in the atezolizumab arm and in 3 patients (0.6%) in the AM arm. In the atezolizumab arm, four deaths were potentially treatment-related; these were due to acute myeloid leukaemia, myocarditis, interstitial lung disease, and multiple organ dysfunction syndrome.

Table 10 Deaths due to adverse events (safety population) (adapted from CS Appendix H)

AEs leading to death	Atezolizumab (n=495)	Active monitoring (n=495)
AEs leading to death	9 (1.8%)	3 (0.6%)
Treatment-related AEs leading to death	4 (0.8%)	0
Treatment-related		
Acute myeloid leukaemia	1 (0.2%)	0
Myocarditis	1 (0.2%)	0
Interstitial lung disease	1 (0.2%)	0
Multiple organ dysfunction syndrome	1 (0.2%)	0
Not classed as treatment-related		
Arrhythmia	1 (0.2%)	0
Cardiac failure acute	1 (0.2%)	0
Pneumothorax	1 (0.2%)	0
Cerebrovascular accident	1 (0.2%)	0
Death (unknown reason)	1 (0.2%)	0
Cardiac tamponade	0	1 (0.2%)[a]
Septic shock	0	1 (0.2%)[a]
Pulmonary embolism	0	1 (0.2%)
Pneumonia	0	1 (0.2%)

AE: adverse event; CS: company submission.
Includes adverse events occurring on or after the start of treatment in randomisation period.
[a]Cardiac tamponade and septic shock occurred in the same patient.
Data cut-off January 2024.

3.4.4 AEs with a difference of at least 5% between arms

AEs with a notable difference (≥ 5%) between the arms are shown in Table 11. These included the following (percentages are for atezolizumab arm): arthralgia (11%), pyrexia (13%), increased alanine aminotransferase (ALT) (11%), increased aspartate aminotransferase (AST) (11%), hypothyroidism (11%), pruritus (10%), rash (10%), upper respiratory tract infection (7%), diarrhoea (7%) and hyperthyroidism (7%).

Table 11 AEs with a difference of ≥5% between treatment arms (safety population) (adapted from CS Table 12)

AE type	Atezolizumab (n=495)	Active monitoring (n=495)
Number of occurrences, n (%)		
Arthralgia	52 (11%)	26 (5%)
Pyrexia	65 (13%)	11 (2%)
Alanine aminotransferase (ALT) increased	54 (11%)	16 (3%)
Aspartate aminotransferase (AST) increased	54 (11%)	16 (3%)
Hypothyroidism	54 (11%)	3 (0.6%)
Pruritus (itching)	51 (10%)	3 (0.6%)
Rash	48 (10%)	5 (1%)
Upper respiratory tract infection	37 (7%)	12 (2%)
Diarrhoea	37 (7%)	9 (2%)
Hyperthyroidism	33 (7%)	3 (0.6%)

AE: adverse event; CS: company submission.
Includes adverse events occurring on or after the start of treatment in randomisation period.
For frequency counts, multiple occurrences of the same AE in an individual are counted only once.
Data cut-off January 2024.

3.4.5 Treatment-related adverse events

The most common atezolizumab-related AEs were hypothyroidism (11%), pruritus (9%), rash (8%), increased AST (8%), increased ALT (8%), hyperthyroidism (6%), pyrexia (6%), and arthralgia (5%).

3.4.6 Serious adverse events (SAEs)

SAEs occurring at ≥ 1% in either arm included pneumonia (1.6% and 1.0%) and pyrexia (1.2% and 0.2%). Treatment-related SAEs reported in two or more patients in the atezolizumab arm included pneumonitis, interstitial lung disease (ILD), meningitis, peripheral neuropathy, pyrexia, drug-induced liver injury, hepatitis, and sarcoidosis (all occurred in ≤ 1% of patients).

3.4.7 AEs leading to dose interruption and discontinuation

AEs leading to discontinuation (occurring in ≥1% of atezolizumab arm) included: pneumonitis (1.4%), hypothyroidism (1.4%), increased AST (1.4%), and increased ALT (1.0%). AEs leading to dose interruptions (occurring in ≥1% of atezolizumab arm) included: hyperthyroidism (2.8%), pyrexia (1.6%), increased AST (1.6%), increased ALT (1.4%), upper respiratory tract infection (1.4%), rash (1.4%), hypothyroidism (1.2%), headache (1.2%), and pneumonia (1%).

3.4.8 Anti-atezolizumab antibodies

Anti-therapeutics antibodies (ATAs), also referred to as anti-drug antibodies (ADAs), were a secondary outcome in IMpower010. Clarification response A13 states that the observed incidence of treatment-

emergent ADAs was 31.2% (152/487) in the ADA evaluable population (cutoff date 21st January 2021), and that no later analyses were conducted.

3.4.9 AEs of special interest (AESIs)

AESIs are shown in Table 12. These broadly correlate with the special warnings and precautions in the atezolizumab summary of product characteristics.[19] The percentages with AESIs in the atezolizumab arm vs. AM arm were as follows: any AESI (52.1% vs. 9.7%); potentially treatment-related AESI (45.9% vs. 0%); serious AESI (4.2% vs. 0.8%); grade 3-4 AESI (7.9% vs. 0.8%); and AESIs requiring systemic corticosteroid treatment (12.3% vs. 1.0%). Deaths due to AESIs occurred in 2 patients (0.4%) in the atezolizumab arm (myocarditis and interstitial lung disease) and 1 patient (0.2%) in the AM arm (cardiac tamponade). In the atezolizumab arm, 11.9% experienced AESIs leading to dose interruption and 10.5% experienced AESIs leading to discontinuation.

Table 12 Overview of AESIs (safety population) (adapted from CS Table 13)

AESI type	Atezolizumab (N=495)	Active monitoring (N=495)
Total number of patients with at least one AESI	258 (52.1%)	48 (9.7%)
Total number of events	520	71
Total number of patients with at least one:		
Related AESI	227 (45.9%)	0
AESI with fatal outcome	2 (0.4%)	1 (0.2%)
Related AESI with fatal outcome	2 (0.4%)	0
Serious AESI	21 (4.2%)	4 (0.8%)
Related Serious AESI	20 (4.0%)	0
Grade 3-4 AESI	39 (7.9%)	4 (0.8%)
Related Grade 3-4 AESI	31 (6.3%)	0
AESI leading to dose interruption of atezolizumab	59 (11.9%)	0
AESI leading to atezolizumab discontinuation	52 (10.5%)	0
AESI requiring systemic corticosteroid treatment	61 (12.3%)	5 (1.0%)
Medical concepts: patients with identified risks for atezolizumab		
Immune-mediated hepatitis (diagnosis and lab abnormalities)	87 (17.6%)	22 (4.4%)
Immune-mediated hepatitis (lab abnormalities)	82 (16.6%)	21 (4.2%)
Immune-mediated rash	91 (18.4%)	10 (2.0%)
Immune-mediated hypothyroidism	84 (17.0%)	3 (0.6%)
Immune-mediated hyperthyroidism	33 (6.7%)	4 (0.8%)
Immune-mediated pneumonitis	19 (3.8%)	3 (0.6%)
Immune-mediated hepatitis (diagnosis)	7 (1.4%)	1 (0.2%)
Infusion-related reactions	8 (1.6%)	0
Immune-mediated adrenal insufficiency	5 (1.0%)	0
Immune-mediated colitis	4 (0.8%)	1 (0.2%)
Immune-mediated diabetes mellitus	4 (0.8%)	1 (0.2%)
Immune-mediated myositis	4 (0.8%)	1 (0.2%)
Immune-mediated myositis (myositis + rhabdomyolysis)	4 (0.8%)	1 (0.2%)
Immune-mediated meningoencephalitis	4 (0.8%)	0
Immune-mediated pancreatitis	2 (0.4%)	1 (0.2%)
Immune-mediated pericardial disorders	1 (0.2%)	2 (0.4%)

AESI type	Atezolizumab (N=495)	Active monitoring (N=495)
Immune-mediated encephalitis	2 (0.4%)	0
Immune-mediated meningitis	2 (0.4%)	0
Immune-mediated myocarditis	2 (0.4%)	0
Immune-mediated severe cutaneous reactions	2 (0.4%)	0
Immune-mediated Guillain-Barre syndrome	1 (0.2%)	0
Immune-mediated hypophysitis	2 (0.4%)	0
Immune-mediated nephritis	1 (0.2%)	0
Medical concepts: patients with potential risks for atezolizumab		
Autoimmune haemolytic anaemia	2 (0.4%)	0
Immune-mediated ocular inflammatory toxicity	1 (0.2%)	1 (0.2%)
Immune-mediated vasculitis	0	1 (0.2%)

AESI: adverse event of special interest; CS: company submission.
Includes adverse events occurring on or after the start of treatment in randomisation period.
Immune-mediated adverse events are those AESIs that were ongoing upon the initiation of systemic corticosteroid therapy and where the systemic corticosteroid therapy was administered no later than 30 days from the start of the adverse event.
Data cut-off January 2024.

3.5 Indirect treatment comparison

3.5.1 Indirect treatment comparison: Overview

The company did not undertake any indirect or mixed treatment comparisons within the CS. However, the final draft guidance for adjuvant pembrolizumab in early NSCLC was published on the 20th of December 2024 and recommended pembrolizumab for the DPP (and subsequently became final guidance on the 5th of February 2025).[20] Therefore, at the clarification stage in response to question A4, the company provided an indirect treatment comparison (ITC) comparing adjuvant atezolizumab versus adjuvant pembrolizumab (henceforth referred to as pembrolizumab unless required for clarity). The ITC was summarised in the clarification Appendix with reference to supporting documents including a feasibility assessment of the network meta-analysis (NMA), and an NMA report. Further clarification of the ITC provided by the company was sought by the EAG; this was received 3 working days before the EAG report was due and is referenced throughout as "additional clarification response".

Due to the lack of direct evidence for the comparison of atezolizumab and relevant comparator treatments, the company provided ITCs on two outcomes (HR for DFS and 3-year DFS), for two subgroups (PD-L1 ≥50% and PD-L1 ≥1%). The company identified three relevant RCTs for inclusion within an NMA: IMpower010[5], PEARLS/KEYNOTE-091[6, 7] and CANOPY-A[21]. The PEARLS/KEYNOTE-091 trial provides evidence on the use of pembrolizumab versus placebo, and the CANOPY-A trial investigated the use of canakinumab versus placebo. The company did not include the CANOPY-A trial within the ITC due to notable differences in trial population and study design, additionally canakinumab is not considered a relevant comparator for atezolizumab. The EAG agrees with this decision and expects this to have minimal impact on any results of the NMA relating to the comparison of atezolizumab with pembrolizumab.

Only the result from the ITC assessing the HR for DFS for the PD-L1 ≥50% population is used within the economic model and is therefore the focus of the EAG review. The results for the other populations and outcomes can be found in the company's NMA feasibility assessment report, the NMA report provided alongside the clarification appendix and the additional clarification response.

As stated previously, the EAG sought further clarification on the presented ITC. The following comprises a summary of the ITC provided during clarification (supported by the additional clarification response) and the analyses conducted by the EAG.

3.5.2 Indirect treatment comparison: Identification of comparator studies

The company's NMA includes one RCT of adjuvant atezolizumab (IMpower010[5]) and one RCT of adjuvant pembrolizumab (PEARLS/KEYNOTE-091[6, 7]). These were identified from the company's clinical SLR, which identified 67 trials of NSCLC treatments in the adjuvant setting (CS[1] Appendix D.1.4 Table 6). Other than these two trials, no other RCTs of adjuvant atezolizumab or pembrolizumab were identified in the company's SLR. The EAG considers that these are the relevant trials for inclusion in the ITC.

3.5.3 Indirect treatment comparison: Quality of comparator studies

Results of a critical appraisal of PEARLS/KEYNOTE-091[6, 7] are presented in CS[1] Appendix D.1.4 (CS Appendix Table 7). The EAG agrees with the company's conclusion that the study is at low risk of bias overall.

3.5.4 Indirect treatment comparison: Comparability of studies

A comparison of study designs for IMpower010[5] and PEARLS/KEYNOTE-091[6, 7] was provided in the supporting documents to clarification question A4, see Table 13. Some study design information relating to the PEARLS/KEYNOTE-091 trial was not included within the feasibility assessment or clarification response, Table 13 has therefore been supplemented with publicly available information from NICE TA1037.[20]

Table 13 Study design of IMpower010 and PEARLS/KEYNOTE-091 trials. Information sourced from Table 3 of the CS[1], supporting documents to clarification response A4 and the publicly available documents for NICE TA ID1037.[20]

Study	IMpower010	PEARLS/KEYNOTE-091
Key references	Roche 2024: IMpower010 CSR[5] Felip *et al.*, 2021[12] (3-year DFS) Felip *et al.*, 2023[13] (4-year OS) Felip *et al.*, 2024[14] (5-year subgroup analyses; conference poster) Wakelee *et al.*, 2024[15] (5-year DFS and OS; conference poster)	O'Brien et al. 2022[6] (first interim analysis) Besse et al. 2023[7] (second interim analysis)
Study design	• Phase III multi-centre open-label RCT	• Phase III multi-centre triple-blinded RCT
Location	• Global	• Global
Population	• Adults with completely resected Stage 1B to IIIA NSCLC (stage IB tumours were ≥4cm) • ECOG PS of 0 or 1 • Received cisplatin-based adjuvant chemotherapy (up to 4 cycles) • No restriction by PD-L1 status or EGFR/ALK mutation status	• Adults with completely resected Stage 1B to IIIA NSCLC (stage IB tumours were ≥4cm) • ECOG PS of 0 or 1 • 86% received adjuvant chemotherapy • No restriction by PD-L1 or EGFR/ALK mutation status
Intervention(s)	• Atezolizumab 1200mg intravenous every 3 weeks for up to 16 cycles (i.e., a maximum of 48 weeks of treatment)	• Pembrolizumab 200mg Q3W for 18 cycles (1 year)
Comparator(s)	• Active monitoring	• Placebo; saline administered Q3W for 18 cycles
Stratification factors	• Sex (male vs. female) • Tumour histology (squamous vs. non-squamous) • Extent of disease (Stage IB vs. II vs. IIIA) • PD-L1 tumour expression by IHC (TC2/3 and any IC vs. TC0/1 and IC2/3 vs. TC0/1 and IC0/1 via SP142 IHC assay)	• Disease stage • Adjuvant chemotherapy • PD-L1 expression • Geography

Study	IMpower010	PEARLS/KEYNOTE-091
Reported outcomes in decision problem	• DFS • OS • AEs	• DFS • OS • AEs • HRQoL assessed by EORTC QLQ-C30(version 3), EORTC QLQ-LC13 and EQ-5D-5L
Duration of follow-up	• Median follow-up 65 months; minimum follow-up 60 months; represents additional 36 months over the data in the previous NICE appraisal (Technology Assessment 823[16])	• Median follow-up 51.7 months as presented at the second interim analysis, Besse et al. [7]
Data cut-off in CS	• 26 January 2024 (final DFS and second interim OS analysis)	• 24 January 2023 (as per Besse et al. [7])

CS, company submission; NSCLC, non-small cell lung cancer; CS,: clinical study report; DFS, disease free survival; OS, overall survival; ECO,: Eastern Cooperative Oncology Group; ALK, anaplastic lymphoma kinase; EGFR, epidermal growth factor receptor; PD-L1, programmed death-ligand 1; PS, performance status; Q3W,: every 3 weeks; AE, adverse event; HRQoL, Health-related quality of life; EORTC QLQ-C30, European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire core quality of life questionnaire; EORTC QLQ-LC13, European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire lung cancer specific; EQ-5D-5L, EuroQol 5-Dimensions (3 level).

The company provided a comparison of baseline characteristics between the two study ITT populations and primarily focussed on comparisons of potential treatment effect modifiers/prognostic factors (see Table 14). The company provided a list of potential treatment effect modifiers/prognostic factors identified by an AI-assisted ad hoc literature search. The following were listed as potential treatment effect modifiers/prognostic factors; older age, male sex, non-Asian ethnicity, smoking history, later tumour stage/high tumour size, non-squamous cell carcinoma, poorer performance status and positive PD-L1 expression. The sources from which these were identified are listed in Section 3.4 of the feasibility assessment.

The EAG highlight that the identification of the factors via this method as opposed to a full systematic literature review may result in a narrowed selection of treatment effect modifiers/prognostic factors. Despite this, the EAG notes that no additional treatment effect modifiers or prognostic factors were highlighted by the EAG clinical advisors and so believe this to be a comprehensive list of factors relevant to this appraisal. The EAG also notes that the company did not distinguish between the treatment effect modifiers or prognostic factors within their summary.

Table 14 Baseline characteristics of the IMpower010 and PEARLS/KEYNOTE-091 trials. Reproduced from supporting materials of the company response to clarification question A4 and CS Table 4.

Study	IMpower010 (atezolizumab [N=507], AM [N=498])	PEARLS/KEYNOTE-091 (pembrolizumab [N=590], placebo [N=587])
Age (Median years)	62.0, 62.0	65.0, 65.0
Sex (% male)	66.5, 67.3	68.0, 68.7
Ethnicity	Not available[b]	Not available
Smoking history	Not available[c]	Not available
Disease stage	IIA:29%, 30% IIB: 18%, 17% IIIA: 40%, 42%	II: 56%, 58% IIIA: 30%, 28%
Tumour stage	[redacted]	Not available
Histology (squamous)	35%, 34%	33%, 38%
Performance status	ECOG 0: 54%, 57% ECOG 1: 46%, 43%	ECOG 0: 64%, 58% ECOG 1: 36%, 42%
PD-L1 < 1%	[redacted]	Not available[a]
PD-L1 ≥ 1%	57%, 52%[d]	Not available
PD-L1 1%-49%	Not available	Not available[a]
PD-L1 ≥ 50%	[redacted]	29%, 28%

ECOG, Eastern Cooperative Oncology Group; PD-L1, programmed death-ligand 1.
[a] Baseline characteristics not available, but endpoint data (DFS) for these subgroups was available.
[b] Quoted as not available within the feasibility assessment but reported in the CS that 71% and 76% of patients were White and 26% and 23% were Asian in the atezolizumab and AM arms respectively.
[c] Quoted as not available within the feasibility assessment provided during clarification but reported in the CS that 78% and 78% of patients has current or previous tobacco use in the atezolizumab and AM arms respectively.
[d] Values based on Table 4 of the CS.

In the PEARLS/KEYNOTE-091 ITT trial population only 86% of patients received adjuvant chemotherapy which contrasts with 100% of patients in IMpower010 (due to the IMpower010 inclusion criteria). The baseline characteristics and outcomes were not available for the subpopulation of patients in PEARLS/KEYNOTE-091 who received adjuvant chemotherapy and therefore the comparison of baseline characteristics provided by the company includes patients within the PEARLS/KEYNOTE-091 trial who did not receive adjuvant chemotherapy; see Table 14. The company stated that using the sub-population of patients who did receive adjuvant chemotherapy would have *"reduced variability and improved the comparability of the studies included in the NMA"* and that although previous evidence (Pignon *et al.*[22]), suggests that there is a statistically significant effect of adjuvant chemotherapy, this effect is "*small in magnitude*". The EAG highlights that the assumption of equivalence of the 86% of patients in the PEARLS/KEYNOTE-091 trial who received adjuvant chemotherapy with those who did not, is a limitation of the analysis and that this may have an uncertain impact on the ITC. However, the desired sub-population data was not available and relied on the omission of a comparatively small proportion of patients (~14%), and thus the EAG is satisfied with this decision.

The company concluded that the trial participants appeared similar in terms of age, sex, tumour histology and the proportion of PD-L1≥ 50% patients. Although, the company stated that there were similar proportions of Stage IIIA patients and ECOG PS 0/1 patients across the two trials, the EAG notes that there is a slightly smaller proportion of Stage IIIA patients in the PEARLS/KEYNOTE-091 trial compared to the IMpower010 trial (difference of approximately 10%). Additionally, the PEARLS-KEYNOTE-091 trial included some stage IB patients and it is unclear what proportion of these were within the PD-L1≥50% subgroup. It also appeared that the PEARLS/KEYNOTE-091 trial had a slightly higher proportion of patients with a performance status of ECOG 0 in the intervention arm than in the IMpower010 trial (difference of approximately 10%).

It was not possible for the company to compare the baseline characteristics of the PD-L1 sub-groups as these were not reported in the PEARLS/KEYNOTE-091 trial. Information regarding ethnicity and smoking history was quoted as not available for either trial, however this information was available for IMpower010 in the CS. Additionally, tumour stage was not reported in the PEARLS/KEYNOTE-091 trial, and so this could not be compared across trials.

The company concluded that overall, patient characteristics and trial designs were sufficiently similar in order to conduct a naïve/unadjusted ITC. As stated above, the EAG notes that the comparison of baseline characteristics was conducted for the ITT population not for the DPP or the populations used within the ITC. The EAG again highlights that there was a slightly higher proportion of Stage IIIA patients in IMpower010 despite the company stating that the disease stages of patients were broadly

similar. However, the EAG clinical advisors advised that they would not expect relative efficacy to differ between disease stages and thus the EAG is satisfied that this would have a minor effect the results of the ITC.

3.5.5 Indirect treatment comparison: Summary and critique of statistical methods

In the absence of head-to-head trials comparing the relative efficacy of atezolizumab and adjuvant pembrolizumab, the company conducted an NMA. It was assumed by the company that the comparator arms of the IMpower010 and PEARLS/KEYNOTE-091 trials, active monitoring and placebo respectively, were sufficiently similar to generate a connected network between the two studies. In the additional clarification response, the company qualified this assumption of similarity by stating that the "*best supportive care received in IMpower010 and placebo received in PEARLS/KEYNOTE-091 involved no active treatments, only observation, scans & saline solution*" and thus could justify the equivalence between the two arms.

The company assessed the proportional hazards assumption via assessment of Schoenfeld residuals for DFS in both trials, see Appendix 7.2 of the feasibility assessment provided with the company clarification response, and surmised that there was no evidence for violation of the assumption based on these plots. The company also assessed the proportional hazards assumption through visual assessment of the log cumulative hazards plots provided in the additional clarification response. The EAG is satisfied with the company's assessment of the proportional hazards assumption but highlights that it is unclear within the feasibility assessment what data cut-off was used for the two trials and that this therefore may not form the basis of an up-to-date assessment of the proportional hazards assumption.

The NMA was conducted in a Bayesian framework using Markov chain Monte Carlo (MCMC). A model using a normal likelihood and an identity link function was chosen, with the NMA conducted on the log-HR scale. Fixed and random effects NMAs were performed, using the AM/placebo arm as the reference treatment within the network. Due to the low number of studies within the network, the company used an informative prior on the between-study heterogeneity parameter, τ. The company used the prior recommended by Turner et al. for the comparison of pharmacological interventions for cause-specific mortality.[23] The company also provided results when using a half-normal prior (scale=0.1) within the additional clarification response.[24]

A vague normal prior, centred at zero, and with a variance of 10000, was chosen for the trial-specific treatment effects. For each model, a burn-in of 20,000 iterations was used, with a further 20,000 iterations to obtain the posterior estimates of the relative effects. Convergence of the samplers was stated to have been assessed, but the methods that were used to assess this were not explicitly stated.

Goodness of fit was assessed using the total residual deviance, and the fit of the fixed and random effects models was assessed using the deviance information criterion (DIC).

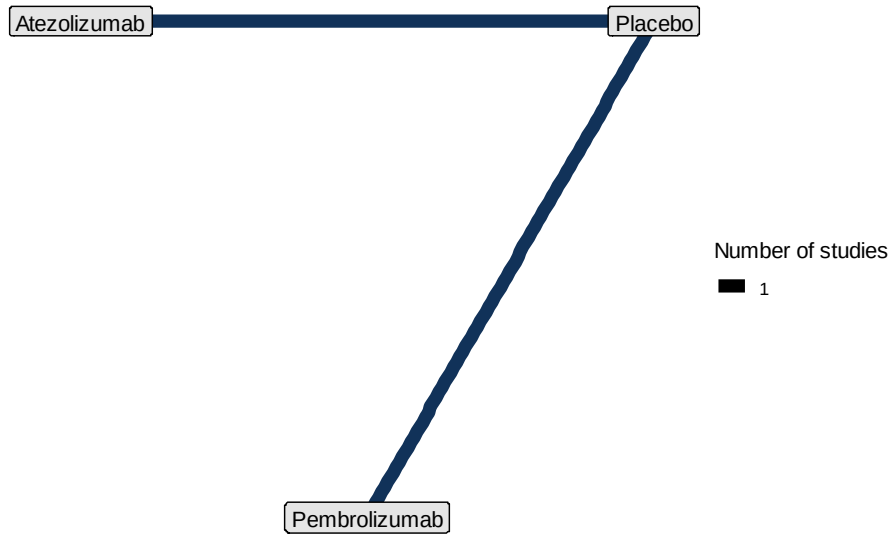
The EAG believes that the statistical approach and models specified by the company were appropriate. However, the company states that the fixed effects model was favoured, due to the sensitivity of the between study heterogeneity parameter estimate and the chosen prior. The EAG believes that use of the fixed effects model does not capture the between study heterogeneity and therefore believes the random effects model should be used, using the informative Turner prior on τ (as implemented by the company).

The company used the following HRs for DFS within the NMA; 0.503 (95% CI: 0.33, 0.76) and 0.83 (95% CI: 0.59, 1.16) for atezolizumab versus AM and pembrolizumab versus placebo respectively. The source of these HRs was not explicitly stated within the clarification response, supporting documents or additional clarification response. However, the EAG were able to source the HR of the pembrolizumab versus placebo from Besse et al. 2023[7] and notes that this HR corresponds to the PD-L1≥50% population. This is discussed further in Section 3.6.

3.5.6 Indirect treatment comparison: Results presented by the company

The network diagram for the NMA conducted by the company is reproduced below in Figure 6.

Figure 6 Network diagram reproduced from Figure 1 in the NMA report provided by the company at the clarification stage.



The company presented results for both the fixed and random effects NMAs, Table 15. In Table 15, only the results for the fixed effects and random effects (using a Turner prior) are summarised as results on the HR scale were not provided for the random effects analysis when using a half-normal prior within the additional clarification response.

Table 15 Company estimated treatment effects for DFS, PD-L1≥50%. Reproduced from Table 3 of the NMA report/Table 33 of the clarification Appendix and Tables 1, 2 and 3 from the additional clarification response.

	Mean posterior HR (95% CrI)	
Treatment comparisons	**Fixed effects model**	**Random effects model (Turner prior)[23]**
Atezolizumab vs. Placebo	[redacted]	[redacted]
Pembrolizumab vs. Placebo	[redacted]	[redacted]
Atezolizumab vs Pembrolizumab	[redacted]	[redacted]
Pembrolizumab vs Atezolizumab	[redacted]	[redacted]
	Mean posterior log-HR (95% CrI)	
Pembrolizumab vs Atezolizumab	[redacted]	[redacted]
Residual deviance	[redacted]	[redacted]
DIC	[redacted]	[redacted]

CrI, credible interval; DIC, deviance information criteria; HR, Hazard ratio
Between study heterogeneity τ = 0.06 (95% CrI 0.00, 0.40)

The residual deviance was reported as [redacted] for both the fixed and random effects, indicating a similar goodness of fit to the data. The mean posterior HR of atezolizumab versus pembrolizumab was [redacted] using the fixed effect model, suggesting that atezolizumab [redacted]. The mean posterior HR of atezolizumab using the random effects model was [redacted] which is [redacted]

In the company's response to additional questions, it was stated that "*In the CEM that was previously sent, the estimates* [redacted] *(fixed effects model) and* [redacted] *(random effects model) are incorrectly used which were calculated by manually log transforming the hazard ratios presented in Table 2 for the comparison. The impact of this discrepancy on the ICER is minimal with the deterministic results continuing to show atezolizumab as dominant at atezolizumab PAS price*." For simplicity, and because no new base case results were provided, the EAG has reported the results in the company's clarification response in Section 4.5.

As detailed in Section 3.6, the EAG noted limitations within the company's NMA which were addressed with additional EAG analyses.

3.6 Additional work on clinical effectiveness undertaken by the EAG

The EAG noted the following limitations in the NMA and subsequent use of the results within the model;

1) the results of the NMA in the company's NMA report (Table 3) in its clarification response do not match the values in the model, when transformed to the log-HR scale (as discussed above),
2) the HR for atezolizumab compared with AM (0.503) in Table 2 in the company's NMA report in its clarification rranesponse(s) does not appear in the CS with no explanation provided,
3) the population used to estimate the relative efficacy of pembrolizumab appears not to equal that deemed most appropriate in TA1037.[20]

For the third limitation, the EAG notes that in TA1037, the EAG in that appraisal highlighted the unintuitive point-estimates in HRs for DFS between the full licensed population (FLP) for pembrolizumab (0.76) and the PD-L1 <50% group (0.72) (and therefore the PD-L1 group above or equal 50% having a HR greater than 0.76) which "*may be driven by data over biological / clinical plausibility.*" The clinical advisors to the EAG also believe that pembrolizumab should have greater effectiveness in the higher PD-L1 group. The EAG believes that the Appraisal Committee for TA1037[20] used the HR from the FLP to be the most plausible estimate of pembrolizumab across both subgroups. In its additional clarification response, the company did not provide an analysis using the HR corresponding to the FLP from the PEARLS/KEYNOTE-091, stating that there was too much heterogeneity between the DPP of the IMpower010 study and the FLP of the PEARLS/KEYNOTE-091 study which "*make it nearly impossible to draw accurate and reliable comparisons between the two populations.*"; the EAG disagrees, noting the apparent use of the data corresponding to the FLP from the PEARLS/KEYNOTE-091 study in TA1037.[20] The EAG also notes that the company did not provide any evidence of treatment effect modifiers for pembrolizumab across the PD-L1 groups to justify its position. The EAG has therefore used the combined data from both PD-L1 groups in its NMA.

Considering the above, the EAG conducted an additional NMA, using the HR for DFS for atezolizumab versus AM [0.48 (0.32, 0.72)], sourced from Table 8 of the CS which corresponds to the Stage II-IIIA PD-L1≥50% population using the most recent data cut-off, and for pembrolizumab versus placebo equal to 0.76 (0.64, 0.91), which corresponds to the FLP of the PEARLS/KEYNOTE-091 study, as reported in slide 11 of the Committee Presentation on the 3rd of October 2024 for TA1037.[20] The EAG chose to use the HR for the sub-population which *included* EGFR/ALK mutations despite this differing from the DPP. This was due to the relatively small number of patients with these mutations and because the PEARLS/KEYNOTE-091 study[6] did not provide corresponding data for the EGFR/ALK negative subgroup.

The company used both fixed effects and random effects models and favoured the fixed effects model for their base case, whereas the EAG believes that the random effects model (using the Turner prior) should be preferred due to heterogeneity in patient populations. For completeness, the EAG has reproduced both fixed and random effects NMAs. The EAG used fixed and random effects models, based on those presented in Example 7 of TSD2[25], and conducted the NMA using WinBUGs.[26] The same number of burn-in samples and number of samples to estimate the posterior means as in the company's analysis, and the same priors were used for both the between study heterogeneity parameter, τ, and the study specific treatment effects. Convergence and autocorrelation were checked via the visual assessment of Gelman convergence and autocorrelations plots. Results of the fixed and random effects NMAs are presented in Table 16.

Table 16 EAG estimated treatment effects.

	Mean posterior HR (95% CrI)	
Treatment comparisons	**Fixed effects model**	**Random effects model**
Atezolizumab vs. Placebo	[redacted]	[redacted]
Pembrolizumab vs. Placebo	[redacted]	[redacted]
Atezolizumab vs. Pembrolizumab	[redacted]	[redacted]
Pembrolizumab vs Atezolizumab	[redacted]	[redacted]
	Mean posterior log-HR (95% CrI)	
Pembrolizumab vs Atezolizumab	[redacted]	[redacted]
Residual deviance	[redacted]	[redacted]

HR, hazard ratio; CrI, credible interval.
Between study heterogeneity standard deviation = 0.11 (95% CrI 0.01, 0.41)

The residual deviance was similar for both the fixed and random effects, indicating a similar goodness of fit to the data. The mean posterior HR of atezolizumab versus pembrolizumab, using the random effects model was [redacted] which suggests that [redacted]

3.7 Conclusions of the clinical effectiveness section

Clinical evidence: The clinical evidence in the CS[1] was based on the IMpower010[5] RCT of adjuvant atezolizumab vs. AM in adults with completely resected Stage 1B to IIIA NSCLC having had cisplatin-based chemotherapy. The DPP consisted of Stage II-IIIA patients with PD-L1 ≥50%, excluding EGFR and ALK alterations (n=106 atezolizumab, n=103 AM). No SACT data for atezolizumab were presented in the CS. In the DPP, median DFS was not reached for atezolizumab vs. 43 months for AM, with a HR of 0.49 (95% CI: 0.32, 0.75), while median OS was not reached for atezolizumab vs. 87

months for AM, with a HR of 0.44 (95% CI: 0.26, 0.74). In the atezolizumab safety population (n=495), 22% had grade 3-4 AEs, 18% serious AEs, 1.8% deaths due to AEs, 29% had AEs leading to dose interruption and 18% had AEs leading to discontinuation, while the most common treatment-related AEs were hypothyroidism (11%), pruritus (9%), rash (8%), increased AST (8%), increased ALT (7%), hyperthyroidism (6%), pyrexia (6%), and arthralgia (5%).

Indirect treatment comparison: Due to the lack of head-to-head trials for atezolizumab with pembrolizumab, the company conducted an NMA to evaluate the comparative efficacy of atezolizumab versus pembrolizumab. However, the EAG noted limitations in this analysis and ran its own NMA. This changed the HR between atezolizumab and pembrolizumab from [redacted] (fixed effects) in the company's analysis to [redacted] (random effects) in the EAG's analysis.

4 COST EFFECTIVENESS

4.1 EAG's comment on company's review of cost-effectiveness evidence

The company detailed its SLR of published cost-effectiveness analyses in Appendix I of the CS with the SLR for HRQoL and for costs and healthcare resource use in Appendix J and K respectively. For each of the three SLRs, an initial search was undertaken in March 2021, with updates in July 2022, July 2023, September 2023 and August 2024. The real-world evidence review described in Appendix L conducted searches in March and April 2021.

Overall, the EAG considers that the company's SLR for published cost-effectiveness analyses was comprehensive, and that there were no observable and/or consequential errors in the search strategies. For the cost and healthcare resource use SLR, whilst the database subject heading and thesaurus terms are comprehensive, the company could have included the following free-text terms i.e. "economic*" OR "pharmacoeconomic*" OR "price" or "pricing". See CRD website for economic evaluation terms for MEDLINE and Embase, including other sources.[27] A further limitation is that the company search terms used in the conference, HTA and website searches were not reported. Additionally, the EAG could not ascertain from the PRISMA flow diagram (CS Appendix, Figure 4, page 143) the number of records retrieved from each search update. The limitation of the PRISMA diagram also applies to the HRQoL SLR. However, the EAG considers that the electronic database searches are comprehensive, and no studies have been missed. For the real-world evidence review, the EAG agrees with the company that this is not an SLR, and that all the real-world evidence is unlikely to be retrieved.

The company identified 41 economic evaluations published in full that related to early-stage NSCLC, which covered a multitude of first-line treatments. Thirty of these publications used a model, which were summarised in Appendix I of the CS[1] and the company concluded that '*The traditional three-state model typically utilised in oncology indications was not generally used; model structures were more complex and included a variety of alternative health states.*' The company stated that '*Overall, no published studies were found that assessed the cost effectiveness of adjuvant treatment with atezolizumab in patients with Stage II–IIIA NSCLC.*'; however, the submissions by the company to the Scottish Medical Consortium (SMC) in 2022[28] and to NICE in 2021 (for TA823[29]) (see pages 92 and 93, and Table 16 of Appendix I of the CS) appear to contradict this statement. The EAG has assumed that the company means that no studies other than those performed by the company itself were identified; the EAG also notes that whilst the SMC submission appears to be directly relevant the submission for TA823 assessed a broader group, which was all patients where the PD-L1 tumour expression was 1% or greater.

In the HRQoL SLR, seven studies were tagged as HRQoL studies (see Figure 3 in Appendix J of the CS) whilst in the cost and healthcare resource SLR, 58 studies were included at full text stage (see Figure 4 in Appendix K of the CS). Individual studies relating to utility, costs or resource use are discussed later in the document, as appropriate.

4.2 Description of company's health economic analysis

4.2.1 Model scope

A summary of the company's base case model is provided in Table 17. The economic analysis was undertaken from the perspective of the National Health Service (NHS) and Personal Social Services (PSS) over a 40-year time horizon using monthly time cycles. Health care resource costs were valued using 2022/23 prices with costs of interventions using 2024 prices. Health outcomes and costs were discounted at a rate of 3.5% per annum as recommended by NICE[4]

Table 17 Summary of the company's base case model

Population	The DPP
Time horizon	40 years with time cycles of 1 month which represents the lifetimes of patients
Intervention	Adjuvant atezolizumab used for a maximum of 1 year
Comparators	Active monitoring
Outcome	Incremental costs per QALY gained
Perspective	NHS and PSS
Discount rate	3.5% per annum for both health outcomes and costs
Price year	2024 for interventions, 2022-2023 for health care resource costs

QALY: quality-adjusted life year; NHS: National Health Services; PSS: Personal Social Services; BSC: Best Supportive Care

Further details on the company's model are contained in Sections 4.1 to 4.4, In these, only the latest version of the company's model (that submitted after the clarification process) is described, unless there is a need to reference the model submitted with the CS.

4.2.1.1 Population

The population included in the company's model relates to the DPP as defined in Section 2.2.

4.2.1.2 Intervention

The intervention under consideration is atezolizumab as described in Section 2.3.2. In the base case, atezolizumab is used for a maximum of 16 cycles, with the distribution for time on treatment taken from IMpower010. Following clarification, the company assumed that 50% of patients received a subcutaneous injection and 50% an IV infusion which was based on company data showing that across

all indications [redacted] of people were receiving atezolizumab as a subcutaneous injection and noting that this figure would likely increase when atezolizumab is used as a monotherapy.

The subcutaneous formulation of atezolizumab was not used in IMpower010 but the EAG notes the company's response to clarification question A14 states that "*in August 2023, the MHRA approved atezolizumab SC for all indications in which the IV formulation is authorised, supported by findings from the IMscin001 study. This approval confirms that regulatory authorities have deemed the SC formulation equivalent in safety and efficacy to the IV formation. Access to atezolizumab SC has also been granted in the UK, further demonstrating that payers also recognise its equivalence in safety and efficacy*". The EAG has accepted clinical equivalence and believes the ratio of injections to infusions is plausible.

4.2.1.3 Comparators

The comparator in the CS was AM for a period of 5 years, after which routine monitoring costs become zero with the patients being discharged from clinical follow-up. At clarification stage, the company added adjuvant pembrolizumab as a comparator. The comparators in the NICE scope that are not included in the company's model are described in Section 2.3.3.

4.2.2 Model structure and logic

The company's model structure is fairly complex and comprises of a series of sub-models following initial progression; these sub-models are similar to standard three state state-transition models often used in oncology. All hypothetical patients start in the disease-free health state until progression or death with patients who reside long enough in the DFS state eventually being denoted as cured of NSCLC (albeit with an increased risk of death compared to the general population). Following clarification, the company changed its approach to the way that cure was modelled, with the EAG being content with the new approach (and sensitivity analysis) undertaken by the company. The details of how cure is modelled are provided in Section 4.2.3.2.

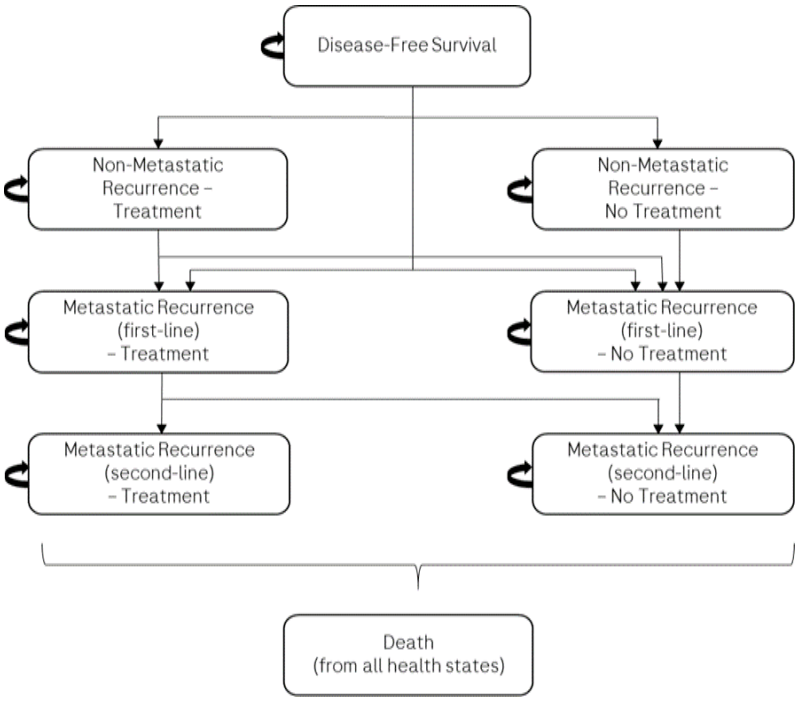
Patients who have progressed from the disease-free state enter either a non-metastatic recurrence health state (henceforth called a local recurrence health state to aid differentiation) or a metastatic progression health state. Treatment options in each of these health states are conditional on the initial treatment received and time since treatment (as patients who have a progression event within 18 months would not receive a second immunotherapy if they had initially been treated with adjuvant atezolizumab or pembrolizumab). Some patients would also be considered too frail for, or unwilling to take, subsequent treatment.

Patients with local recurrence can also have a progression event (to metastatic disease) or die. The possible transitions for patients with metastatic progression are dependent on whether patients are receiving treatment. Those patients who are receiving treatment can either have a progression event or die, with progression assigning the patient to a second metastatic progression health state, whereas patients not receiving treatment can only die. In the second metastatic progression health state the only transition is to death. A depiction of the company's model structure is shown in Figure 7. In response to clarification question B9,[2] the company confirmed that transition between first metastatic recurrence and second metastatic recurrence was not activated in the model.

The model notably does not use any of the OS data observed in IMpower010.[30] Whilst this is uncommon, the structure that the company has adopted, which is the linking together of separate models which simulate the experience of patients through different health states, is conceptually appropriate provided that the OS that is generated by the model aligns with that observed with the pivotal study (as discussed in Section 4.3). The company's approach has some advantages when OS data are immature (as in the atezolizumab arm where the Kaplan Meier plot has over 75% survival at the end of follow-up) and there is potential for patients to be cured of the NSCLC. OS was modelled based upon DFS and the proportion of events that were predicted to be deaths as opposed to progression. For first-line treatments data was taken from IMpower010 whilst for second-lines and subsequent treatments, data on time to an event and the proportions that were deaths were taken from targeted literature reviews.

Whilst the EAG notes that a conceptual model which incorporates a cure fraction has potential advantages over the approach undertaken by the company the EAG believes that the company's methodology is suitable for decision-making.

Figure 7 The company's model structure (reproduced from company's submission, Figure 17)



For later lines of treatment, see Sections 4.2.3.3 to 4.2.3.5, the company has assumed that time to a progression event (either progressed disease or death) are distributed exponentially. The exponential model fits to the data sources are presented in Appendix M of the CS. For completeness, the company also provided the best-fitting models and associated Akaike information criteria (AIC) and Bayesian information criterion (BIC) for comparison, but these were not considered within the company analyses. Whilst the use of the exponential model may not always be the best fitting distribution, the EAG noted that 1) this assumption allowed the model to be simplified, particularly in relation to calculations within tunnel states; and 2) that as the company was often fitting distributions to match a published average value any error was likely to have little impact on the ICER. As such, the EAG was comfortable with the approach taken by the company.

4.2.3 Evidence used to inform the company's model parameters

The evidence used to inform the company's model are discussed in the following sections and cover

- Patient characteristics (Section 4.2.3.1)
- Risk of a progression event for patients in DFS (Section 4.2.3.2)
- Risk of a progression event for patients in the local recurrence health state (Section 4.2.3.3)
- Risk of a progression event for patients in the first metastatic recurrence health state (Section 4.2.3.4)
- Risk of a progression event for patients in the second metastatic recurrence health state (Section 4.2.3.5)
- Adverse events (Section 4.2.3.6)

- Health-related quality of life associated with model states (Section 4.2.3.7)
- Costs (Section 4.2.3.8)

4.2.3.1 Patient characteristics at model entry

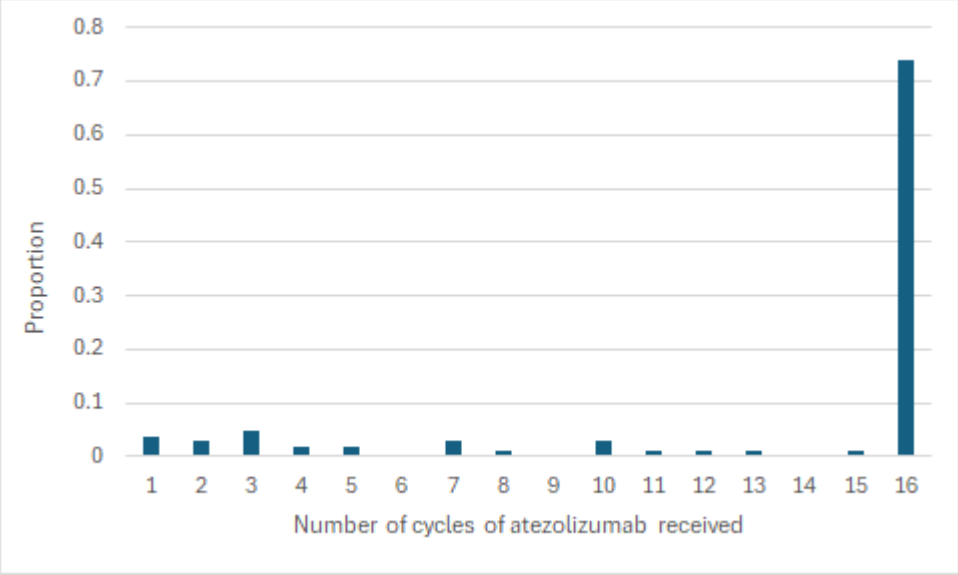
It is assumed that on model entry 66.90% of the cohort are male, with an age of 61.20 years, a weight of 74.03kg and a body surface area of 1.84m^2. These data are stated in the CS[1] to be taken from IMpower010, using a data cut-off of the 26th of January 2024 and are presumed to be mean values. In the company's model, these values do not change based on the population selected and, in the CS, it is not clear that these values are specific to the DPP, however the EAG does not believe that potentially having slightly more accurate values would have a marked impact on the incremental cost effectiveness ratio (ICER), defined throughout as cost per quality-adjusted life years (QALY) gained. The EAG performed a scenario analysis where patient characteristics were aligned with SACT data.

4.2.3.2 Events and time on treatment in the disease-free survival health state

4.2.3.2.1 Time on treatment for atezolizumab, active monitoring, and pembrolizumab

The number of cycles of atezolizumab received was taken directly from data observed for the DPP in IMpower010, with a cut-off date of the 26th of January 2024. This is presented in Figure 8. The majority of patients (74%) received the maximum of 16 cycles of atezolizumab.

Figure 8 The distribution of patients by number of atezolizumab cycles received



For AM, the company assumed no active treatment, whereas for pembrolizumab, the company assumed that all patients had 17 cycles, which was reported as the mean dose in Table 36 of the company's clarification response.[2] The EAG notes that time on treatment data which would allow a more accurate

estimation of pembrolizumab costs was redacted in the company's submission for adjuvant pembrolizumab.[31]

4.2.3.2.2 Estimation of the time to a DFS event

The company undertook analyses of the DFS data for atezolizumab and AM from IMpower010. Extrapolation techniques for DFS were employed to facilitate extrapolation over a (lifetime) time horizon of 40 years. Seven parametric distributions (Exponential, Weibull, Log-Logistic, Log-Normal, Gompertz, Generalised Gamma and Gamma) were fit to the DFS data. A proportional hazards model was rejected based on the convergence and separation of the log-cumulative hazards (see Figure 18 of the CS) and thus parametric distributions were fitted independently for the atezolizumab and AM arms. The EAG highlights that this approach contrasts with the PH assumption made in Section 3.5 but is comfortable that the assumptions made in indirect treatment comparison are pragmatic and facilitate the incorporation of the relative treatment of pembrolizumab compared with atezolizumab into the economic model.

The statistical fit of the trial data to the parametric distributions was assessed according to AIC and BIC (

Table 18) and visual inspection (Figure 9 and Figure 10). In clarification question A17,[2] the company provided smoothed hazards for the atezolizumab and AM arms to supplement the assessment of the parametric fits.

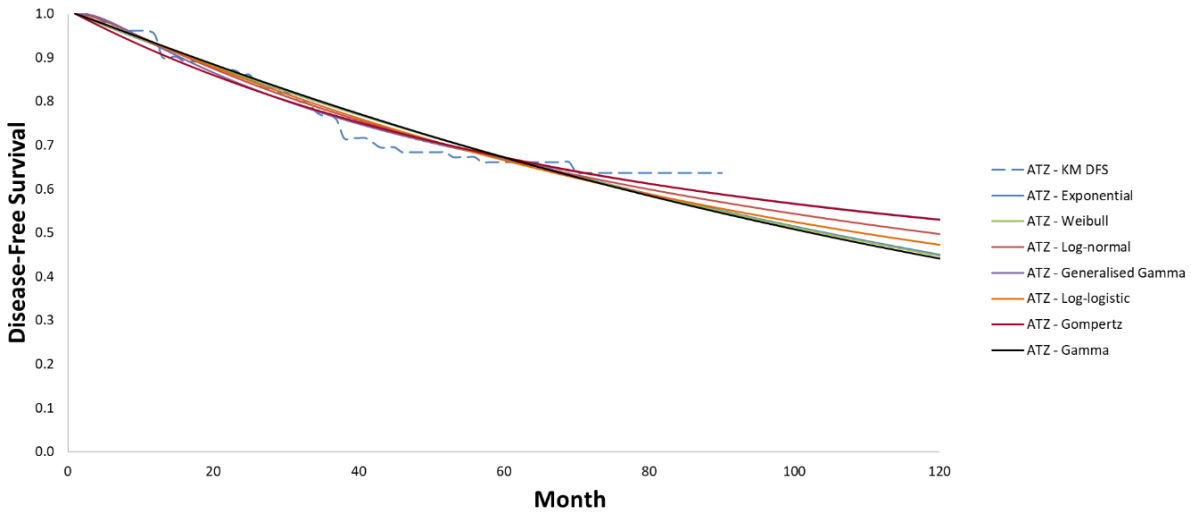
Additionally, the company compared extrapolated DFS at 1, 5, 10, and 20 years between arms (see Tables 19 and 20 of the CS), however, at clarification (question B10[2]) the company agreed that there was limited usefulness in comparing values at 10 and 20 years as a cure proportion was applied at 5 years.

Table 18 AIC and BIC for parametric model fits to DFS data for the DPP (based on Table 18 of the CS).

Distribution	Atezolizumab arm				BSC arm			
	AIC (Rank)		BIC (Rank)		AIC (Rank)		BIC (Rank)	
Exponential	410.2	2	412.9	**1**	581.2	7	583.9	6
Gamma	412.2	7	417.5	6	579.1	6	584.4	7
Generalised Gamma	410.5	3	418.5	7	566.3	**1**	574.2	**1**
Gompertz	410.8	4	416.1	3	573.7	4	578.9	4
Log-logistic	411.2	5	416.5	4	572.2	3	577.5	3
Log-normal	409.1	**1**	414.5	2	569.7	2	575.0	2
Weibull	412.2	6	417.5	5	577.7	5	583.0	5

AIC, Akaike Information Criterion; BIC, the Bayesian Information Criterion; DFS, disease-free survival; DPP, decision problem population. Bold indicates the best fitting distribution based on goodness of fit

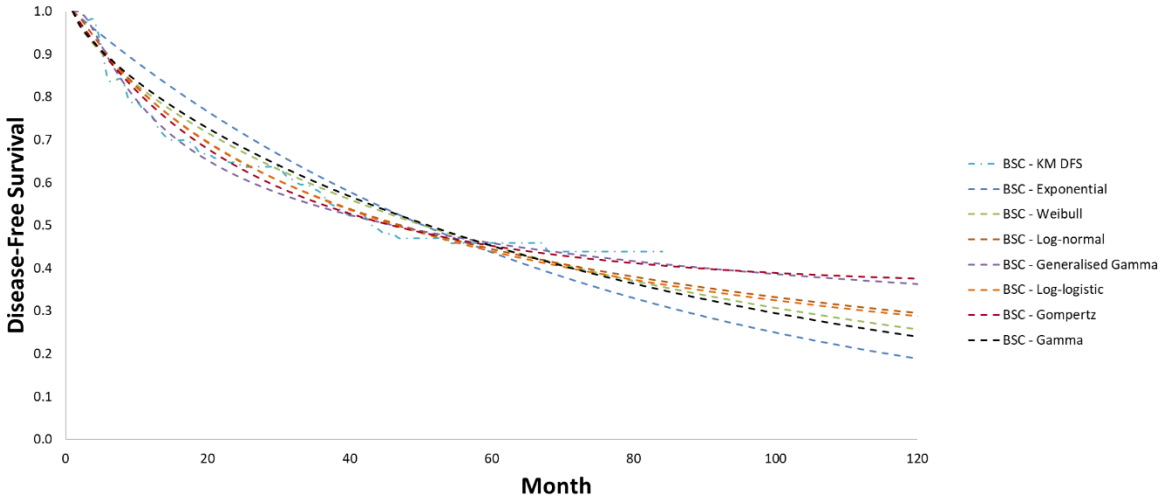
Figure 9 Kaplan-Meier estimate of DFS for the DPP, atezolizumab arm and parametric model fits (reproduced from Figure 19 of the CS).



DFS, disease-free survival; DPP, decision problem population; ATZ, atezolizumab.

For atezolizumab, a Gompertz extrapolation was chosen as it was the only distribution that produced an extrapolation that clinicians thought plausible, other than the generalised gamma which did not converge for probabilistic analyses. The EAG was comfortable with these choices and noted that the use of alternative distributions did not have a big impact on the ICER.

Figure 10 Kaplan-Meier estimate of DFS for the DPP, AM arm and parametric model fits (reproduced from Figure 20 of the CS).



DFS, disease-free survival; DPP, decision problem population; BSC, best supportive care (AM); AM, active monitoring.

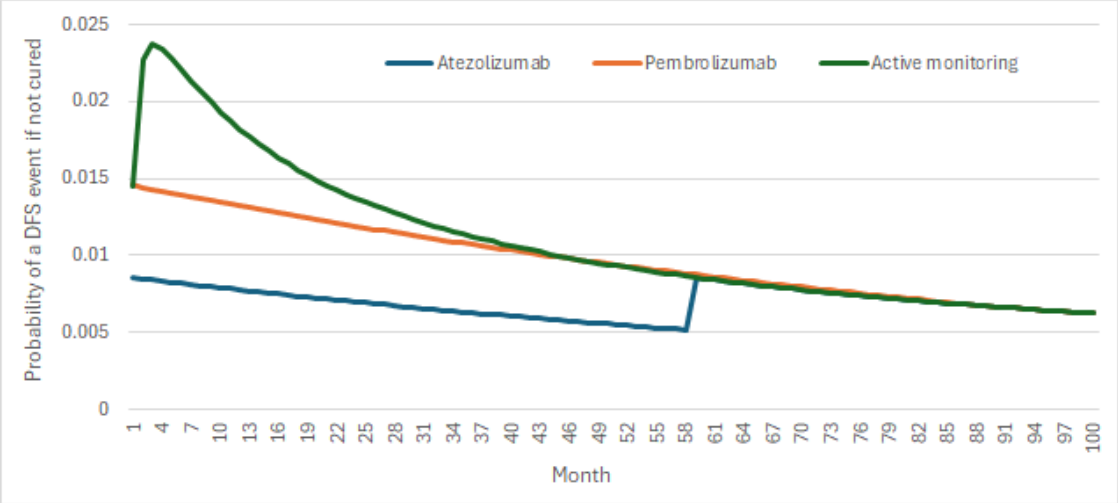
For AM, the log-normal distribution was chosen as it had a better statistical and visual fit than the log-logistic distribution, with clinicians believing that these were the only two distributions that produced plausible extrapolations. The EAG was comfortable with these choices and noted that the use of alternative distributions did not have a big impact on the ICER.

The company stated that it adjusted the distributions for both atezolizumab- and AM-treated patients by assuming that at 5 years, 89% of the patients who are in DFS are considered 'cured' of that NSCLC event (henceforth just termed cured) and that there was no more residual impact of atezolizumab treatment. This meant that the risks were identical for atezolizumab- and AM-treated patients after 5 years which was aligned with assumptions in previous appraisals.[32-35] The value of 0.89 was taken from Chaudry *et al*.[36] and was the proportion of patients who had survived 2 years and who did not have a DFS event in the subsequent 3 years. Based on clinical advice, the company also assumed that at 7 years all patients in the DFS state were cured, with data from Chaudry *et al*.[36] showing only a small decrease in DFS between 7 and 8 years which may be attributed to death (of non-NSCLC causes). A linear increase in the cure proportion between year 5 and year 7 was assumed. However, the company's implementation of this appeared incorrect, with the proportion starting at 0% rather than at 89%. This has been corrected by the EAG and made the ICER more favourable to atezolizumab compared with AM. The EAG highlights that the proportions provided in Chaudry *et al*.[36] are not those ideally required, but however notes that the sensitivity analyses run by the company assuming that cure only occurs at 7 years did not show a marked increase in the ICER (<£600) and were comfortable with the company's intended assumptions.

Cured patients had an assumed mortality rate that was 1.25 greater than the average risk for patients at this age and male to female ratio[37]; this value had been accepted in TA823[29] and will be termed a standardised mortality rate (SMR). The company's base case estimates that the median time to a DFS event was [redacted] months in the atezolizumab arm and [redacted] months in the AM arm.

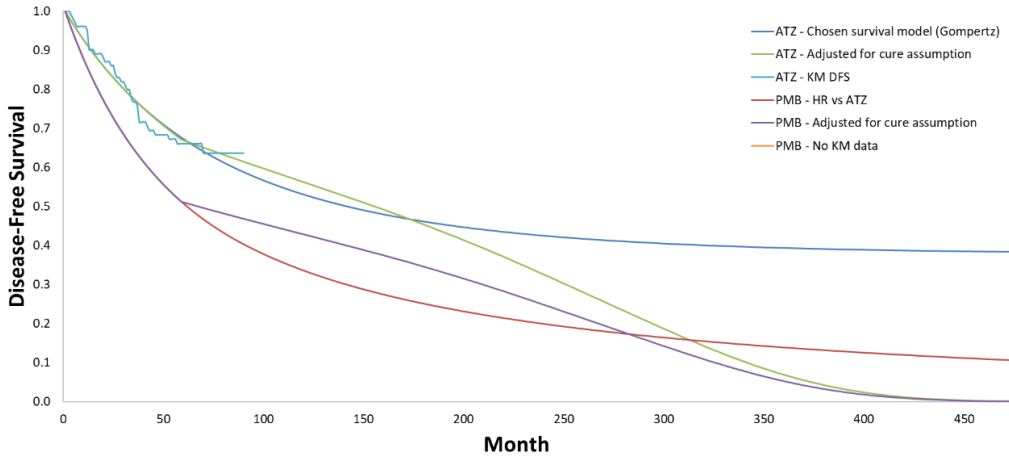
Based on the analyses described in Section 3.5, the company assumed that a HR could be applied to the risk of a DFS event when pembrolizumab was the initial treatment, but for a period of five years only. The probabilities of a DFS event per month for atezolizumab, pembrolizumab and AM if patients are not cured, in the company's base case, are shown in Figure 11 and the DFS for atezolizumab and pembrolizumab (following application of the HR) are shown in Figure 12.

Figure 11 Probability of a DFS event across time for non-cured patients in the company's base case.



DFS: disease-free survival.

Figure 12 DFS curve extrapolations for pembrolizumab and atezolizumab with and without cure adjustment. Reproduced from Figure 20 of the company clarification response Appendix.



ATZ: atezolizumab; DFS: disease-free survival; HR: hazard ratio; KM: Kaplan-Meier; PMB: pembrolizumab

4.2.3.2.3 Probability of a DFS event being death or progression

Following a progression event, the probability of death, a local recurrence or a metastatic recurrence was taken from pooled atezolizumab and AM data observed in IMpower010 for the DPP with a cut-off date of the 26th of January 2024. The full data are provided in Table 22 of the CS, with the pooled data being 16.5% death events, 37.6% local recurrences and 45.9% metastatic recurrences. The company states that pooling was performed following the comments of the Evidence Review Group in TA823[29] who suggested that using treatment-specific proportions was not appropriate. These values were also applied to patients who had a DFS event when pembrolizumab was the initial treatment. Clinical advice provided to the EAG stated they were comfortable with this approach.

4.2.3.3 Events and time on treatment for patients in local recurrence.

The risk of a progression event in local recurrence is dependent on the treatment being received, which is conditional on the treatment received in DFS, either atezolizumab, pembrolizumab, or AM, and for the atezolizumab- or pembrolizumab-treated patients, dependent on the time since initial treatment. Patients who had started treatment with atezolizumab or pembrolizumab 18 months or more previously had the same treatment proportions as patients who received AM initially whereas those patients who had a DFS within 18 months of atezolizumab or pembrolizumab treatment did not receive subsequent durvalumab or pembrolizumab treatment. The EAG notes that following clarification, when pembrolizumab was added as a comparator, this allows double pembrolizumab treatment, and believed that atezolizumab could also be used in local recurrence,[4] but was not included by the company. The EAG believes this potential inconsistency would not noticeably alter the ICER.

The company assumed four further treatment options (the dose and treatment duration of each drug is provided in Table 23 of the CS) and no treatment as shown in Table 19. These values were based on clinical advice. Regardless of initial treatment, 30% of patients were assumed to be too frail for, or unwilling to take, subsequent treatment. The EAG notes that pembrolizumab for people with local recurrence has not been included in other appraisals, but a sensitivity analysis run by the EAG, removing pembrolizumab as an option, and reallocating people equally between radiotherapy, cisplatin, vinorelbine, and durvalumab, and radiotherapy decreased the ICER by less than £400. Due to this small decrease, and as clinicians advising the EAG stated that the proportions shown in Table 19 were plausible, the EAG has not amended the company's values.

The average time of treatment, sourced from Antonio *et al.*[38] is also shown in Table 19. The model adjusts the proportion of patients receiving treatment in later cycles to ensure that the average time on treatment is matched. Additional details on the calculation of median treatment duration are provided in the footnotes of in Table 28 of the CS. Clinicians advising the EAG stated that the median durations of treatment shown in Table 19 were plausible.

Table 19 Treatment distributions for patients with local recurrence

Description	Radiotherapy, cisplatin, vinorelbine and durvalumab	Radiotherapy, cisplatin and vinorelbine	Radiotherapy	Pembrolizumab	No Treatment
Median duration of treatment (months)	10.0[38]	3.0[38]	3.0[38]	10.0[38]	N/A
Within 18 months of starting atezolizumab or pembrolizumab treatment	[redacted]	[redacted]	[redacted]	[redacted]	30%
After 18 months of starting atezolizumab or pembrolizumab treatment, or AM	[redacted]	[redacted]	[redacted]	[redacted]	30%

AM: Active monitoring; N/A Not appropriate

The company assumed treatment-specific progression events, as shown in

Table 20. These values are based on data reported in TA578[39] which considered durvalumab maintenance treatment. All patients not on treatment were assumed to die rather than progress.

Table 20 also contains the average time to a progression event from the local recurrence health state and sources for these estimates. The time to a progression event for radiotherapy, cisplatin, vinorelbine, and durvalumab and radiotherapy, cisplatin, and vinorelbine were taken from the PACIFIC study.[40] It was assumed that radiotherapy alone would have the same value as radiotherapy, cisplatin, and vinorelbine and that pembrolizumab would have the same value as radiotherapy, cisplatin, vinorelbine, and durvalumab; further details are provided in Section B.3.3.7.1 of the CS. Clinical advice to the EAG suggested that the values in

Table 20 were plausible.

Table 20 Proportion of progression events that are death / progression from local recurrence

Description	Radiotherapy, cisplatin, vinorelbine and durvalumab	Radiotherapy, cisplatin and vinorelbine	Radiotherapy	Pembrolizumab	No Treatment
Average time to a progression event (months)	4.3[40]	3.9[40]	3.9[40]	4.3[40]	2.5[41]
Percentage of progression events that are death	25.0%	19.1%	19.1%	25.0%	100%
Percentage of progression events that are progressed disease	75.0%	80.9%	80.9%	75.0%	0%

4.2.3.4 Events and time on treatment for patients in metastatic recurrence (1st recurrence).

The risk of a progression event in the first metastatic recurrence is dependent on the treatment being received, which is conditional on the treatment received in DFS, atezolizumab, pembrolizumab, or AM, and for the atezolizumab- or pembrolizumab-treated patients, dependent on the time since initial treatment. Patients who had started treatment with atezolizumab or pembrolizumab 18 months or more previously had the same treatment proportions as patients who received AM initially, with patients who had relapsed within 18 months or pembrolizumab or atezolizumab treatment receiving pemetrexed alone. There is a slight limitation, confirmed by the company in clarification question B23, that patients could have received durvalumab or pembrolizumab in local recurrence and the time to a rechallenge should start then, although both the EAG and the company agree that this omission would have minimal impact on the ICER and would greatly increase model complexity.

The company assumed the division of patients amongst four treatment options (the dose and treatment duration of each drug is provided in Table 24 of the CS) as shown in Table 21. These values were based on clinical advice. Regardless of initial treatment, 40% of patients were assumed to be too frail for, or unwilling to take, subsequent treatment. Clinicians advising the EAG stated that the proportions shown in Table 21 were plausible.

The average time of treatment is also shown in Table 21, the model adjusts the proportion of patients receiving treatment in later cycles to ensure that the average time on treatment is adhered to. Additional

details on the calculation of median treatment duration from the sources cited in Table 21 (Reck *et al*.[42] for pembrolizumab, Gandhi *et al*.[43] for pembrolizumab and carboplatin, plus individual patient data for atezolizumab and for pemetrexed and carboplatin from IMPower110) are provided in the footnotes of Table 28 of the CS. Clinicians advising the EAG stated that the median durations of treatment shown in Table 21 were plausible.

Table 21 Treatment distributions for patients with a first metastatic recurrence

Description	Pembrolizumab	Atezolizumab	Pembrolizumab, pemetrexed and carboplatin	Pemetrexed and carboplatin	No Treatment
Median duration of treatment (months)	7.0[42]	5.3†	10.0[43]	3.5†	N/A
Within 18 months of starting atezolizumab or pembrolizumab treatment	[redacted]	[redacted]	[redacted]	[redacted]	40%
After 18 months of starting atezolizumab or pembrolizumab treatment, or AM	[redacted]	[redacted]	[redacted]	[redacted]	40%

AM: Active monitoring; N/A Not appropriate
† Taken from the primary clinical study report of IMpower110

The company assumed treatment-specific progression events, as shown in

Table 22. These values are based on data collected in IMpower010 and was assumed equal for all regimens containing pembrolizumab or atezolizumab. All patients not on treatment were assumed to die rather than have disease progression.

Table 22 also contains the average time to a progression event from the first metastatic recurrence health state. and sources for these estimates which were de Castro *et al*.[44] for pembrolizumab, individual patient data for atezolizumab from IMpower110,[30] Garassino *et al*.[45] for pembrolizumab, pemetrexed and carboplatin, Spigel *et al*.[30] for pemetrexed and carboplatin, and Wong *et al.*[41] for no treatment; further details are provided in Section B.3.3.7.2 of the CS. Clinical advice to the EAG suggested that the values in

Table 22 were plausible.

Table 22 Proportion of progression events that are death / progression from the first metastatic recurrence health state

Description	Pembrolizumab	Atezolizumab	Pembrolizumab, pemetrexed and carboplatin	Pemetrexed and carboplatin	No Treatment
Average time to a progression event (months)	2.9[44]	2.9[30]	3.2[45]	2.1[30]	2.2[41]
Percentage of progression events that are death	29.9%	29.9%	29.9%	25.3%	100%
Percentage of progression events that are progressed disease	70.1%	70.1%	70.1%	74.7%	0%

4.2.3.5 Events and time on treatment for patients in metastatic recurrence (2nd recurrence).

The risk of a progression event in the second metastatic recurrence is independent of previous treatment, but dependent on the treatment that a patient received for the 2nd recurrence. Therefore, initial treatment does not influence the outcome.

The company assumed four treatment options (the dose and treatment duration of each drug is provided in Table 25 of the CS) and no treatment as shown in

Table 23. These values were based on clinical advice. Regardless of initial treatment, 70% of patients were assumed to be too frail for, or unwilling to take, subsequent treatment. Clinicians advising the EAG stated that the proportions shown in

Table 23 were plausible.

The average time of treatment is also shown in

Table 23, the model adjusts the proportion of patients receiving treatment in later cycles to ensure that the average time on treatment is adhered to. The average duration of treatment was taken from Reck *et al*.[46] for nintedanib and docetaxel and used individual patient data owned by the company from the IMpower110 study[30] for gemcitabine and carboplatin and from OAK for docetaxel. Clinicians advising the EAG stated that the median durations of treatment and treatment distributions shown in

Table 23 were plausible.

Table 23 Treatment distributions for patients with a second metastatic recurrence

Description	Nintedanib and docetaxel	Gemcitabine and carboplatin	Docetaxel	No Treatment
Median duration of treatment (months)	15[46]	15†	9††	N/A
For all patients	[redacted]	[redacted]	[redacted]	70%

N/A Not appropriate
† Taken from individual patient data from IMpower110
†† Taken from individual patient data from OAK

All progression events from the 2nd-line metastatic health state were assumed to be deaths. The company assumed treatment-specific time to death, as shown in Table 24. The values for nintedanib and docetaxel was taken from the LUME-Lung 1 study.[46] As the company could not find evidence for gemcitabine and carboplatin this value was set to that of nintedanib and docetaxel. For docetaxel alone, the company had access to individual patient data from the OAK study and used this to inform the parameter, for no treatment, data from Wong *et al.*[41] were used. Further details are provided in Section B.3.3.7.3 of the CS. Clinical advice to the EAG suggested that the average survival times in Table 24 were plausible.

Table 24 Average time to death (months) for the second metastatic recurrence health state according to treatment option.

Description	Nintedanib and docetaxel	Gemcitabine and carboplatin	Docetaxel	No Treatment
Average time to death (months)	2.7[44]	2.7[30]	3.2[45]	2.2[41]

4.2.3.6 Adverse events

Only AEs at grade 3 and higher were included in the company submission as grades 1 and 2 have mild to moderate symptoms that may not require medical attention. This approach is common in health technology assessment models. Previous NICE appraisals in this area have limited the AEs in the model to those with an incidence of 2% to 5% or greater.[32, 33, 47, 48] Applying the same criteria in the adjuvant setting, the company stated that there were no AEs of Grade 3 or greater with an incidence of more than 2% in the IMpower010 study,[30] so no AEs were included in this setting. However, in the model a small cost for dealing with AEs, less than £5 a month for the first 11 cycles, was included in the atezolizumab arm, although no utility losses were modelled. The EAG is not concerned by this deviation from the description in the CS. In the model received after clarification, the AEs for pembrolizumab were set equivalent to atezolizumab with no justification for this decision; however, given the low impact of AEs on the ICER, the EAG does not believe this is an issue.

Patients receiving treatment in the local recurrence health state in IMpower010[30] also had no AEs of Grade 3 or greater with an incidence of more than 2%, and thus the CS states that no AEs were included in this setting. However, in the model a small cost for dealing with AEs, less than £5 a month was included for patients, regardless of initial treatment, although no utility losses were modelled. The EAG is not concerned by this deviation from the description in the CS.

Table 29 of the CS details the AEs that were Grade 3 or higher for patients receiving treatment in the metastatic health state (both first- and second-line) using data from Reck *et al*.[42] for pembrolizumab, Herbst *et al*.[49] for atezolizumab, and also for carboplatin and pemetrexed, Gandhi *et al*.[43] for pembrolizumab, carboplatin and pemetrexed, Reck *et al*.[46] for nintedanib and docetaxel, and also for gemcitabine and carboplatin, and data on file for the OAK study for docetaxel alone. Table 44 and Table 46 of the CS provide the estimated costs per AE, whilst Table 45 and 47 of the CS provide the costs associated with AEs in the metastatic health state; these are summarised in Table 25. Whilst it appears counter-intuitive that the combination of pembrolizumab, pemetrexed and carboplatin has a lower monthly cost of AEs than both pembrolizumab alone and pemetrexed and carboplatin together, these values have little impact on the ICER.

Table 25 Monthly cost of managing adverse events in the metastatic recurrence health states by treatment received

Treatment received	Monthly cost of managing adverse events (£)
Pembrolizumab	38.16
Atezolizumab	23.17
Pembrolizumab, pemetrexed and carboplatin	6.96
Pemetrexed and carboplatin	45.14
Nintedanib and docetaxel	46.46
Gemcitabine and carboplatin	46.46
Docetaxel	5.13

No utility losses were associated with treatment-related AEs as the company stated that these would be double counted. Ideally these would have been included, with an attempt to disentangle any double counting, but the EAG believes that the exclusion of disutilities associated with AEs would have a minor impact on the ICER as these are likely to be small, apply to all patients in the metastatic health states irrespective of initial treatment, and there will be potentially some aspects of double counting should utility data be collected whilst the patient was experiencing the AE.

The clinicians providing advice to the EAG stated that they were not aware of any AEs that were associated with an extremely high cost or were severely debilitating to the patient that happen less frequently than in 2% of patients and thus they were comfortable with the company's approach.

4.2.3.7 Health-related quality of life in each health state

The IMpower010 study[30] did not collect patient reported data on HRQoL and therefore the company used published literature to estimate the utility in each health state (DFS, local recurrence, the first metastatic health state, and the second metastatic health state).

4.2.3.7.1 Health-related quality of life associated with model health states

For utility in the DFS health state the company identified four studies for DFS and selected Grutters *et al*.[50] as "*it appears to be the only source that presents evidence separately for patients with early- and [late]-stage NSCLC. Specifically, it uses estimates presented in the publication for patients whose initial treatment modality was surgery plus adjuvant chemotherapy*." This reported a value of 0.81 for patients who had been initially treated with surgery and chemotherapy and had no adverse events. The EAG notes that this used the EuroQol 5-dimensions (EQ-5D) visual analogue scale, rather than the index score, but has assumed that this value is still applicable for modelling purposes. The company assumed a 5% decrease in this value, resulting in a utility of 0.77 for patients receiving active treatment (either atezolizumab or pembrolizumab) but this value was not justified.

For other health states, the company used data from a regression model presented in Chouaid *et al*.[51] which reported EuroQol 5-dimensions (with 3 levels of severity) (EQ-5D-3L) data for patients with advanced NSCLC. The utility for local recurrence was assumed to be 0.77, with a 0.07 decrement associated with Stage IV disease which was assumed to represent metastatic cancer. The EAG comments that this approach underestimates the impact of metastatic cancer, as the decrement for Stage IV disease is independent of further progressions and line of treatment. The EAG believes that the utility decrement for progressed disease on second line treatment would be 0.18 (0.11+0.07), and the decrement for progressed disease after second line treatment would be 0.33 (0.26+0.07).

A summary of the initial utility values used in the model is provided in

Table 26. Utility is age- and sex- adjusted in the model as time progresses. The company assumes that utility is reduced by 5% whilst on atezolizumab or pembrolizumab treatment.

Table 26 Summary of initial utilities used in the company's model

Health State	Utility	Source
Disease-free survival not on atezolizumab or pembrolizumab treatment	0.81	Grutters *et al.*[50]
Disease-free survival on atezolizumab or pembrolizumab treatment	0.77	Assumed 5% lower than DFS survival reported in Grutters *et al.*[50]
Local recurrence	0.77	Chouaid *et al.*[51]
First-metastatic recurrence	0.70	Chouaid *et al.*[51]
Second-metastatic recurrence	0.70	Chouaid *et al.*[51]

4.2.3.7.2 Caregiver disutility

No caregiver disutility was assumed in the model.

4.2.3.8 Costs

This section provides a description of the resource costs included in the company's model (excluding those associated with AEs which are detailed in Section 4.2.3.6). The model included costs associated with: 1) acquisition and administration costs of drugs, 2) additional costs associated with being in a particular health state and 3) cost of death.

4.2.3.8.1 Drug acquisition costs

As advised by NICE, the list price for all branded drugs has been used, with the exception of atezolizumab which uses its PAS price. Prices of proprietary medicines have been taken from the BNF, whereas generic medicines have been taken from the electronic marketing information tool (eMIT). The prices used in the company's model are shown in Table 27. The price for gemcitabine differs from that reported in the company's clarification response, although this has very little impact on the ICER. The EAG notes that the eMIT price for gemcitabine provided by NICE appeared different to that in the CS, being £36.04 for 1200mg and £47.75 for 2200mg. although if changed this made minimal difference to the ICER (identical to the nearest penny) so this has not been altered.

One vial or subcutaneous injection of atezolizumab is sufficient per cycle, however, two vials of pembrolizumab are needed per cycle.

Table 27 Summary of drug costs included within the model

	Dose per vial / pack (mg)	Cost per vial/pack (£)
Atezolizumab (subcutaneous)	1875	[redacted]
Atezolizumab (intravenous)	1200	[redacted]
Carboplatin	50	6.71
	600	38.93
Cisplatin	50	19.69
	100	37.34
Docetaxel	20	4.49
	160	19.70
Durvalumab	120	592.00
	500	2466.00
Gemcitabine	1200	35.24
	2200	47.08
Nintedanib	60	2151.00
Nivolumab	40	439.00
	240	2633.00
Pembrolizumab	100	2630.00
Pemetrexed	100	18.34
	500	28.76
Radiotherapy	Per fraction	306.69
Vinorelbine	10	76.45
	50	181.95

As advised by NICE, the EAG has produced a confidential appendix which includes the comparator PAS (cPAS) for nivolumab and for durvalumab, which is a simple discount for both drugs. The confidential appendix also contains medicines procurement supply chain prices for pemetrexed with a range of prices all lower than that used by the company.

4.2.3.8.2 Drug administration costs

The administration costs for the majority of treatments were set to £431.16 which was the cost of NHSE reference cost SB12Z in 2022-2023 which represents delivering simple parenteral chemotherapy at first attendance, for the first administration and a cost of £392.61 for subsequent administrations (based on NHSE reference cost SB15Z in 2022-2023, which represents delivering subsequent elements of a chemotherapy cycle. The exceptions were atezolizumab when provided as a subcutaneous injection, which was assumed to be administered by a Band 5 nurse, requiring 7 minutes of time, at a cost of

£6.18. and for nintedanib, which is orally administered, but was associated with 12 minutes of hospital pharmacist (band 6) time every 4 weeks at a cost of £10.00. The company assumed that atezolizumab was delivered 50% of the time as an IV infusion and 50% of the time as a subcutaneous injection.

4.2.3.8.3 Background health state costs

Table 37, Table 40, and Table 43 of the CS present non-pharmaceutical related follow-up costs in DFS, the local recurrence health state and the metastatic health state, respectively. These detail the use of: CT chest scans, chest radiographies, electrocardiograms, community nurse visits, clinical nurse specialist visits, GP home visits, GP surgery visits, outpatient visits, and therapist visits. The frequency of resource use by health state was provided by UK clinical expert, with costs taken from the Personal Social Service Research Unit.[52] Together, the company (in the model, which does not tally with the written documents) estimated monthly costs (excluding CT scans) of £53.36 for being in DFS, £173.06 for being in the local recurrence health state, £368.88 for being in the first-metastatic recurrence health state and £708.80 for being in the second-metastatic recurrence health state. For patients receiving treatment, the costs of CT scans (£128.31 per scan) were included, with a CT scan every 6 months for the first 2 years followed by one every 12 months for the next 3 years for patients in DFS, four scans per year for people in local recurrence and the first metastatic recurrence health state, and none in the second metastatic health state. The EAG comments that in amending the cost of a GP appointment, the company appears to have assumed that the costs in Jones *et al*.[52] were for an hour rather than a 10 minute consultation and used £8.17 per appointment; the EAG amended this back to a value of £49 in its analyses. The clinicians providing advice to the EAG were broadly satisfied with the assumption related to resource use.

Beyond a period of 5 years, routine monitoring costs become zero with the patients being discharged from clinical follow-up. At clarification, the company introduced the functionality to allow atezolizumab (or pembrolizumab) patients to receive follow-up for 6 years, as clinical advice to the EAG suggested that patients would be discharged 5 years after the end of atezolizumab (or pembrolizumab) treatment, although this wasn't included in the company's base case.

4.2.3.8.4 Costs associated with lung-cancer related deaths.

The model assumes that patients dying of lung cancer incurred a cost of £19,943, whereas patients dying due to non-lung cancer related reasons would incur no costs. The clinicians advising the EAG were critical of this approach, stating that patients could die of other diseases, such as respiratory diseases, heart attacks and other cancers, which are associated with considerable expense. At clarification, the company provided the functionality to have a cost associated with non-lung cancer death, and explored using a value of £12,726, based on Table 7.2.2 in Jones *et al*.[52]

4.3 The company's model validation and verification

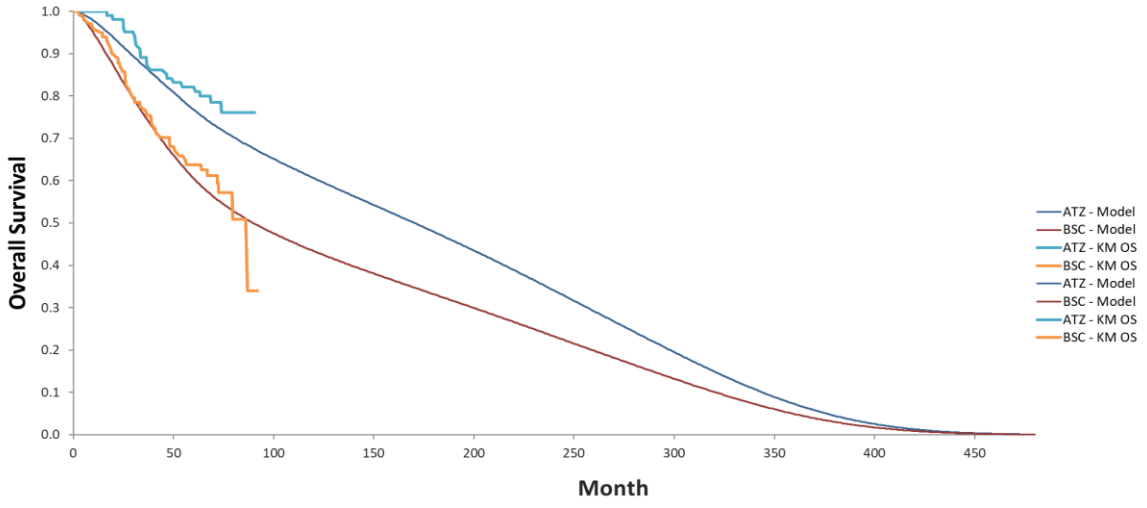
The company states that the "*modelling approach and structure was extensively validated in 2022 and in 2024 to ensure the validated of our assumptions through literature and leading UK oncologists during multiple Advisory boards*". The implementation of the model was generally good, with few errors and limitations, which were largely addressed by the company during the clarification process.

The model notably does not use any of the OS data observed in IMpower010.[30] Whilst this is uncommon, the structure that the company has adopted which is the linking together of separate models, which simulate the experience of patients through different health states and lines of treatment, is conceptually appropriate provided that the OS that is generated by the model aligns closely with that observed with the pivotal study. Clinical advice provided to the EAG agreed with the company's assumption that expected improvements in DFS would be expected to translate into expected improvements in OS.

In its clarification response (question B3[2]), the company provided a plot (Figure 13) which compared the modelled and observed OS data for atezolizumab and AM. The company's interpretation was that "*based on visual fit, it can be assumed that the current model slightly underestimates OS. This is likely due to the conservative assumptions taken to adjust DFS; cure assumption, SMR and treatment waning effect.*". The company also provided the extrapolated OS of pembrolizumab in the supporting appendix of the clarification response, based on the application of the HR to the atezolizumab DFS curve, Figure 14.

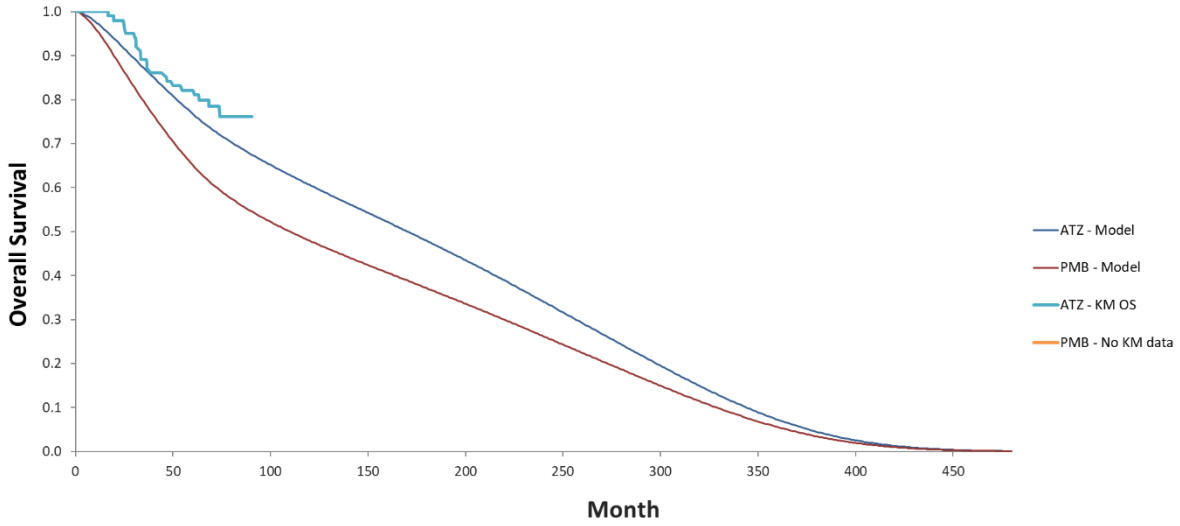
The EAG concurs that the modelled estimates generally lie below the Kaplan-Meier curves and that there appears to be no bias in favour of atezolizumab.

Figure 13 Comparing overall survival from IMpower010 and overall survival generated by the company's model (reproduced from Figure 19 of the company's clarification response)



ATZ: atezolizumab, BSC: best supportive care KM: Kaplan Meier; OS: overall survival

Figure 14 Modelled OS for atezolizumab (compared against the IMpower010 KM data) and the modelled OS for pembrolizumab (reproduced from Figure 21 of the appendix of the company clarification response)



ATZ: atezolizumab, BSC: best supportive care KM: Kaplan Meier; OS: overall survival

4.4 QALY weighting for severity

The company did not make a case that atezolizumab in the DPP meets the criteria for obtaining a disease severity weighting. The EAG agrees with the company's assessment noting that neither the absolute QALY shortfall (of 12 or more) criterion nor the proportionate QALY shortfall (of more than 0.85) criterion are met in the company's base case.

4.5 The company's cost-effectiveness results

The base case results in the clarification response are summarised in Table 28. The deterministic ICER of atezolizumab was £3233 compared with AM, with atezolizumab dominating pembrolizumab (being less expensive and generating more health).

Probabilistic ICERs could not be generated for all three comparators in a single analysis, as the model was set up to only compare two treatments. As such, pairwise analyses were undertaken. An analysis run by the EAG estimated that the ICER of atezolizumab compared to AM was £3406 in the company's base case and that the probability that this ICER was less than £20,000 per QALY gained was [redacted]%, which increased to [redacted]% when the threshold was £30,000 per QALY gained. A similar analysis comparing atezolizumab with pembrolizumab was run by the EAG which indicated that atezolizumab dominated pembrolizumab and that the probability that this ICER was less than £20,000 per QALY gained was [redacted]%, and [redacted]% for a threshold of £30,000 per QALY gained. However, whilst the incremental costs and incremental QALYs were similar to those reported in the clarification response (which did not provide absolute costs or QALYs) the EAG highlights that pembrolizumab was associated with less QALYs than AM (based on 1000 iterations). This suggests a potential problem in

the face validity of the PSA results. This problem was not apparent for the probabilistic analysis comparing atezolizumab and AM (or when using the amended EAG NMA results).

Table 28 The company's base case results

	Costs (£)	QALYs	Incremental Cost (£)	Incremental QALYs	Cost per QALY gained (£)*
Deterministic					
AM	[redacted]	[redacted]	-	-	-
Atezolizumab	[redacted]	[redacted]	[redacted]	[redacted]	3233
Pembrolizumab	[redacted]	[redacted]	[redacted]	[redacted]	Dominated
Probabilistic**					
AM	[redacted]	[redacted]	-	-	-
Atezolizumab	[redacted]	[redacted]	[redacted]	[redacted]	3464
Probabilistic**					
Atezolizumab	[redacted]	[redacted]	-	-	-
Pembrolizumab	[redacted]	[redacted]	[redacted]	[redacted]	Dominated

AM: active monitoring; EA: exploratory analysis QALY: quality-adjusted life year
*full incremental analysis
***Run by the EAG.*

Deterministic sensitivity analyses presented in Figure 19 of the CS indicated that the two most influential analyses were reducing the utility of patients in DFS previously treated with atezolizumab to a value of 0.695, and increasing the utility of patients in DFS treated with AM to a value of 0.902, both of which increased the ICER; however, neither increased the ICER in the CS of £2428 to greater than £5000 per QALY gained. The EAG notes that these scenarios are likely to be clinically implausible. The company presents a large number of deterministic scenario analyses in Table 54 of the CS (although none are particularly remarkable). Whilst these results were not provided after changes made in clarification, the EAG does not believe the conclusions will change in the new analyses.

4.6 EAG Critique of company's submitted economic evaluation

4.6.1 Adherence to the NICE Reference Case

The company's economic analysis is generally in line with the NICE Reference Case[4] (see Table 29). This table summarises data presented in other sections of the report.

Table 29 Adherence of the company's economic analysis to the NICE Reference Case

Element	Reference case	EAG comments
Population	The scope developed by NICE	The company has excluded patients with an EGFR mutation or who have ALK-positive NSCLC as it is not seeking reimbursement in such patients.
Comparators	As listed in the scope developed by NICE	Adjuvant osimertinib and adjuvant alectinib were excluded as the company is not seeking reimbursement for patients with an EGFR mutation or with ALK-positive NSCLC.
Perspective on outcomes	All direct health effects, whether for patients or, when relevant, carers	All direct health effects for patients were included. Impacts on caregivers were not included.
Perspective on costs	NHS and PSS	This is aligned with the NICE Reference Case.
Type of economic evaluation	Cost-utility analysis with full incremental analysis	The results of the analyses are presented in terms of incremental costs per QALY gained.
Time horizon	Long enough to reflect all important differences in costs or outcomes between technologies being compared	The model assumed a 40-year time horizon with time cycles of 1 month which was sufficient to simulate the lifetime of patients.
Synthesis of evidence on health effects	Based on systematic review	This was based on a systematic review for later lines of treatment, but taken from IMpower010[30] for patients in DFS. The overall survival data in IMpower010 was not used, with evidence from multiple later lines of treatment adopted instead.
Measuring and valuing health effects	Health effects should be expressed in QALYs. The EQ-5D is the preferred measure of HRQoL in adults.	This is partially aligned with the NICE Reference Case. Health gains are valued in terms of QALYs. EQ-5D data reported by patients with advanced NSCLC for the local recurrence and metastatic health states. For DFS, the data came from a study where EQ-5D visual analogue scale was used rather than the EQ-5D index score.
Source of data for measurement of HRQoL	Reported directly by patients and/or carers	This is aligned with the NICE Reference Case.
Source of preference data for valuation of changes in HRQoL	Representative sample of the UK population	Excluding DFS, this is aligned with the NICE Reference Case, however for DFS this was not possible as the EQ-5D visual analogue scale was used.
Equity considerations	An additional QALY has the same weight regardless of the other characteristics of the individuals receiving the health benefit, except in specific circumstances.	No additional QALY weighting was applied.

Element	Reference case	EAG comments
Evidence on resource use and costs	Costs should relate to NHS and PSS resources and should be valued using the prices relevant to the NHS and PSS.	Resource costs relate to NHS and PSS. Drug costs were valued at current prices. Other resource costs were valued using estimates from Personal Social Service Research Unit.[52]
Discounting	The same annual rate for both costs and health effects (currently 3.5%)	This is aligned with the NICE Reference Case.

EAG: external assessment group; EQ-5D: EuroQol 5-Dimensions; NICE: national institute for health and care excellence; PSS: personal social services; QALY: quality-adjusted life year

4.6.2 The main issues identified by the critical appraisal

Box 1 summarises issues identified within the EAG's critical appraisal of the company's economic analyses; none of these are considered key. The EAG has not commented on possible errors or limitations which have only a slight impact on the ICER.

Box 1 Summary of the issues identified within the company's health economic model

1) Limitations in the company's indirect treatment comparison with pembrolizumab
2) Potentially incorrect proportion assumed cured after 60 months in DFS
3) Incorrect administration costs in cycle 1 for atezolizumab
4) Uncertainty in the follow-up time for people on atezolizumab and pembrolizumab
5) Incorrect costs associated with a GP appointment
6) Assumption of no costs associated with deaths not due to lung cancer, but with a sizeable cost associated with lung cancer deaths.
7) Underestimation of the impact of metastatic cancer on utility.

4.6.2.1 Limitations in the company's indirect treatment comparison with pembrolizumab

As described in Section 3.6, the EAG noted limitations with the company's NMA. The relative treatment efficacies estimated by the EAG using a random effects model were used rather than those provided by the company in its clarification response.

4.6.2.2 Potentially incorrect proportion assumed cured after 60 months in DFS.

From the evidence submitted in the CS and at clarification, it appeared that the company intended to have a bulk of patients assumed cured at 5 years, which would then increase linearly to 100% at 7 years. The model did not do this, however, and so the EAG has amended it.

4.6.2.3 Incorrect administration costs in cycle 1 for atezolizumab.

In the CS the company assumed that 100% of patients received atezolizumab as a subcutaneous injection, with this assumption changed at clarification, to 50% injection and 50% intravenous infusion. The model did not update administration costs for the first cycle, although did for subsequent cycles.

4.6.2.4 Uncertainty in the follow-up time for people on atezolizumab and pembrolizumab.

Clinical advice to the EAG suggested that patients would be followed up for 5 years after treatment which would mean a follow-up time of 6 years for patients receiving atezolizumab or pembrolizumab. The company included this functionality in the model but did not include it in its base case. When using this, the EAG identified that changing the follow-up time to 6 years for atezolizumab increased the costs

of AM by £214 and the costs of atezolizumab by £72, which lacked face validity as the costs for AM should not alter.

4.6.2.5 Incorrect costs associated with a GP appointment.

In the CS, the company had costed a GP appointment at £51, which the EAG queried as the highest value for a 10-minute appointment based on PSSRU research was £49.[52]. At clarification, it appears as though the company mistook the £49 for an hourly rate, and then divided this by 6, to arrive at a cost of £8.17.

4.6.2.6 Assumption of no costs associated with deaths not due to lung cancer, but with a sizeable cost associated with lung cancer deaths.

In the company's base case, there is a cost of £19,943 associated with a lung cancer death, but zero costs associated with other deaths. The clinicians advising the EAG were critical of this approach, stating that patients could die of other diseases, such as respiratory diseases, heart attacks and other cancers, which are associated with considerable expense.

4.6.2.7 Underestimation of the impact of metastatic cancer on utility.

As described in Section 4.2.3.7.1, the company only used the decrement for Stage IV disease from Chouaid *et al*.[51] and not the decrements associated with progression in patients with metastatic cancer. As the EAG did not have precise data on the proportions of patients who reached a metastatic state in second-line and third line treatment, it has assumed a decrement of 0.25 in utility associated with metastatic disease, which is broadly between the metastatic second-line progression decrement (0.18) and the metastatic third-line progression decrement (0.33). This results in a utility of 0.52 for patients with metastatic disease at the start of the model.

4.7 Exploratory analyses undertaken by the EAG

4.7.1 Overview of the EAG's exploratory analyses

All analyses presented in this section reflect the PAS price of atezolizumab and the list price of comparators; analyses using the PAS price for comparators are provided for the Appraisal Committee in a confidential appendix. Section 4.7.2 details the exploratory analyses and scenario analyses run by the EAG.

4.7.2 EAG's exploratory analyses – methods

The following changes were made to the company's base case to inform the EAG base case. Each exploratory analysis (EA) is described below. Appendix 1 details how these can be implemented in the company's model.

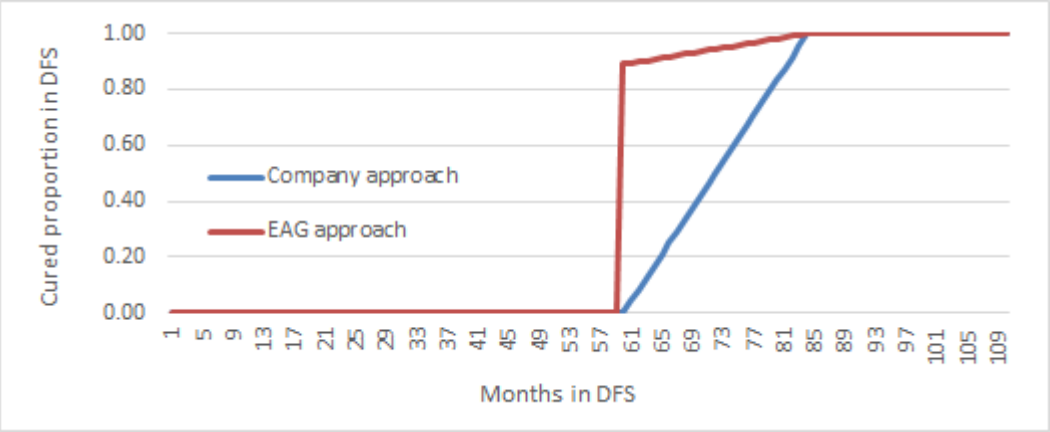
EA1 Amending the NMA comparing pembrolizumab with atezolizumab

The EAG amended the model so that the results from the EAG's random effects NMA were used rather than the company's NMA results.

EA2 Amending the proportion of patients assumed cured at 60 months in DFS

The EAG amended the model so that 89% of patients who had been in DFS for 60 months were considered cured with this percentage increasing to 100% at 7 years. The differences in the cure proportions using the company's approach and the EAG's approach are shown in Figure 15.

Figure 15 Proportion of patients assumed cured in DFS by time.



EA3 Incorrect administration costs in cycle 1 for atezolizumab

The EAG has amended the model so that the administration cost of the first cycle of atezolizumab costs £218.67 rather than £6.18.

EA4 Uncertainty in the follow-up time for people on atezolizumab and pembrolizumab

The EAG intended to include the follow-up costs for a period of 6 years for atezolizumab and pembrolizumab using the company's functionality, but this did not appear to be correctly implemented (see 4.6.2.3). To estimate the additional costs the EAG used the percentage of patients in DFS at 60 months for atezolizumab ([redacted]%) and for pembrolizumab ([redacted]%) and multiplied these by the yearly cost of background health state costs, excluding CT scans, of DFS (£640.37).

EA5 Incorrect costs associated with a GP appointment

The EAG has amended the model so that the cost of a GP appointment was set to £49 rather than £6.18.

EA6 Assumption of no costs associated with deaths not due to lung cancer, but with a sizeable cost associated with lung cancer deaths

The EAG has amended the model so that the costs of a non-lung cancer death was £12,726, based on Table 7.2.2 in Jones *et al*.[52]

EA7 Underestimation of the impact of metastatic cancer on utility.

The EAG has amended the model so that the utility decrement associated with metastatic cancer is 0.25. The standard error has been left at the company's value for probabilistic analyses.

The EAG base case combines EA1 through to EA7. Results are presented using both the deterministic and probabilistic versions of the model.

The following sensitivity analyses (SA) were undertaken using the EAG's base case. Appendix 1 details how these can be implemented in the company's model.

SA1 Uncertainty in the cure assumption

Whilst the EAG believes that the assumptions related to cure in its base case (after EA1) is relevant for decision making the EAG performed a sensitivity analysis where there was no assumed cure until 10 years of residing in DFS, at which point 100% of patients in DFS were considered cured. This was undertaken to allow the NICE Appraisal Committee to see the impact of an alternative (pessimistic) assumption.

SA2 Uncertainty in patient characteristics

The EAG performed a sensitivity analysis where the characteristics of patients in the SACT data set (67 years of age and 52.0% male) were used instead of the values in the company's base case (61.2 and 66.9% male respectively).

SA3 Assessing if atezolizumab met the cost-comparison criteria when compared with pembrolizumab

Following discussions with NICE, an analysis was undertaken reporting the average costs of atezolizumab and pembrolizumab in the first year (including administration costs) and comparing the relative efficacy of the treatments.

4.7.3 Results of the EAG's exploratory analyses

The results of the EAG's base case are provided in Table 30. These consider the PAS discount for atezolizumab, but not for any other drug in the decision problem. The EAG deterministic ICER for atezolizumab compared with AM was £3453 with a similar probabilistic ICER (£3462). Atezolizumab dominated pembrolizumab in both the deterministic and probabilistic analyses.

Table 30 Results from the EAG's exploratory analyses

	Costs (£)	QALYs	Incremental Cost (£)	Incremental QALYs	Cost per QALY gained (£)*
The company's deterministic base case					
AM	[redacted]	[redacted]	-	-	-
Atezolizumab	[redacted]	[redacted]	[redacted]	[redacted]	3233
Pembrolizumab	[redacted]	[redacted]	[redacted]	[redacted]	Dominated
EA1 (amending the indirect treatment comparison with pembrolizumab)					
AM	[redacted]	[redacted]	-	-	-
Atezolizumab	[redacted]	[redacted]	[redacted]	[redacted]	3233
Pembrolizumab	[redacted]	[redacted]	[redacted]	[redacted]	Dominated
EA2 (amending the cure proportion at 5 years)					
AM	[redacted]	[redacted]	-	-	-
Atezolizumab	[redacted]	[redacted]	[redacted]	[redacted]	2642
Pembrolizumab	[redacted]	[redacted]	[redacted]	[redacted]	Dominated
EA3 (increasing the administration costs in cycle 1 for atezolizumab)					
AM	[redacted]	[redacted]	-	-	-
Atezolizumab	[redacted]	[redacted]	[redacted]	[redacted]	3347
Pembrolizumab	[redacted]	[redacted]	[redacted]	[redacted]	Dominated
EA4 (increasing the follow up times for atezolizumab and pembrolizumab to 6 years)					
AM	[redacted]	[redacted]	-	-	-
Atezolizumab	[redacted]	[redacted]	[redacted]	[redacted]	3476
Pembrolizumab	[redacted]	[redacted]	[redacted]	[redacted]	Dominated
EA5 (increasing the cost of GP appointments to £49)					
AM	[redacted]	[redacted]	-	-	-
Atezolizumab	[redacted]	[redacted]	[redacted]	[redacted]	3214
Pembrolizumab	[redacted]	[redacted]	[redacted]	[redacted]	Dominated
EA6 (increasing the cost of non-lung cancer deaths to £12,726)					
AM	[redacted]	[redacted]	-	-	-
Atezolizumab	[redacted]	[redacted]	[redacted]	[redacted]	3748
Pembrolizumab	[redacted]	[redacted]	[redacted]	[redacted]	Dominated
EA7 (increasing the utility decrement of metastatic disease)					
AM	[redacted]	[redacted]	-	-	-

	Costs (£)	QALYs	Incremental Cost (£)	Incremental QALYs	Cost per QALY gained (£)*
Atezolizumab	[redacted]	[redacted]	[redacted]	[redacted]	3162
Pembrolizumab	[redacted]	[redacted]	[redacted]	[redacted]	Dominated
EAG base case (EA1 – EA7)					
AM	[redacted]	[redacted]	-	-	-
Atezolizumab	[redacted]	[redacted]	[redacted]	[redacted]	3453
Pembrolizumab	[redacted]	[redacted]	[redacted]	[redacted]	Dominated
Probabilistic EAG base case (vs AM)					
AM	[redacted]	[redacted]	-	-	-
Atezolizumab	[redacted]	[redacted]	[redacted]	[redacted]	3462
Probabilistic EAG base case (vs pembrolizumab)					
Atezolizumab	[redacted]	[redacted]	-	-	-
Pembrolizumab	[redacted]	[redacted]	[redacted]	[redacted]	Dominated

AM: active monitoring; EA: exploratory analysis; QALY: quality-adjusted life year

*full incremental analysis

The EAG's probabilistic analyses indicated that atezolizumab had a [redacted] chance of being cost-effective at a willingness to pay of £20,000 per QALY compared with AM, which was [redacted] at a threshold of £30,000. For the comparison with pembrolizumab, atezolizumab was dominant; the probability that this ICER was less than £20,000 per QALY gained was [redacted]%, and [redacted]% for a threshold of £30,000 per QALY gained. The issue noted regarding the relative QALYs for AM and for pembrolizumab in the probabilistic analyses for the company's base case analysis was not identified in the EAG's analyses.

The EAG sensitivity analyses are shown in Table 31. These show that with a pessimistic assumption relating to cure, the ICER for atezolizumab compared with AM was still low (£5849) which was also true when SACT data were used (£4630). Atezolizumab remained dominant compared with pembrolizumab in both scenarios.

Table 31 EAG sensitivity analysis results

	Costs (£)	QALYs	Incremental Cost (£)	Incremental QALYs	Cost per QALY gained (£)
The EAG's deterministic base case					

AM	[redacted]	[redacted]	-	-	-
Atezolizumab	[redacted]	[redacted]	[redacted]	[redacted]	3453
Pembrolizumab	[redacted]	[redacted]	[redacted]	[redacted]	Dominated
SA1 (assuming no cure until 10 years in DFS)					
AM	[redacted]	[redacted]	-	-	-
Atezolizumab	[redacted]	[redacted]	[redacted]	[redacted]	58617
Pembrolizumab	[redacted]	[redacted]	[redacted]	[redacted]	Dominated
SA2 (using SACT data for patient characteristics)					
AM	[redacted]	[redacted]	-	-	-
Atezolizumab	[redacted]	[redacted]	[redacted]	[redacted]	4642
Pembrolizumab	[redacted]	[redacted]	[redacted]	[redacted]	Dominated

For SA3, the cost per year (including administration costs) was [redacted] for a full course of atezolizumab (16 cycles) and £96,133 for a full course of pembrolizumab (17 cycles). As seen in Section 3.6, the EAG's preferred HR for atezolizumab compared to pembrolizumab was [redacted]. As such, the criteria for cost-comparison, or having a similar or lower cost than a comparator, and a similar, or better, efficacy would appear to have been met.

4.8 Discussion

All of the EAG's results produced ICERs for atezolizumab compared with AM which were below £6000. All analyses indicated that atezolizumab dominated pembrolizumab. A scenario analysis framing the problem as a cost-comparison of atezolizumab compared with pembrolizumab indicated that atezolizumab appeared more efficacious and had a lower PAS price than the list price of pembrolizumab.

These results did not, however, use the confidential PAS prices of pembrolizumab and for other drugs used in the treatment sequence. The results when these discounts are included have been provided to the Appraisal Committee in a confidential appendix.

5 OVERALL CONCLUSIONS

Clinical evidence: The clinical evidence was based on the IMpower010[5] RCT of adjuvant atezolizumab vs. AM in adults with completely resected Stage IB to IIIA NSCLC having had cisplatin-based chemotherapy. The DPP consisted of Stage II-IIIA patients with PD-L1 ≥50%, excluding EGFR and ALK alterations (n=106 atezolizumab, n=103 AM). In the DPP, median DFS was not reached for atezolizumab vs. 43 months for AM, with a HR of 0.49 (95% CI: 0.32, 0.75), while median OS was not reached for atezolizumab vs. 87 months for AM, with a HR of 0.44 (95% CI: 0.26, 0.74). In the atezolizumab safety population (n=495), 22% had grade 3-4 AEs, 18% serious AEs, 1.8% deaths due to AEs, 29% had AEs leading to dose interruption and 18% had AEs leading to discontinuation.

Direct comparison with AM: The company fitted separate parametric curves to atezolizumab and AM DFS; the EAG are content with this approach. The company did not use OS data from IMpower010, however, as this was considered immature, but modelled OS through linked progression and treatment models. More details are provided in Section 4.2.2, but the EAG was comfortable with this approach.

Indirect treatment comparison: Due to the lack of head-to-head trials for atezolizumab with pembrolizumab, the company conducted an NMA to evaluate the comparative efficacy of atezolizumab versus pembrolizumab. However, the EAG noted limitations in this analysis and ran its own NMA. This changed the HR between atezolizumab and pembrolizumab from [redacted] (fixed effects) in the company's analysis to [redacted] (random effects) in the EAG's analysis. The corresponding HRs for pembrolizumab versus atezolizumab were applied to the DFS for atezolizumab to generate results for pembrolizumab.

Modelling methodology:
The EAG believed that the company's model structure was suitable for decision making although preferred alternative parameterisation of some variables compared with the company. These changes were explored with EAs and SAs.

Cost-effectiveness results:
All of the EAG's results produced ICERs for atezolizumab compared with AM which were below £6000. All analyses indicated that atezolizumab dominated pembrolizumab. These results did not, however, use the confidential PAS prices of pembrolizumab and for other drugs used in the treatment sequence. The results when these discounts are included have been provided to the Appraisal Committee in a confidential appendix.

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7 Appendix 1: Running the EAG EAs and SAs

This appendix details how to replicate the EAG's EAs and SAs. All analyses are initiated from the worksheet entitled 'EAG Controls'. To change comparator set C14 to 1 (pembrolizumab) or 2 (AM).

Results of the EAG analyses are recorded in cells B23:G26 for deterministic analyses and in cells B29:J31 for probabilistic analyses.

EA1: Set cell C11 to 1.

EA2: Set cell C6 to 1

EA3: Set cell C5 to 1

EA4: Set cell C7 to 1

EA5: Set cell C2 to 1

EA6: Set cell C3 to 1

EA7: Set cell C8 to 1

To run the EAG base case copy cells F2:F11 into cells C2:C11

SA1: Set cell C9 to 1

SA2: Set cell C10 to 1

Single Technology Appraisal

Atezolizumab for adjuvant treatment of resected non-small-cell lung cancer (MA review of TA823) [ID6324]

EAG report – factual accuracy check and confidential information check

"Data owners may be asked to check that confidential information is correctly marked in documents created by others in the evaluation before release." (Section 5.4.9, NICE health technology evaluations: the manual).

You are asked to check the EAG report to ensure there are no factual inaccuracies or errors in the marking of confidential information contained within it. The document should act as a method of detailing any inaccuracies found and how they should be corrected.

If you do identify any factual inaccuracies or errors in the marking of confidential information, you must inform NICE by **5pm on Monday 3 March 2025** using the below comments table.

All factual errors will be highlighted in a report and presented to the appraisal committee and will subsequently be published on the NICE website with the committee papers.

Please underline all confidential information, and information that is submitted as [redacted] should be highlighted in turquoise and all information submitted as 'depersonalised data' in pink.

Issue 1

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
[Table 5 Baseline characteristics in IMpower010 (adapted from CS Table 4), page 24] Rounding errors: ● Race, n (%), Other - 4 (**3**), 2 (**3**)	● Race, n (%), Other - 4 (**4**), 2 (**2**)	Rounding errors	4/115 = 3.48% so this has been left as 3%. 2/114 = 1.75% so this has been corrected to 2%; apologies for the error.

Issue 2

Description of problem	Description of proposed amendment	Justification for amendment	EAG Response
[Table 9 Safety summary (safety population) (adapted from CS Table 10), page 30] Rounding errors: ● Total number of patients with at least one: Serious AESI - 21 (4%), 4 (**0.8%**) ● Total number of patients with at least one: Grade 3–4 AESI - 39 (8%), 4 (**0.8**%)	● Total number of patients with at least one: Serious AESI - 21 (4%), 4 (**1%**) ● Total number of patients with at least one: Grade 3–4 AESI - 39 (8%), 4 (**1**%)	Inconsistent rounding, rounded up for atezolizumab arm but not BSC arm	In this table, the EAG had presented percentages <1% to 1 decimal place for precision. For consistency, all the percentages in the table are now presented to 1 decimal place (as in the CS).

Issue 3

Description of problem	Description of proposed amendment	Justification for amendment	EAG Response
[Table 10 Deaths due to adverse events (safety population) (adapted from CS Appendix H), page 31] Cardiac tamponade and septic shock should be two separate rows as they are two separate adverse events.	Cardiac tamponade and septic shock should be two separate rows as they are two separate adverse events.	Incorrect grouping	Cardiac tamponade and septic shock are now presented in two separate rows as requested, with a footnote clarifying that these occurred in the same patient.

Issue 4

Description of problem	Description of proposed amendment	Justification for amendment	EAG Response
[3.4.5 Treatment-related adverse events, page 32] Rounding error: …increased ALT (**7**%)	increased ALT (**8**%)	Rounding error	This is written as 7.5% in the CS, and we assumed this would equate to 37/495 = 7.47% which rounds to 7% not 8% (while 38/495 would presumably be written as 7.7% in the CS). However, on the request of the company this has been amended from 7% to 8%.

Issue 5

Description of problem	Description of proposed amendment	Justification for amendment	EAG Response
[3.4.9 AEs of special interest (AESIs), page 33] Rounding errors: …serious AESI (4% vs. **0.8**%); grade 3-4 AESI (8% vs. **0.8**%)	…serious AESI (4% vs. **1**%); grade 3-4 AESI (8% vs. **1**%)	Inconsistent rounding, rounded up for atezo arm but not BSC arm	In this section, the EAG had presented percentages <1% to 1 decimal place for precision. For consistency, all percentages in this section are now presented to 1 decimal place.

Issue 6

Description of problem	Description of proposed amendment	Justification for amendment	EAG Response
[Table 12 Overview of AESIs (safety population) (adapted from CS Table 13), pages 33-34] Rounding errors: ● Serious AESI (4% vs. **0.8**%) ● Grade 3-4 AESI (8% vs. **0.8**%)	● Serious AESI (4% vs. **1**%) ● Grade 3-4 AESI (8% vs. **1**%) ● Immune-mediated hypothyroidism 84 (17%) 3 (**1**%) ● Immune-mediated hyperthyroidism 33 (7%) 4 (**1**%)	Inconsistent rounding, rounded up for atezo arm but not BSC arm	In this table, the EAG had presented percentages <1% to 1 decimal place for precision. For consistency, all the percentages in the table are now presented to 1 decimal place (as in the CS).

• Immune-mediated hypothyroidism 84 (17%) 3 (**0.6**%) • Immune-mediated hyperthyroidism 33 (7%) 4 (**0.8**%) Immune-mediated pneumonitis 19 (4%) 3 (**0.6**%)	Immune-mediated pneumonitis 19 (4%) 3 (**1**%)		

Issue 7

Description of problem	**Description of proposed amendment**	**Justification for amendment**	**EAG Response**
[Table 27, page 57]	include 840 mg atezolizumab formulation, £2,665.38 list price, net price [redacted]	As stated on the BNF and a PAS price is available for this formulation	The title of Table 27 is "*Summary of drug costs included within the model*". The 840mg dose of atezolizumab is not included in the model and so we have not changed the table.

Issue 8

Description of problem	Description of proposed amendment	Justification for amendment	EAG Response
[page 58] text	Assumeds instead of assumes	Typo error	Changed to assumed

Issue 9

Description of problem	Description of proposed amendment	Justification for amendment	EAG Response
[Table 28, page 61]	The incremental cost of Atezo vs. AM is incorrect, should be [redacted] Incorrect incremental QALYs. Should be [redacted].	Incorrect calculation	The typo related to the incremental cost has been corrected. The incremental QALY value was correct (rounding caused the perceived error)

Issue 10

Description of problem	Description of proposed amendment	Justification for amendment	EAG Response
[Table 30, page 68]	The incremental cost of Atezo vs. AM is incorrect, should be [redacted]	Incorrect calculation	The company's stated value was already in Table 30, so no change has been made.