NICE National Institute for Health and Care Excellence

Single Technology Appraisal

Atezolizumab for adjuvant treatment of resected non-small-cell lung cancer [ID3852]

Committee Papers

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

SINGLE TECHNOLOGY APPRAISAL

Atezolizumab for adjuvant treatment of resected non-small-cell lung cancer [ID3852]

Contents:

The following documents are made available to consultees and commentators:

1. **Company submission** from Roche
2. **Clarification questions and company responses**
3. **Patient group, professional group and NHS organisation submissions** from:
   a. British Thoracic Oncology Group
4. **Evidence Review Group report** prepared by Peninsula Technology Assessment Group (PenTAG)
5. **Evidence Review Group report – factual accuracy check**
6. **Company additional evidence** from Roche
7. **Additional analyses post-first committee meeting** from Roche
8. **Evidence Review Group critique of the company additional analyses** prepared by Peninsula Technology Assessment Group (PenTAG)
9. **Company response to ERG critique of additional analyses** from Roche

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 [ID3852]

Document B

Company evidence submission

October 2021

File name	Version	Contains confidential information	Date
ID3852_Atezolizumab_DocB_eNSCLC_[ACIC]_v2.0_Mar2022	V3.0	Yes	8Mar2022

Contents

Tables and figures

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

B.1.1 Decision problem

The submission covers the technology's full, proposed marketing authorisation for this indication:

[redacted]

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 fully resected NSCLC after adjuvant cisplatin-based chemotherapy	Adults with resected, Stage II–IIIA early non-small cell lung cancer (eNSCLC), expressing PD-L1 ≥ 1% of tumour cells	The PD-L1 ≥ 1% population is in line with marketing authorisation
Intervention	Atezolizumab (as an adjuvant treatment)	Per final scope	N/A
Comparator(s)	Established clinical management without atezolizumab (that is, active monitoring) For adults with EGFR mutation-positive NSCLC: Osimertinib (subject to NICE appraisal)	Established clinical management without atezolizumab (that is, active monitoring)	• Data from the IMpower010 trial demonstrated potential benefit from adjuvant atezolizumab after chemotherapy for some NSCLC patients (e.g., PD-L1+) with epidermal growth factor receptor (EGFR+) mutations. However, the sample size of EGFR/ALK+ NSCLC patients were small and insufficient to fully characterise the treatment effect and to draw conclusions on the risk/benefit profile for adjuvant atezolizumab in these populations. • In addition, based on results from the ADAURA trial, and recent FDA and EMA approvals, osimertinib is likely to become standard of care

			for EGFR+ NSCLC patients in the adjuvant setting. • Roche Products Ltd, along with clinical experts, do not expect the IMpower010 regimen to replace osimertinib for these patients and therefore, we do not consider osimertinib to be a relevant comparator.
Outcomes	The outcome measures to be considered include: • Overall survival • Disease-free survival • Response rate • Adverse effects of treatment • Health-related quality of life	The outcome measures to be considered include: • Overall survival • Disease-free survival • Adverse effects of treatment	• Response rates and health-related quality of life were not measured. - Response rates are not measurable in resected NSCLC patients. - Patients with early NSCLC are generally asymptomatic, and their disease burden are relatively low when compared to patients in the metastatic setting. In addition, patients in the IMpower010 trial did not receive an active control therapy.
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.	• Cost per quality-adjusted life year (QALY) • Time horizon suitably long to reflect differences	N/A

	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 (PSS) perspective. The availability of any commercial arrangements for the intervention, comparator and subsequent treatment technologies will be taken into account. The availability of any managed access arrangement for the intervention will be taken into account.	• NHS PSS perspective Patient access scheme (PAS) to be taken into account.	
Subgroups to be considered	If evidence allows, subgroup analysis by level of PD-L1 expression will be considered. Guidance will only be issued in accordance with the marketing	Patients with resected, Stage II–IIIA eNSCLC, expressing PD-L1 ≥ 1% of tumour cells and without EGFR/ALK+ mutations.	• In the IMpower010 trial, NSCLC patients with anaplastic lymphoma kinase genetic alternations (ALK+) did not appear to benefit with atezolizumab compared with best supportive care (BSC).

	authorisation. Where the wording of the therapeutic indication does not include specific treatment combinations, guidance will be issued only in the context of the evidence that has underpinned the marketing authorisation granted by the regulator.		• Data from the IMpower010 trial demonstrated potential benefit from adjuvant atezolizumab after chemotherapy for some NSCLC patients (e.g., PD-L1+) with epidermal growth factor receptor (EGFR+) mutations. • The sample size of EGFR/ALK+ NSCLC patients were small and insufficient to fully characterise the treatment effect and to draw conclusions on the risk/benefit profile for adjuvant atezolizumab in these populations. • We do not expect the IMpower010 regimen to be used for these patients, and have therefore presented DFS data excluding EGFR/ALK+ NSCLC patients.
Special considerations including issues related to equity or equality	N/A	N/A	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) (1). 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 (2-4). 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 (2, 5). The PD-L2/PD-1 interaction is left intact, potentially preserving peripheral immune homeostasis (6). 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 (3, 7).
Marketing authorisation/ CE mark status	[redacted]

	[redacted]
Indications and any restriction(s) as described in the summary of product characteristics (SmPC)	Atezolizumab is currently approved by the European Medicines Agency (EMA) for the following indications (8): • **Atezolizumab 840 mg and 1,200mg concentrate for solution for infusion** **For non-small cell lung cancer:** • 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% tumour cells (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 • 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:** • As monotherapy, for the treatment of adult patients with locally advanced or metastatic urothelial carcinoma (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:**

	• In combination with bevacizumab, for the treatment of adult patients with advanced or unresectable hepatocellular carcinoma (HCC) who have not received prior systemic therapy **For triple-negative breast cancer:** • In combination with nab-paclitaxel, for the treatment of adult patients with unresectable locally advanced or metastatic triple-negative breast cancer (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 is: • 840 mg administered intravenously every two weeks, or • 1,200 mg administered intravenously every three weeks, or • 1,680 mg administered intravenously every four weeks Treatment with atezolizumab is recommended until loss of clinical benefit or unmanageable toxicity (8).
Additional tests or investigations	[redacted] (9)
List price and average cost of a course of treatment	Atezolizumab: • £ 3,807.69 per 20 ml vial (1,200 mg); • £ 2,665.38 per 14 ml vial (840 mg) Price for full treatment course: £53,139.84
Patient access scheme	Atezolizumab: [redacted] (existing PAS)

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

B.1.3.1 Disease overview

Incidence and mortality

Lung cancer is the most common type of cancer worldwide. In 2018, there were over 2 million new cases of lung cancer, contributing to 12.3% of the total number of new cancer cases diagnosed (10). Globally, it is responsible for causing an estimated 1.8 million cancer-related deaths (11).

In the UK, lung cancer is the third most common type of cancer, with approximately 47,800 new cases every year (12). Between 2016 and 2018, there were approximately 35,100 annual lung cancer deaths, accounting for 21% of all cancer deaths in the UK (12).

Histology

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 2018 National Lung Cancer Audit (NLCA), 88% of all lung cancer cases were diagnosed as NSCLC (13).

NSCLC can be further divided into two major histologic types: non-squamous and squamous cell carcinoma; with a smaller subset categorised as large cell carcinoma, neuroendocrine tumours, and sarcomatoid carcinoma (14). Non-squamous histology accounts approximately 70% of NSCLC (15), whereas squamous histology accounts for approximately 25-30% of cases (16, 17).

Diagnosis, staging and screening

Current methods of detecting lung cancer include chest X-ray, computed tomography (CT) scan, magnetic resonance imaging (MRI), positron emission tomography (PET) scan, sputum analysis, and lung biopsy (18). 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) (19, 20). 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 (21). See Table 3 for the proportion of NSCLC cases by stage at diagnosis.

Table 3: NSCLC stages at diagnosis in the UK (22)

Staging	Proportion of incident cases at diagnosis (%)
IA	8.95
IB	6.37
IIA	4.32
IIB	3.91
IIIA	12.85
IIIB	8.72

Despite potentially curative surgery for these patients, their survival rates are heavily dependent on the stage of disease. The 5-year survival for early NSCLC patients following complete surgical resection is estimated at 68–92% for Stage I disease, 53–60% for Stage II disease, and 13–36% for Stage III disease (21). 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[1] (Data on File) (23).

It is evident that the sooner lung cancer is diagnosed, the better the prognosis for the patient. However, despite the advancement in technology and the extensive cancer research, 57% of lung cancer patients are diagnosed with advanced or metastatic disease (18). This is primarily due to the asymptomatic nature of early NSCLC, when diagnosis is generally incidental (24, 25), and highlighting the need for effective screening programmes to ensure identification of 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 (26, 27). 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 (28). Taking these promising national and international findings into account, NHS England plan to roll out further lung cancer screening pilots. If successful, these will be implemented nationally, in line with the NHS Long Term Plan (29). With the

[1] A total of 10 UK clinical experts were consulted at an advisory board.

implementation of lung cancer screening, it is likely that the proportion of early NSCLC will increase.

Treatment options

For patients with early NSCLC, surgery (lobectomy) is the primary treatment option with curative intent, and can be complemented by neoadjuvant or adjuvant chemotherapy. However, according to clinical expert opinion, neoadjuvant therapy is rarely used in the UK (Data on File) (23). Furthermore, according to National Institute for Health and Care Excellence (NICE) guidelines, neoadjuvant chemotherapy is not recommended outside a clinical trial for patients with Stage I–II NSCLC that are suitable for surgery (30).

Current European Society for Medical Oncology (ESMO) and National Comprehensive Cancer Network (NCCN) guidelines recommend four cycles of adjuvant platinum-based chemotherapy for resectable Stages II-III NSCLC (as per AJCC 8th edition) and in selected patients with high-risk Stage IB (>4cm) disease (31, 32).

A 2008 lung-adjuvant-cisplatin evaluation (LACE) analysis reported cisplatin-based adjuvant chemotherapy significantly improved survival in patients with NSCLC (33). The analysis demonstrated a 5% improvement in 5-year overall survival (OS) rates with adjuvant chemotherapy and an OS hazard ratio 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.

Although surgical resection for early NSCLC is the best curative option, 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% (34-36), 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.

In recent years, the discovery of key molecular characteristics has offered new hope for patients with NSCLC. More specifically, the presence of mutations in the epidermal growth factor receptor (EGFR) gene and ROS proto-oncogene 1 (ROS1), rearrangements in anaplastic lymphoma kinase (ALK) and RET proto-oncogene (RET), and expression of programmed death ligand 1 (PD-L1) serve as potential targets in our armamentarium against

NSCLC (37-39). Although these targets have been successfully exploited in advanced or metastatic NSCLC, early NSCLC patients can only benefit from these efforts in specific scenarios, such as the use of durvalumab in unresectable Stage III NSCLC (40), or the use of osimertinib in patients with resectable tumours harbouring EGFR mutations (41). In the absence of EGFR mutations, patients with resectable NSCLC rely entirely on platinum-based chemotherapy as the sole adjuvant treatment option. Considering the high recurrence rates, there remains an immediate need for novel adjuvant treatments that can extend patients survival following complete resection beyond the benefit conferred by adjuvant chemotherapy.

Quality of life

Patients with early NSCLC are generally asymptomatic, and their disease burden are 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 (42, 43). 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 (44).

Though surgical intervention is the recommended treatment for early NSCLC, patients experienced a worsening of symptoms such as fatigue, pain, dyspnoea, insomnia, constipation, diarrhoea, and financial difficulties 30 days post-surgery (45). 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) (46). 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 (47).

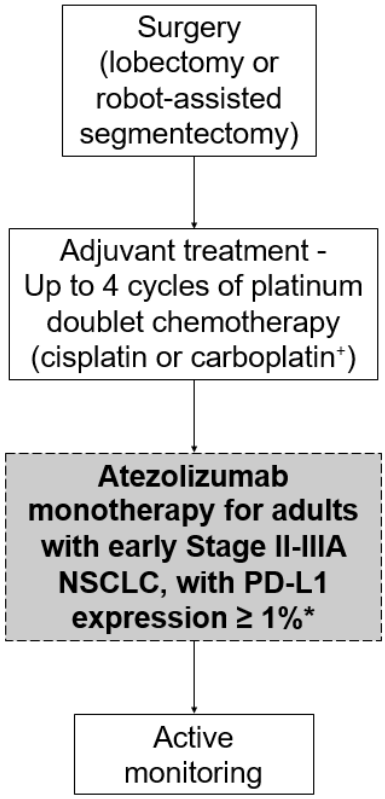
The IMpower010 study did not collect patient reported outcomes (PROs), as PROs were not widely used at the time of study design. This is also observed in other similar adjuvant cancer immunotherapy studies, where PROs were not consistently collected (48-50). Additionally, as these patients do not have 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 Disease management pathway

The information presented in Figure 1 is based on the NICE guidelines for the diagnosis and management of lung cancer (30). This was further confirmed by clinical experts, who agreed that the current NICE management pathway is in line with UK clinical practice (Data on File) (23).

Figure 1: Current treatment pathway for early NSCLC adult patients (including atezolizumab positioning)



***** The current NICE lung cancer management guidelines for adjuvant NSCLC are not defined by PD-L1 expression, as there are currently no PD-1/L1 inhibitors licensed in the adjuvant setting. Additionally, the guidelines are not defined by EGFR/ALK status, as there were no licensed targeted treatments for these mutations in the adjuvant setting at the time of guideline development. However, osimertinib is now licensed for adjuvant therapy after tumour resection in patients with NSCLC who are harbouring an EGFR mutation (51) and is currently undergoing review by NICE (52).

+ Carboplatin is used in the current clinical practice, but usage varies greatly across the country. It is not currently recommended by NICE (30) and was not included as an intervention in the IMpower010 trial.

The grey box indicates the proposed positioning of adjuvant atezolizumab.

Abbreviations: ALK, anaplastic lymphoma kinase; EGFR, epidermal growth factor receptor; NSCLC, non-small cell lung cancer.

Source: Clinician interviews conducted by Roche (23, 24).

B.1.3.3 Current clinical practice in the UK

To understand the current management of early NSCLC in the UK, Roche conducted interviews with UK clinical experts (Data on File) (23).

Although surgery remains the preferred treatment for early NSCLC, patients in the UK have historically been less likely to undergo surgery than patients in other countries. In 2017, NLCA found that 18.4% of all NSCLC patients underwent surgery, which had doubled from approximately 9% in 2006 (53). For patients with Stage I–II NSCLC, who also had a good performance status, surgical rates had increased from approximately 52% in 2015 to approximately 61% in 2017, though regional variations exist (53). 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.

Following surgery, NICE recommends the use of adjuvant cisplatin-based chemotherapy for Stage IB (> 4cm) to Stage III patients (30). 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 (54). 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 (55). Usage data of adjuvant chemotherapy in the UK is limited, though clinical experts report 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) (23). In addition, the majority of patients (50–75%) who begun adjuvant chemotherapy completed 4 cycles. Reasons for patients not having adjuvant chemotherapy included perceived lack of clinical benefit, toxicity, patient fitness and patient preference.

ESMO guidelines considers carboplatin an accepted alternative when cisplatin administration is not feasible (56). On the contrary, carboplatin is not recommended by NICE (30). Nonetheless, carboplatin is used in UK clinical practice; however, its usage varies greatly across the country (Data on File). UK clinical experts noted that carboplatin is used when cisplatin cannot be tolerated or is contraindicated; in patients with renal or hearing impairment, or due to capacity constraints, as administration of carboplatin is shorter (23). Although the IMpower010 trial stipulated the use of cisplatin-based adjuvant chemotherapy, [redacted].

PD-L1 testing in early NSCLC is common, though it is not mandated by NICE guidelines (unlike Stage III and Stage IV NSCLC, where anti-PD-1/anti-PD-L1 therapies are licensed). Five out of six clinical experts reported that PD-L1 is tested in early NSCLC at their respective centres (Data on File) (23). The one centre that did not test for PD-L1 in the early setting reported no issues with implementation. Therefore, it is anticipated that introduction of atezolizumab into the adjuvant setting would not have a significant impact on the current PD-L1 testing landscape.

B.1.4 Equality considerations

Roche 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 (TNM 7th edition) (57). There are no other similar trials investigating the effectiveness of atezolizumab as an adjuvant treatment. Details are summarised below (Table 4).

Table 4: Clinical effectiveness evidence

<table>
<tr><td>Study</td><td colspan="5">IMpower010</td></tr>
<tr><td>Study design</td><td colspan="5">Global, randomised, Phase III, multi-centre, open-label study</td></tr>
<tr><td>Population</td><td colspan="5">Patients with completely resected Stage IB (tumours greater ≥ 4cm) to 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 0-1</td></tr>
<tr><td>Intervention(s)</td><td colspan="5">Atezolizumab</td></tr>
<tr><td>Comparator(s)</td><td colspan="5">BSC following resection and cisplatin-based adjuvant chemotherapy</td></tr>
<tr><td rowspan="2">Indicate if trial supports application for marketing authorisation</td><td>Yes</td><td>✓</td><td rowspan="2">Indicate if trial used in the economic model</td><td>Yes</td><td>✓</td></tr>
<tr><td>No</td><td></td><td>No</td><td></td></tr>
<tr><td>Rationale for use/non-use in the model</td><td colspan="5">The IMpower010 trial comprises the relevant population, intervention, comparators and outcomes</td></tr>
<tr><td>Reported outcomes specified in the decision problem</td><td colspan="5">• Disease-free survival (DFS)
• Overall survival (OS)
• Adverse effects of treatment</td></tr>
<tr><td>All other reported outcomes</td><td colspan="5">N/A</td></tr>
</table>

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

IMpower010 investigates the efficacy and safety of atezolizumab versus BSC in patients with Stage IB-IIIA NSCLC (as per UICC/AJCC staging system, 7th edition) following complete resection and adjuvant cisplatin-based chemotherapy.

In this submission, the following outcomes are reported* (CCOD: 21 January 2021):

- **Primary endpoint of DFS in the Stage II–IIIA PD-L1 ≥ 1% population**
- **OS in the Stage II-III PD-L1 ≥ 1% population**
- **Exploratory analyses of incidence of, and time to disease relapse in the Stage II–IIIA PD-L1 ≥ 1% population**
- **Subsequent treatments in the Stage II–IIIA PD-L1 ≥ 1% population**
- **Additional subgroup analyses by EGRF/ALK status**

* [redacted]. Other relevant data from the IMpower010 trial are presented in the Appendices.

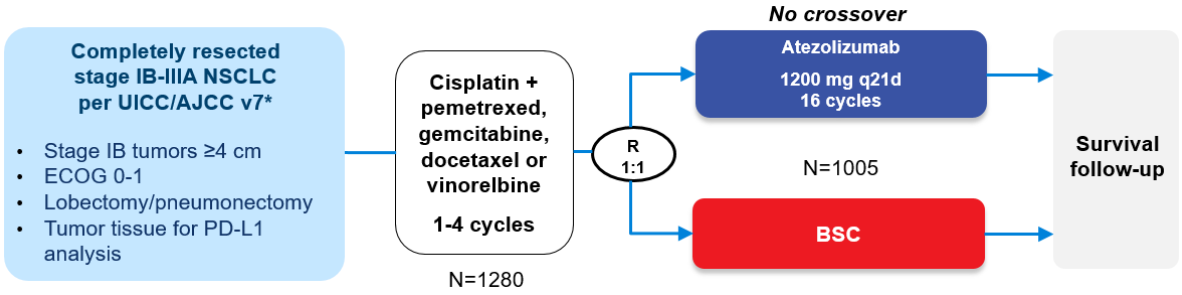
B.2.3.1 Methodology

Unless otherwise stated, B.2.3–B.2.6 is based on the IMpower010 clinical study report (CSR) (Data on File).

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 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.

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 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 (58-60).

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.

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 patients 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 or BSC. Randomisation was stratified by sex (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).

Cycles of treatment

In the experimental arm, atezolizumab was administered intravenously on Day 1 of each 21-day cycle for a total of 16 cycles (which equates to approximately one year of treatment). Patients randomised to the BSC arm received no treatment in the randomisation phase and were continually followed up starting on Day 1 of each 21-day cycle.

The one-year adjuvant treatment duration of atezolizumab was considered a balance between maintaining the treatment medication until a time when many patients experienced relapse to ensure optimal efficacy outcomes, whilst maintaining tolerability and potential additional toxicity (including long-term immune-related adverse events [irAEs]) in patients with higher survival rates.

To ensure the same frequency of study, disease recurrence and safety assessments between the atezolizumab arm and BSC arm, patients in the BSC arm were required to undergo medical contact every 3 weeks during the first year for symptom and adverse event (AE) assessment.

Crossover from the BSC arm to the atezolizumab arm was not permitted.

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.

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.

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. Patients who 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 (61). 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% (Table 5). 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 ≥ 1% group, baseline characteristics were 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.

Table 5: Summary of PD-L1 IHC assay comparisons (62)

PD-L1 IHC assay (*based on key atezolizumab studies)*	PD-L1 expression			
	High	**Medium or high**	**Any**	**None**
SP142 PD-L1 IHC (Ventana) (63)	**TC3 or IC3** PD-L1 expression on ≥ 50% of TCs (TC3) or PD-L1-expressing ICs being ≥ 10% of the tumour area (IC3)	**TC2/3 or IC2/3** PD-L1 expression on ≥ 5% of TCs (TC2/3) or PD-L1-expressing ICs being ≥ 5% of the tumour area (IC2/3)	**TC1/2/3 or IC1/2/3** PD-L1 expression on ≥ 1% of TCs (TC1/2/3) or PD-L1-expressing ICs being ≥ 1% of the tumour area (IC1/2/3)	**TC0 and IC0** PD-L1 expression on < 1% of TCs (TC0) and PD-L1-expressing ICs being < 1% of the tumour area (IC0)
SP263 PD-L1 IHC (Ventana)	**TC ≥ 50%** PD-L1 expression on ≥ 50% of TCs	**TC ≥ 25%** PD-L1 expression on ≥ 25% TCs	**TC ≥ 1%** PD-L1 expression on ≥ 1% of TCs	**TC < 1%** PD-L1 expression on < 1% of TCs

Abbreviations: IC: immune cell; IHC: immunohistochemistry; TC: tumour cell; TPS: tumour proportion score; WT: wild-types

B.2.3.3 Endpoints and assessments

The primary efficacy endpoint was duration of DFS as assessed by the investigator:

- 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

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 randomization])
- 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 Rationale for the IMpower010 study design and the target patient population in this submission

In this submission, the patient population of interest is the Stage II–IIIA population whose tumours expressed PD-L1 on 1% or more of tumour cells by the SP263 immunohistochemistry assay.

In IMpower010, treatment with atezolizumab significantly reduced the risk of disease recurrence or death in patients with resected, PD-L1 TC ≥ 1% Stage II–IIIA NSCLC (DFS HR: 0.66) when given after adjuvant platinum-based chemotherapy (See section B.2.6.2). Atezolizumab also demonstrated a relative risk reduction in all randomised patients with Stage II–IIIA NSCLC (DFS HR: 0.79) (Appendix H). Although this represents a statistically significant 21% reduction in the risk of disease recurrence, the benefit was mainly driven by the PD-L1 TC ≥ 1% subgroup. The DFS boundary for statistical significance was not crossed in the ITT population (Appendix H). This may be due to the inclusion of Stage IB NSCLC patients (12%) in this population, as they tend to relapse later than Stage II-III NSCLC included in the trial.

Atezolizumab demonstrated a statistically significant and clinically meaningful reduction in risk of disease recurrence or death in patients with resected, PD-L1 TC ≥ 1%, Stage II–IIIA NSCLC when given after adjuvant platinum-based chemotherapy (DFS HR: 0.66).

[redacted]

B.2.3.5 Baseline characteristics

Between 26 February 2016 and 16 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 were generally well-balanced between treatment arms in the randomised population and generally consistent with that expected for the target patient population (Table 6). Patients were predominantly White (73.4%) or Asian (24.1%) with a median age of 62 years. The study was well balanced for disease stage (stratification factor), and lymph node dissection or sampling, which almost all patients had. Treatment characteristics were also well-balanced between arms in the ITT population, including types and number of cycles of chemotherapy regimen, types of surgical intervention and the median time from surgery to first adjuvant atezolizumab or BSC (Table 6).

Table 6: Patient demographics and baseline characteristics by groups (PD-L1 TC ≥ 1%, all randomised, and ITT populations)

Characteristics	All patients (N=1005)	PD-L1 TC ≥ 1% (SP263) (Stage II–IIIA)		All randomised (Stage II–IIIA)		ITT (Stage IB–IIIA)	
		Atezolizumab (n=248)	BSC (n=228)	Atezolizumab (n=442)	BSC (n=440)	Atezolizumab (n=507)	BSC (n=498)
Median age, y (range)	62 (26-84)	61 (34-82)	62 (26-84)	62 (33-82)	62(26-84)	62 (33-83)	62 (26-84)
Age ≥65 y, n (%)	382 (38.0)	92 (37.1)	97 (42.5)	161 (36.4)	177 (40.2)	184 (36.3)	198 (39.8)
Sex, male, n (%)	672 (66.9)	171 (69.0)	147 (64.5)	295 (66.7)	294 (66.8)	337 (66.5)	335 (67.3)
Race, n (%)							
White	738 (73.4)	162 (65.3)	166 (72.8)	307 (69.5)	324 (73.6)	362 (71.4)	376 (75 .5)
Asian	242 (24.1)	78 (31.5)	56 (24.6)	121 (27.4)	106 (24.1)	130 (25.6)	112 (22.5)
Other	25 (2.5)	8 (3.2)	6 (2 .6)	14 (3.2)	10 (2.3)	15 (3.0)	10 (2.0)
ECOG PS, n (%)							
0	556 (55.3)	140 (56.5)	125 (54.8)	239 (54.1)	252 (57.3)	273 (53.8)	283 (56.8)
1	446 (44.4)	107 (43.1)	102 (44.7)	201 (45.5)	187 (42.5)	232 (45.8)	214 (43.0)
Histology, non-squamous, n (%)	659 (65.6)	152 (61.3)	143 (62.7)	292 (66.1)	296 (67.3)	328 (64.7)	331 (66.5)
Stage, n (%)							
IB	123 (12.2)	-	-	-	-	65 (12.8)	58 (11.6)
IIA	295 (29.4)	85 (34.3)	76 (33.3)	147 (33.3)	148 (33.6)	147 (29.0)	148 (29.7)
IIB	174 (17.3)	46 (18.5)	37 (16.2)	90 (20.4)	84 (19.1)	90 (17.8)	84 (16.9)
IIIA	413 (41.1)	117 (47.2)	115 (50.4)	205 (46.4)	208 (47.3)	205 (40.4)	208 (41.8)
Mediastinal lymph node dissection, n (%)	811 (80.7)	-	-	-	-	402 (79.3)	409 (82.1)
Mediastinal lymph node sampling, n (%)	181 (18.0)	-	-	-	-	93 (18.3)	88 (17.7)
Type of surgery, n (%)[a]							
Lobectomy	785 (78.1)	-	-	-	-	394 (77.7)	391 (78.5)
Pneumonectomy	160 (15.9)	-	-	-	-	77 (15.2)	83 (16.7)
Bilobectomy	50 (5.0)	-	-	-	-	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)	-	-	-	-	77 (15.2)	75 (15.1)

Characteristics	All patients (N=1005)	PD-L1 TC ≥ 1% (SP263) (Stage II–IIIA)		All randomised (Stage II–IIIA)		ITT (Stage IB–IIIA)	
		Atezolizumab (n=248)	BSC (n=228)	Atezolizumab (n=442)	BSC (n=440)	Atezolizumab (n=507)	BSC (n=498)
Cisplatin-gemcitabine	165 (16.4)	-	-	-	-	88 (17.4)	77 (15.5)
Cisplatin-vinorelbine	303 (30.1)	-	-	-	-	152 (30.0)	151 (30.3)
Cisplatin-pemetrexed	385 (38.3)	-	-	-	-	190 (37.5)	195 (39.2)
Tobacco use history, n (%)							
Never	222 (22.1)	51 (20.6)	41 (18.0)	100 (22.6)	96 (21.8)	114 (22.5)	108(21.7)
Current/previous	783 (77.9)	197 (79.4)	187 (82.0)	342 (77.4)	344 (78.2)	393 (77.5)	390 (78.3)
PD-L1 by SP263, TC ≥1%, n (%)[b]	535 (54.6)	248 (100)	228(100)	248 (57.8)	228 (53.0)	283 (57.4)	252 (51.9)
EGFR mutation status , n (%)[c]							
Positive	117 (11.6)	23 (9.3)	20 (8.8)	49 (11.1)	60 (13.6)	53 (10.5)	64 (12.9)
Negative	527 (52.4)	123 (49.6)	125 (54.8)	229 (51.8)	234 (53.2)	261 (51.5)	266 (53.4)
Unknown	361 (35.9)	102 (41.1)	83 (36.4)	164 (37.1)	146 (33.2)	193 (38.1)	168 (33 .7)
ALK rearrangement status, n (%)[c]							
Positive	33 (3.3)	12 (4.8)	11 (4.8)	14 (3.2)	17 (3.9)	15 (3.0)	18 (3.6)
Negative	574 (57.1)	133 (53.6)	121 (53.1)	251 (56.8)	256 (58.2)	280 (55.2)	294 (59.0)
Unknown[d]	398 (39.6)	103 (41.5)	96 (42.1)	177 (40.0)	167 (38.0)	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.

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

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

See Appendix D for details of the number of eligible participants and patient disposition for the IMpowere010 trial.

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

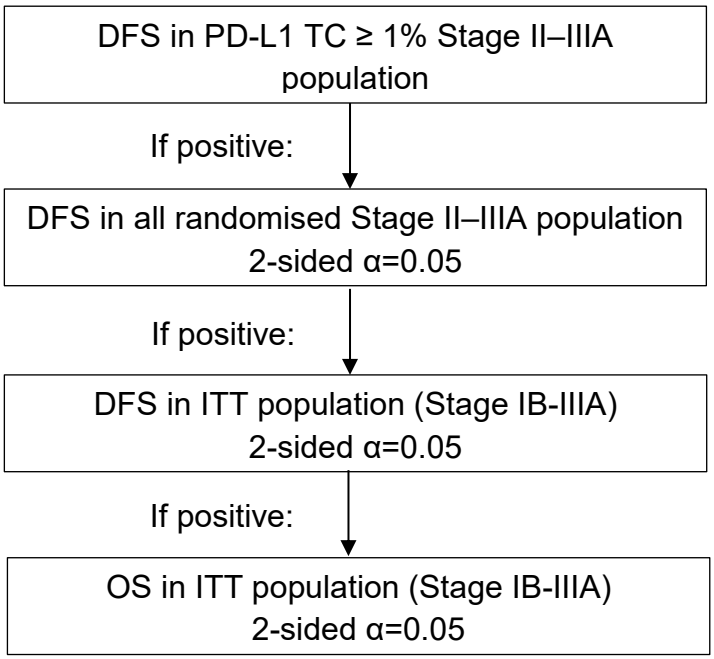
Secondary efficacy analysis of:

- OS in ITT Stage IB–IIIA population

[redacted]

The IMpower010 statistical analysis plan is summarised below (Figure 3). DFS was tested hierarchically followed by OS**Error! Reference source not found.**. 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. However, as the significance boundary for DFS was not crossed at the interim analysis in the ITT population (Stage IB–IIIA), testing will continue to the final DFS analysis in ITT population (Stage IB–IIIA).

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 7).

Table 7: 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 (33). Therefore, Stage IB patients were not included in the first population to be tested. • Data read outs for PD-L1/PD-1 therapies in advanced and metastatic NSCLC indicated a positive correlation between PD-L1 expression and clinical benefit (38, 60, 64). • 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 (65), 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 8). See Appendix D for the complete quality assessment of other relevant trials.

Table 8: Risk of bias assessment for IMpower010

Trial	Was randomisation carried out appropriately?	Was the concealment of treatment allocation adequate?	Were the groups similar at the outset of the study in terms of prognostic factors?	Were the care providers, participants, and outcome assessors blind to treatment allocation?	Were there any unexpected imbalances in dropouts between groups?	Is there any evidence to suggest that the authors measured more outcomes than they reported?	Did the analysis include an intention-to-treat analysis? If so, was this appropriate and were appropriate methods used to account for missing data?
IMpower010	Yes	Yes	Yes	No	No	No	Yes

B.2.6 Clinical effectiveness results from IMpower010

IMpower010 is the first Phase III study of adjuvant immunotherapy to demonstrate a DFS improvement in the fully resected early NSCLC patients following platinum-based chemotherapy.

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 atezolizumab monotherapy as adjuvant treatment compared to BSC in the PD-L1 ≥ 1% TC Stage II–IIIA NSCLC population.

Additionally, a statistically significant improvement (21% reduction) in DFS was observed in all randomised Stage II–IIIA NSCLC patients (HR: 0.79; 95% CI: 0.64, 0.96; p=0.02).

Results of DFS in the ITT population showed a trend in favour of atezolizumab over BSC, however the pre-specified DFS interim analysis alpha boundary (two-sided α=0.0368) was not crossed.

At interim analysis, the OS data was immature and not formally tested. However, a trend was observed towards reduction in risk of death (stratified HR=0.77; 95% CI: 0.51, 1.17) with atezolizumab administration in patients with PD-L1 TC ≥ 1% Stage II–IIIA NSCLC.

An exploratory analysis investigating incidence of relapse revealed that 25–30% fewer patients experienced relapse in the atezolizumab arm, for the PD-L1 TC ≥ 1% and all-randomised Stage II–IIIA NSCLC populations

The difference in rate of relapse between the atezolizumab and BSC arm was most prominent in the PD-L1 TC ≥ 1% Stage II–IIIA population, with a relapse rate of: 29% vs 45%, respectively.

Generally, a consistent DFS benefit with atezolizumab versus BSC was observed across clinical subgroups, including high-risk patients such as node-positive N1 disease (HR: 0.59; 95% CI: 0.36, 0.97) and N2 disease (HR: 0.66; 95% CI: 0.44, 0.99).

B.2.6.1 Overview of efficacy

At the clinical cut-off date (CCOD) on 21 January 2021, after a median duration of survival follow-up of 32.2 months, 399 DFS events and 187 death events had occurred in the ITT population.

The primary efficacy endpoint was met with a statistically significant and clinically meaningful improvement in DFS for the atezolizumab arm compared to the BSC arm in the PD-L1 ≥ 1% Stage II–IIIA population (key patient population in this submission). The exploratory secondary endpoint of OS suggested a trend in favour of atezolizumab over BSC in the PD-L1 ≥ 1% TC Stage II–IIIA population. Exploratory analysis of incidence of relapse, as well as overall treatment benefit with atezolizumab on DFS favoured the PD-L1 ≥ 1% Stage II–IIIA population.

An overview of key efficacy results for DFS and OS in the PD-L1 ≥ 1% TC Stage II–IIIA, all randomised Stage II–IIIA NSCLC, and ITT populations are provided below (Table 9).

Table 9: Overview of efficacy of IMpower010

	Atezolizumab	BSC
Primary endpoint		
DFS in PD-L1 SP263 ≥ 1% TC Stage II–IIIA, n	248	228
Patients with event, n (%)	88 (35.5)	105 (46.1)
Median DFS, months (95% CI)	NE (36.1, NE)	35.3 (29.0, NE)
Stratified HR (95% CI)	0.66 (0.50, 0.88)	
p-value (Stratified Log-rank)	0.0039	
3-year DFS, % (95% CI)	60.0 (52.8, 67.1)	48.2 (40.7, 55.7)
DFS in all randomised (Stage II–IIIA), n	442	440
Patients with event, n (%)	173 (39.1)	198 (45.0)
Median DFS, months (95% CI)	42.3 (36.0, NE)	35.3 (30.4, 46.4)
Stratified HR (95% CI)	0.79 (0.64, 0.96)	
p-value (Stratified Log-rank)	0.0205	
DFS in ITT (Stage IB–IIIA), n	507	498
Patients with event, n (%)	187 (36.9)	212 (42.6)
Median DFS, months (95% CI)	NE (36.1, NE)	37.2 (31.6, NE)
Stratified HR (95% CI)	0.81 (0.67, 0.99)	
p-value (Stratified Log-rank)	0.0395	
Key secondary endpoints		
OS ITT (Stage IB–IIIA), n	507	498

	Atezolizumab	BSC
Patients with event, n (%)	97 (19.1)	90 (18.1)
Median OS, months (95% CI)	NE (NE)	NE (NE)
Stratified HR (95% CI)	1.07 (0.80, 1.42)	
DFS in PD-L1 SP263 ≥ 50% TC Stage II–IIIA, n	115	114
Patients with event, n (%)	[redacted]	[redacted]
Median DFS, months (95% CI)	NE (42.3, NE)	35.7 (29.7, NE)
Unstratified HR (95% CI)	0.43 (0.27, 0.68)	
Key exploratory endpoint		
OS in PD-L1 SP263 ≥ 1% TC Stage II–IIIA, n	248	228
Patients with event, n (%)	[redacted]	[redacted]
Median OS, months (95% CI)	[redacted]	[redacted]
Stratified HR (95% CI)	0.77 (0.51, 1.17)	

Abbreviations: BSC, best supportive care; DFS, disease-free survival; HR, hazard ration; INV, investigator; ITT, intent-to-treat; NE, not estimable; OS, overall survival; 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 drugs. For example, approval of adjuvant osimertinib in EGFR+, resected early NSCLC on the basis of DFS from the ADAURA study (66); 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 (67).

DFS in PD-L1 ≥ 1% TC Stage II–IIIA population

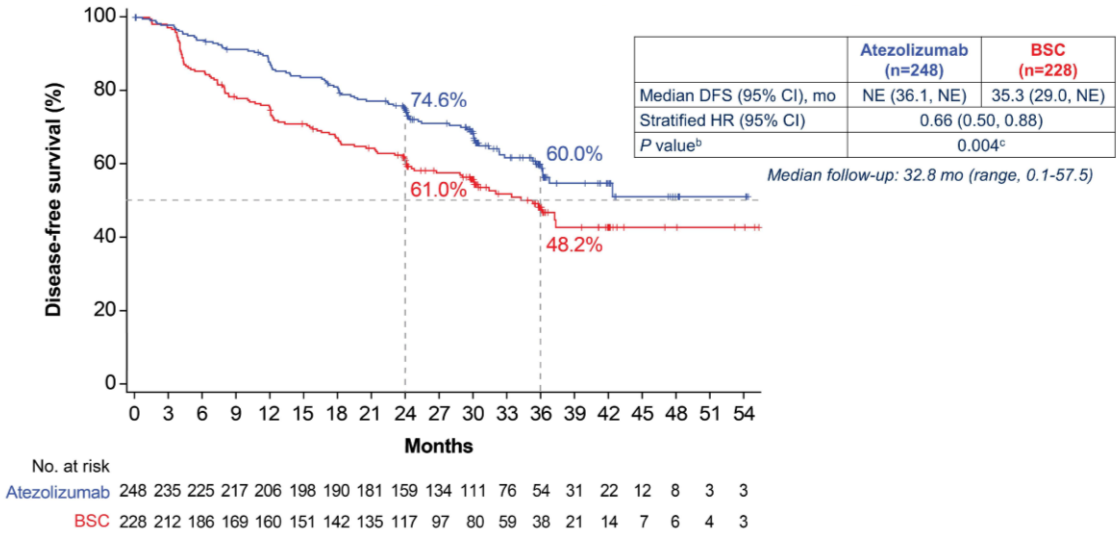
In IMpower010, after a median follow up of 32.8 months, DFS showed a statistically significant and clinically meaningful improvement in the atezolizumab arm compared to the BSC arm in Stage II–IIIA patients with PD-L1 ≥ 1%. At the CCOD on 21 January 2021, a higher proportion of patients in the BSC arm (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% relative risk reduction of a DFS event with atezolizumab compared to BSC.

The Kaplan-Meier (KM) estimated median DFS was not reached in the atezolizumab arm due to the low number of events 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 randomization in favor of the atezolizumab arm and was maintained thereafter (Figure 4).

See Appendix H for DFS results in the all randomised Stage II–IIIA and the ITT populations.

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



	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

The results of the sensitivity analyses to assess the impact of loss to follow-up on DFS and impact of two or more consecutive missed visits prior to a DFS event were consistent with those observed in the primary analysis in the PD-L1 ≥ 1% TC Stage II–IIIA population, and support the observed DFS benefit of atezolizumab over BSC. See Appendix H for further details.

B.2.6.4 Secondary efficacy endpoints

OS in the PD-L1 ≥ 1% TC Stage II–IIIA 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 (68). 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.

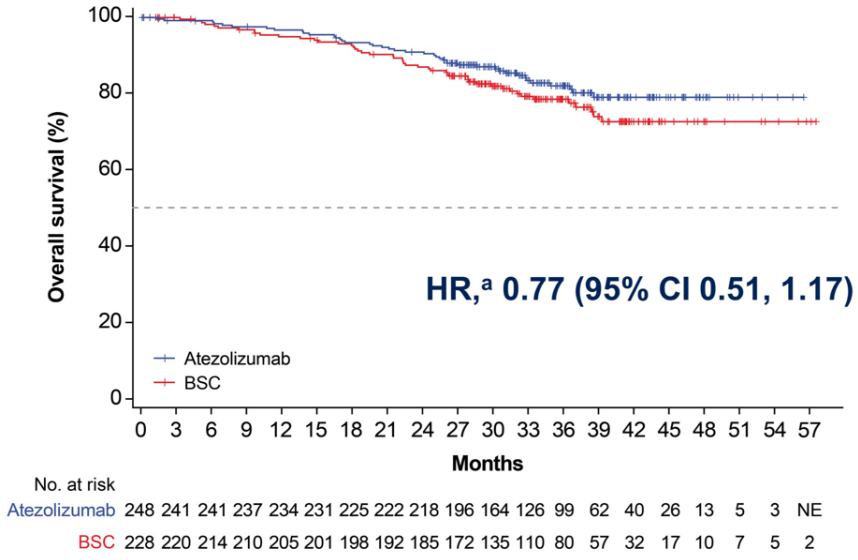
OS was not formally tested at the time of analysis, as statistical significance for DFS was not met in the ITT population (Appendix H).

[redacted]

[redacted]. Exploratory analysis of OS suggested a trend in favour of atezolizumab over BSC in the PD-L1 ≥ 1% TC Stage II–IIIA population. The stratified HR was 0.77 (95% CI: 0.51, 1.17), which corresponds to a 23% relative reduction in the risk of death with atezolizumab compared to BSC, with the KM curve showing a separation in favour of atezolizumab (Figure 5). These data should be interpreted with caution as they were highly immature at the time of analysis. The median OS could not be estimated in either arm due to the low number of deaths at the time of the CCOD. OS analyses will continue to be followed up as data matures.

See Appendix H for OS results in the all randomised Stage II–IIIA and the ITT populations.

Figure 5: Kaplan-Meier plot of OS (PD-L1 ≥ 1% TC Stage II–IIIA population)



Abbreviations: CI, confidence interval; HR, hazard ratio; NE, not evaluable

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

B.2.6.5 Exploratory endpoints

Disease Relapse

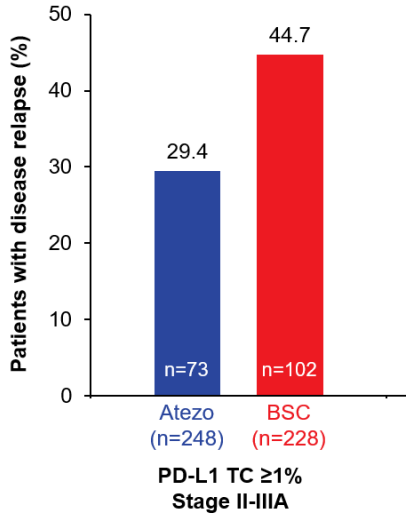
In current clinical practice, between a third and two thirds of patients with early NSCLC who undergo resection experience relapse (69). Therefore, it is important to be aware of when relapse typically occurs, as delaying relapse is commonly associated with a positive impact for patients, such as improvement in quality of life by delayed presentation of advanced or metastatic disease, which is associated with substantial morbidity.

A post-hoc exploratory analysis was conducted to investigate the incidence of disease relapse (Figure 6) and the time from randomisation to relapse (Figure 7).

Incidence of disease relapse in the PD-L1 ≥ 1% TC Stage II–IIIA population (70)

As an exploratory, post-hoc analysis, rate of relapse was evaluated in all randomised patients (after surgery and chemotherapy) whose DFS event was that of disease recurrence. In the PD-L1 ≥ 1% TC Stage II–IIIA population, 29% of patients experienced relapse in the atezolizumab arm compared with 45% in the BSC arm, within the current follow-up period (Figure 6). See Appendix H for rate of relapse in all randomised Stage II–IIIA and the ITT populations.

Figure 6: Patients with disease relapse (70)

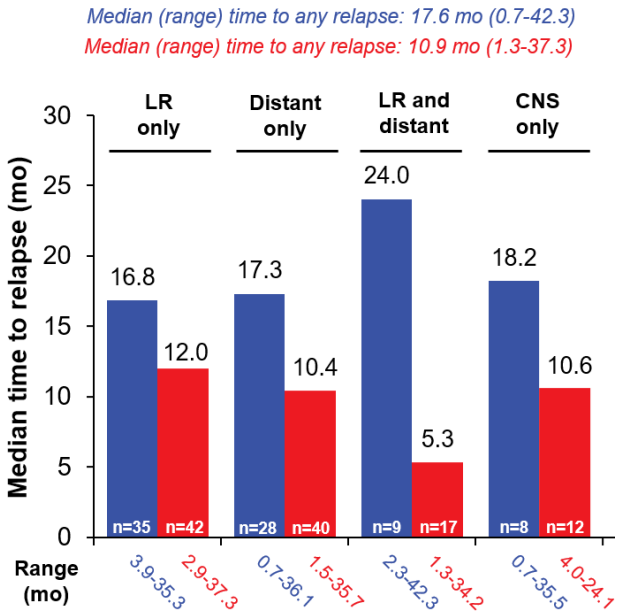


Presented as an exploratory post-hoc descriptive analysis.
Clinical data cut-off date (CCOD): 21 Jan 2021.

Time from randomisation to relapse in the PD-L1 ≥ 1% Stage II–IIIA population

In a further post-hoc analysis, it was found that the PD-L1 TC ≥ 1% Stage II–IIIA population had a longer time to relapse in the atezolizumab arm than those in the BSC arm, regardless of whether the relapse was locoregional or distant (Figure 7). The median time to any relapse was 17.6 months (0.7–42.3) in the atezolizumab arm, compared to 10.9 months (1.3–37.3) in the BSC arm. See Appendix H for time to relapse in all randomised Stage II–IIIA and the ITT populations.

Figure 7: Median time to relapse in the PD-L1 ≥ 1% Stage II–IIIA population

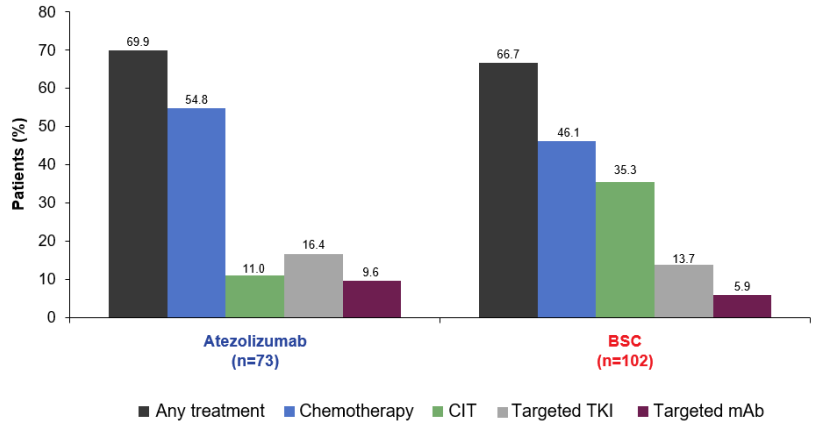


Presented as an exploratory post-hoc descriptive analysis.
Abbreviations: LR, locoregional; CNS, Central Nervous System.

Subsequent anti-cancer therapy in the PD-L1 TC ≥ 1% Stage II–IIIA population (70)

Among patients who experienced disease relapse, it is important to characterise treatment patterns in order to understand the potential impact of subsequent therapies on long-term outcomes, such as OS. In the PD-L1 TC ≥ 1% Stage II–IIIA population, a higher rate of post-relapse cancer immunotherapy (CIT) use was observed in the BSC arm compared to the atezolizumab arm (35% vs 11%) (Figure 8). Proportions of chemotherapy and other post-relapse treatments were similar between treatment arms. A list of all non-protocol anti-cancer therapies can be found in Appendix H.

Figure 8: Post-relapse systemic non-protocol anticancer therapy in the PD-L1 TC ≥ 1% Stage II–IIIA population (70)



Abbreviations: CIT, cancer immunotherapy; mAb, monoclonal antibody; TKI, tyrosine kinase inhibitor.

B.2.7 Subgroup analysis

The generalisability of the observed DFS treatment effect with atezolizumab relative to BSC in the PD-L1 ≥ 1% TC Stage II–IIIA population was investigated in pre-defined subgroups based on key baseline demographics, baseline disease characteristics and biomarker status. Results from the PD-L1 ≥ 1% TC Stage II–IIIA key patient population are presented below.

See Appendix H for subgroup analysis in all randomised Stage II–IIIA and the ITT populations.

B.2.7.1 DFS in the PD-L1 ≥ 1% TC Stage II–IIIA population

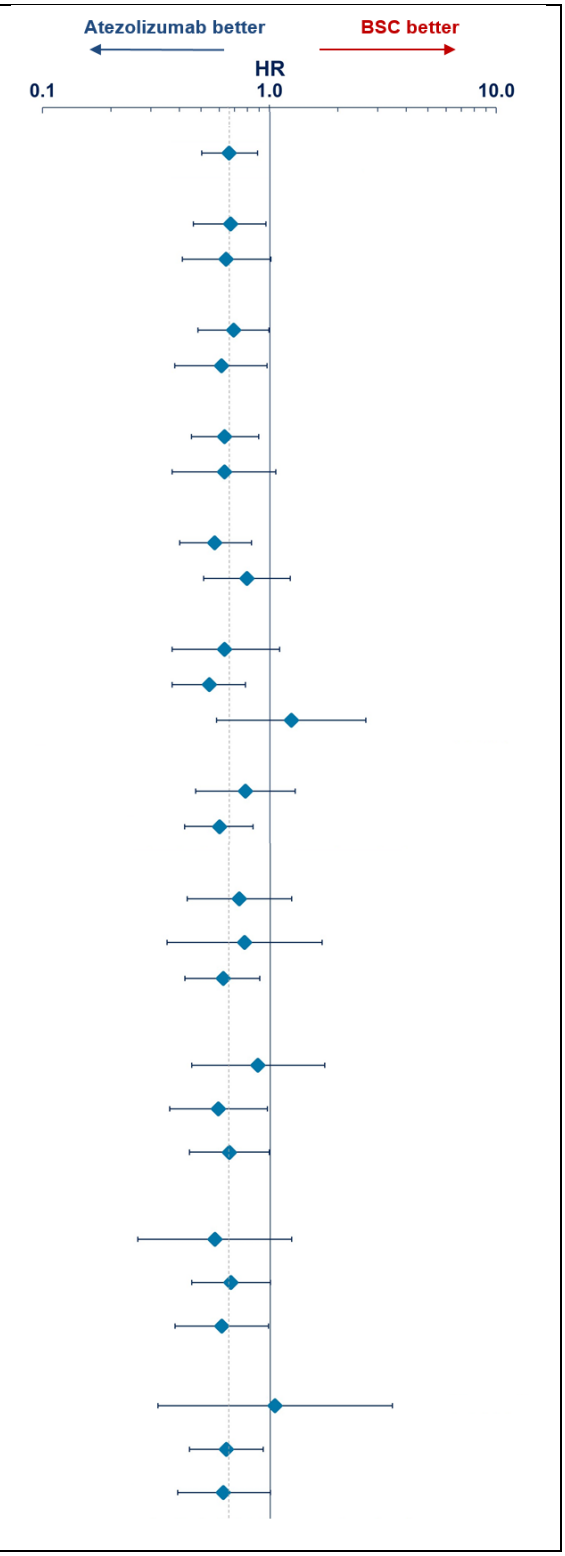
In the subgroup analyses, the atezolizumab treatment effect on DFS was consistent across the majority of pre-defined subgroups, and consistent with the benefit observed in the overall PD-L1 ≥ 1% TC Stage II–IIIA population (Table 10). Patients who were current smokers or treated with cisplatin + gemcitabine did not show improved DFS with atezolizumab compared to BSC (Appendix H). However, results for these subgroups should be interpreted with caution due to the small sample size.

Patients with ALK+ NSCLC in the PD-L1 ≥ 1% TC Stage II–IIIA population did not appear to benefit from atezolizumab compared with BSC. While the data shown in the DFS forest plot suggest that EGFR+ patients in the PD-L1 ≥ 1% TC Stage II–IIIA population may experience a benefit from adjuvant atezolizumab after chemotherapy, the ADAURA trial has already established adjuvant osimertinib as the standard of care for these patients. In addition, due to the small sample sizes for EGFR/ALK+ patients and the wide confidence intervals observed, it is insufficient to fully characterise the treatment effect and draw conclusions on the risk/benefit profile for adjuvant atezolizumab in these populations.

Table 10: Subgroup analysis of DFS in the PD-L1 ≥ 1%[a] TC Stage II–IIIA population by disease characteristics

Subgroup	n	HR (95% CI)[b]
All patients	476	0.66 (0.50, 0.88)
Age		
<65 y	287	0.67 (0.46, 0.96)
≥65 y	189	0.64 (0.41, 1.01)
Sex		
Male	318	0.69 (0.48, 0.99)
Female	158	0.61 (0.38, 0.97)
Race		
White	328	0.63 (0.45, 0.89)
Asian	134	0.63 (0.37, 1.06)
ECOG PS		
0	265	0.57 (0.40, 0.83)
1	209	0.79 (0.51, 1.23)
Tabaco use history		
Never	92	0.63 (0.37, 1.10)
Previous	309	0.54 (0.37, 0.78)
Current	75	1.24 (0.58, 2.64)
Histology		
Squamous	181	0.78 (0.47, 1.29)
Non-squamous	295	0.60 (0.42, 0.84)
Stage		
IIA	161	0.73 (0.43. 1.24)
IIB	83	0.77 (0.35, 1.69)
IIIA	232	0.62 (0.42, 0.90)
Regional lymph node stage (pN)		
N0	106	0.88 (0.45, 1.74)
N1	194	0.59 (0.36, 0.97)
N2	176	0.66 (0.44, 0.99)
EGFR mutation status		

Yes	43	0.57 (0.26, 1.24)
No	248	0.67 (0.45, 1.00)
Unknown[c]	185	0.61 (0.38, 0.98)
ALK rearrangement status		
Yes	23	1.05 (0.32, 3.45)
No	254	0.64 (0.44, 0.93)
Unknown[c]	199	0.62 (0.39, 1.00)



[a] Per SP263 assay. [b] Stratified for all patients; unstratified for all other subgroups. [c] 89.2% and 80.7% of patients in the ITT population with unknown EGFR and or ALK status, respectively, had squamous NSCLC and were not required to undergo local or central testing.
Clinical data cut-off date (CCOD): 21 Jan 2021

B.2.7.2 DFS in the all randomised Stage II–IIIA population, with and without EGFR/ALK+ disease

At the time of IMpower010 study design and initiation in 2015, patients with EGFR/ALK+ NSCLC were enrolled as efficacy of anti-PD-L1 therapies in these subgroups were unknown, hence there was no clear rationale for excluding these populations. Nevertheless, central testing for EGFR and ALK mutations was conducted for patients with non-squamous histology where tissue was available, and most of these patients (approximately 81%) had a confirmed EGFR or ALK status.

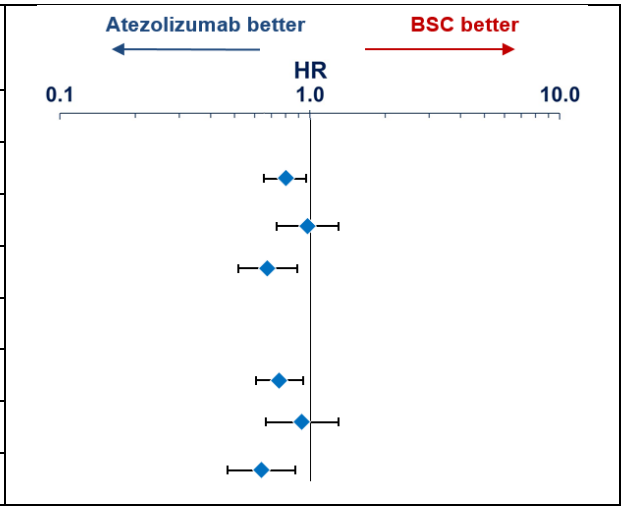
Adjuvant osimertinib is now licensed for EGFR+ early NSCLC following resection (41) and represents a new standard of care for these patients. Other Phase III studies, such as ALINA, are underway to investigate the use of targeted therapies in the adjuvant setting for ALK+ early NSCLC (71).

[redacted]. However, the data below presents the DFS benefit in the population, excluding patients with EGFR/ALK+ disease, to better reflect the target population for the IMpower010 regimen. It is also in line with clinical expert opinion where the IMpower010 regimen is unlikely to be used in place of adjuvant osimertinib in EGFR+ NSCLC patients.

In this exploratory, post-hoc analysis of the PD-L1 TC ≥ 1% Stage II–IIIA population, the DFS HR appeared to improve further in favour of atezolizumab when EGFR/ALK+ patients were excluded (HR = 0.62; 95% CI: 0.45, 0.86), compared to when they were included (HR = 0.66; 95% CI: 0.50, 0.88) (Table 11).

Table 11: Subgroup analysis of DFS by EGFR/ALK+ disease status

Subgroup	n	HR (95% CI)[a,b]
Including EGFR/ALK+		
All patients	882	0.79 (0.64, 0.96)
TC <1%[c]	383	0.97 (0.72, 1.31)
TC ≥1%	476	0.66 (0.50, 0.88)
Excluding EGFR/ALK+		
All patients	743	0.74 (0.59, 0.93)
TC <1%	312	0.92 (0.65, 1.30)
TC ≥ 1%	410	0.62 (0.45, 0.86)



[a] Per SP263 assay. [b] Stratified for all patients and PD-L1 TC ≥ 1%; unstratified for all other subgroups. [c] DFS analyses in the PD-L1 TC <1% were exploratory.

B.2.8 Meta-analysis

B.2.9 Indirect and mixed treatment comparisons

No indirect treatment comparisons (ITCs) were carried out. The IMpower010 trial included relevant comparators.

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.

B.2.10.1 Overview of safety

An overview of the key safety results is provided in

Table 12**. The key findings are as follows:**

- **Atezolizumab was well tolerated and safety data were consistent with its well-established safety profile. No new or unexpected safety signals were identified for atezolizumab in this study.**
- **As expected, adverse events (AEs) were more frequent across all categories (including all grade AEs, Grade 3-4 AEs, and serious AEs (SAEs) in the atezolizumab arm compared to the BSC arm, as the latter was comprised of active monitoring only.**
- **The incidence of Grade 5 AEs was 1.6% (8 patients) in the atezolizumab arm and 0.6% (3 patients) in the BSC arm. These events were distributed across several system organ class (SOC). Of the events in the atezolizumab arm, four were considered by the investigator to be treatment-related.**
- **Adverse events of special interest (AESIs) were more frequent in the atezolizumab arm compared to the BSC arm (51.7% vs 9.5%), and the most common were hepatic laboratory abnormalities, rash, and hypothyroidism.**

The majority of AESIs were of Grade 1-2 severity, and were generally manageable by withholding atezolizumab and/or appropriate treatment.

Table 12: Safety summary (safety-evaluable population)

	Atezolizumab (n=495)	BSC (n=495)
Total number of patients with at least one AE, n (%)	459 (92.7)	350 (70.7)
Total number of events, n	[redacted]	[redacted]
Total number of patients with at least one, n (%)		
AE with fatal outcome	8 (1.6)	3 (0.6)
Related AE with fatal outcome	4 (0.8)	0
Serious AE	87 (17.6)	42 (8.5)
Related Serious AE	37 (7.5)	0
Grade 3-4 AE	108 (21.8)	57 (11.5)
Related Grade 3-4 AE	53 (10.7)	0
Related AE	[redacted]	[redacted]
AE leading to dose interruption of atezolizumab	142 (28.7)	0
AE leading to atezolizumab discontinuation	90 (18.2)	0
Total number of patients with at least one AESI, n (%)	256 (51.7)	47 (9.5)
Total number of AESIs, n	[redacted]	[redacted]
Total number of patients with at least one, n (%)		
AESI with fatal outcome	[redacted]	[redacted]
Related AESI with fatal outcome	[redacted]	[redacted]
Serious AESI	[redacted]	[redacted]
Related Serious AESI	[redacted]	[redacted]
Grade 3-4 AESI	[redacted]	[redacted]
Related Grade 3-4 AESI	[redacted]	[redacted]
Related AESI	[redacted]	[redacted]
AESI leading to dose interruption of atezolizumab	[redacted]	[redacted]
AESI leading to atezolizumab discontinuation	[redacted]	[redacted]

Abbreviations: AE, adverse event; AESI, adverse event of special interest.

B.2.10.2 Adverse events (AEs)

The proportion of patients with at least one AE was higher in the atezolizumab arm (92.7%) than the BSC arm (70.7%) (

Table 12).

The most common (≥ 20% of patients in either arm) SOC in which AEs were reported (atezolizumab vs BSC, respectively) were:

- Infections and infestations ([redacted]

- Respiratory, thoracic and mediastinal disorders ([redacted]
- General disorders and administration site conditions ([redacted]
- Investigations ([redacted]
- Gastrointestinal disorders ([redacted]
- Musculoskeletal and connective tissue disorders ([redacted]
- Nervous system disorders ([redacted]
- Skin and subcutaneous tissue disorders ([redacted]

The AEs by preferred term (PT) with a notable difference (≥ 5%) between the arms are shown in Table 13. While there were differences between arms, all events presented are consistent with the known safety profile for atezolizumab.

Table 13: AEs with a difference of at least 5% between treatment arms by preferred term (safety-evaluable population)

MedDRA Preferred Terms	Atezolizumab (n=495)	BSC (n=495)
Number of occurrences, n (%)		
Arthralgia	[redacted]	[redacted]
Pyrexia	[redacted]	[redacted]
Alanine aminotransferase (ALT) increased	[redacted]	[redacted]
Aspartate aminotransferase (AST) increased	[redacted]	[redacted]
Hypothyroidism	[redacted]	[redacted]
Pruritus	[redacted]	[redacted]
Rash	[redacted]	[redacted]
Diarrhoea	[redacted]	[redacted]
Hyperthyroidism	[redacted]	[redacted]

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.

Serious adverse events (SAEs)

The proportion of patients with at least one SAE was higher in the atezolizumab arm (17.6%) than in the BSC arm (8.5%). 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.

Treatment-related AEs

The proportion of patients with atezolizumab-related AEs was 67.7% (

Table 12). 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%).

Treatment-related Grade 3–4 AEs in the PD-L1 ≥ 1% TC Stage II–IIIA population

In the safety evaluable population, the proportion of patients with atezolizumab-related Grade 3–4 AEs was 10.7% (

Table 12). This was comparable to results observed in the PD-L1 ≥ 1% TC Stage II–IIIA population (patient group of interest) at 14.8% (Table 14). In this patient population, the most common atezolizumab-related Grade 3-4 AEs were abnormal hepatic function, pneumonitis, and rash (all at 1.2%).

Table 14: Treatment-related Grade 3–4 AEs/SAEs (PD-L1 ≥ 1% TC Stage II–IIIA population)

	Atezolizumab (n=244)*
Total number of patients with at least one AE, n (%)	36 (14.8)
Number of occurrences of Grade 3-4 AEs/SAEs, n (%)	
Alanine aminotransferase increased	[redacted]
Aspartate aminotransferase increased	[redacted]
Asthenia	[redacted]
Axonal neuropathy	[redacted]
Colitis	[redacted]
Demyelinating polyneuropathy	[redacted]
Diarrhoea	[redacted]
Drug eruption	[redacted]
Drug-induced liver injury	[redacted]
Dyspepsia	[redacted]
Encephalitis	[redacted]
Gait disturbance	[redacted]
Gastritis	[redacted]
Genital rash	[redacted]
Hepatic function abnormal	[redacted]
Hyperglycaemia	[redacted]
Hypersensitivity	[redacted]
Hyponatraemia	[redacted]

	Immune-mediated adverse reaction	[redacted]
	Inappropriate antidiuretic hormone secretion	[redacted]
	Interstitial lung disease	[redacted]
	Leukopenia	[redacted]
	Meningitis	[redacted]
	Multiple organ dysfunction syndrome	[redacted]
	Myalgia	[redacted]
	Myocarditis	[redacted]
	Neuropathy peripheral	[redacted]
	Neutropenia	[redacted]
	Parapsoriasis	[redacted]
	Platelet count decreased	[redacted]
	Pneumonia	[redacted]
	Pneumonitis	[redacted]
	Pyrexia	[redacted]
	Rash	[redacted]
	Rash maculo-papular	[redacted]
	Sarcoidosis	[redacted]
	Secondary adrenocortical insufficiency	[redacted]
	Septic shock	[redacted]
	Thrombocytopenia	[redacted]
	Vomiting	[redacted]

*The difference in patient population (n=244 vs n=248) was due to four patients not receiving at least one dose of atezolizumab after randomisation.
Abbreviations: AE, adverse event; SAE, serious adverse event.

AEs that led to withdrawal of treatment or dose interruption

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 [redacted].

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 [redacted]

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.

Overall, the proportion of patients who experienced AESIs was [redacted] in the atezolizumab arm and [redacted] in the BSC arm (**Error! Not a valid bookmark self-reference.**). The majority of AESIs were of Grade 1–2 severity. Grade 3–4 AESIs were reported in [redacted] ([redacted] patients) in the atezolizumab arm and [redacted] ([redacted] 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 [redacted] ([redacted] patients) in the atezolizumab arm and [redacted] ([redacted] patients) in the BSC arm. The proportion of patients in the atezolizumab arm who experienced AESIs leading to treatment discontinuation and dose interruption was [redacted] and [redacted] 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.

Table 15: Overview of AESIs (safety-evaluable population)

	Atezolizumab (n=495)	BSC (n=495)
Total number of patients with at least one AE, n (%)	256 (51.7)	47 (9.5)
Total number of events, n	[redacted]	[redacted]
Total number of patients with at least one, n (%)		
AE with fatal outcome	[redacted]	[redacted]
Related AE with fatal outcome	[redacted]	[redacted]
Serious AE	[redacted]	[redacted]
Related Serious AE	[redacted]	[redacted]
Grade 3-4 AE	[redacted]	[redacted]
Related Grade 3-4 AE	[redacted]	[redacted]
Related AE	[redacted]	[redacted]
AE leading to dose interruption of atezolizumab	[redacted]	[redacted]
AE leading to atezolizumab discontinuation	[redacted]	[redacted]

Investigator text for AEs encoded using MedDRA version 23.1.
Includes adverse events occurring on or after the start of treatment in randomisation period.

B.2.10.3 Deaths

At the CCOD on 21 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 16). 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 (1.6% atezolizumab vs. 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 (to either chemotherapy or atezolizumab). 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 16: Deaths and causes of death (safety-evaluable patients)

	Atezolizumab (n=495)	BSC (n=495)	All patients (N=990)
All deaths, n (%)	[redacted]	[redacted]	[redacted]
≤ 30 days from last study treatment/safety visit, n (%)	[redacted]	[redacted]	[redacted]
> 30 days from last study treatment/safety visit, n (%)	[redacted]	[redacted]	[redacted]
Primary cause of death, n (%)			
Adverse event	[redacted]	[redacted]	[redacted]
Disease relapse	[redacted]	[redacted]	[redacted]
Other	[redacted]	[redacted]	[redacted]

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

B.2.11 Ongoing studies

Analyses in IMpower010 are event-driven; therefore, it is difficult to provide exact timings on when further analyses will become available. However, patients will continue to be followed up. Final analyses are planned for DFS in the ITT population (which did not cross the threshold for significance at the DFS interim analysis) and OS (which were immature at the time of the interim DFS analysis).

B.2.12 Innovation

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 (21).

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 (31). Adjuvant chemotherapy can provide further benefit; however, it only provides a modest 5% improvement in OS at 5 years (HR 0.89) (33). Aside from chemotherapy, no other adjuvant treatment options are available other than osimertinib for patients with EGFR+ early NSCLC (66), however EGFR+ patients are only a small subset of NSCLC patients (72-74).

Though surgery represents a potential cure for resectable early NSCLC patients, recurrence rates remain high, with an approximate rate of recurrence of 41–68% for patients with Stage I–III NSCLC. Upon locoregional recurrence, patients may receive a potentially curative treatment with chemo-radiation. However, if patients progress to metastatic disease, the aim of treatment is no longer cure, but to prolong life and reduce disease burden. Additionally, as NHS England implement lung cancer screening programmes, the proportion of early NSCLC patients are likely to increase in the UK. This further highlights the urgent need for more effective treatment options, especially in this potentially curative setting.

Cancer immunotherapy alone, or in combination with chemotherapy, has demonstrated an overall survival benefit in unresectable, Stage III NSCLC, and in Stage IV NSCLC. Recently, trials of cancer immunotherapy in the neoadjuvant setting for NSCLC have also been positive (75, 76). In the adjuvant setting, atezolizumab offers an innovative approach to therapy. By targeting PD-L1 expression, anti-tumour mechanisms are reactivated. This stimulates T-cells to monitor for residual tumours cells, potentially eliminating the formation of micro-metastases following complete surgical resection. This results in a prolonged anti-tumour immune response, to reduce the risk of recurrence.

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. Atezolizumab reduced the risk of recurrence, new primary NSCLC, or death by 34% (DFS HR 0.66) compared to BSC, in the PD-L1 ≥ 1% Stage II–IIIA population. A consistent DFS benefit was seen across key clinical subgroups in the PD-L1 TC ≥ 1% Stage II–IIIA population in favour of atezolizumab, including high-risk patients, such as those with node-positive disease. In addition, there were no new safety signals for atezolizumab in IMpower010, with the safety profile consistent with that established for atezolizumab monotherapy (77-79).

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 positive 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.

Due to the positive results of IMpower010 and the potential for a paradigm shift in the management of early NSCLC, adjuvant atezolizumab was granted priority review under the FDAs Real-Time Oncology Review programme. Which has led to the recent FDA approval of atezolizumab for the adjuvant treatment of Stage II–IIIA NSCLC, whose tumours have PD-L1 expression on ≥ 1% of tumour cells, following resection and platinum-based chemotherapy. Therefore, atezolizumab is the first and only cancer immunotherapy currently available for adjuvant treatment of NSCLC. The review was conducted under the Project Orbis initiative due to its innovative and clinical significance. In addition, atezolizumab has been granted an 'Innovation Passport' through MHRA's Innovative Licensing and Access Pathway (ILAP).

[redacted]

B.2.13 Interpretation of clinical effectiveness and safety evidence

B.2.13.1 Atezolizumab vs BSC

The IMpower010 trial met its primary endpoint, demonstrating statistically significant and clinically meaningful DFS improvement in patients receiving adjuvant atezolizumab compared with BSC in the PD-L1 TC ≥ 1% Stage II–IIIA population (key patient population in this submission).

The aim of offering adjuvant atezolizumab after chemotherapy is to prevent or delay relapse. In the primary analysis, the efficacy boundary for patients with PD-L1 ≥ 1% Stage II–IIIA NSCLC was crossed, demonstrating a 34% reduction in risk of disease recurrence, formation of new NSCLC, or death (DFS HR 0.66) in favour of atezolizumab compared with BSC.

Although immature, the secondary endpoint of OS demonstrated a trend indicating a 23% reduction in risk of death for atezolizumab compared with BSC (OS HR 0.77; 95% CI: 0.51, 1.17), in the PD-L1 ≥ 1% Stage II–IIIA population. These data will require longer-term follow-up and patients will be monitored as survival data matures.

Due to the high recurrence rates in early NSCLC following resection, it is clinically important to understand when relapse occurs, as delaying relapse is associated with a positive impact for patients. In the exploratory post-hoc analysis, 29% of patients experienced relapse for atezolizumab compared with 45% in the BSC arm. This is reflected in the DFS benefit observed in the PD-L1 ≥ 1% Stage II–IIIA population. Amongst patients who experienced relapse, those in the atezolizumab arm appeared to have a longer time to relapse than those in the BSC arm, regardless whether the relapse was locoregional or distant. With a median time to any relapse of 17.6 months (0.7–42.3) in the atezolizumab arm compared to 10.9 months (1.3–37.3) in the BSC arm (post-hoc analysis).

Among patients who experienced disease relapse, it is important to understand the impact of how adjuvant treatment with atezolizumab may affect subsequent treatment paradigms. Post-relapse CIT treatment was more common in BSC compared with atezolizumab (BSC 35% vs atezolizumab 11%), suggesting the use of adjuvant atezolizumab decreased the need for subsequent CIT treatments.

In the exploratory, post-hoc analysis of the PD-L1 ≥ 1% Stage II–IIIA population, the DFS HR appeared to be better for atezolizumab when excluding EGFR/ALK+ patients (Excluding: HR = 0.62; 95% CI: 0.45, 0.86; Including: HR = 0.66; 95% CI: 0.50, 0.88), reflecting the target patient population for the IMpower010 regimen. However, these data should be interpreted with caution due to the small number of patients with a positive EGFR (n=43) and ALK (n=23) status.

The safety profile for atezolizumab monotherapy was consistent with previous clinical studies (38, 60, 64, 80), and no new safety signals were identified. Immune-mediated adverse events occurred more frequently in patients treated with atezolizumab, which was expected as these were known risks with checkpoint inhibitors (80). Approximately half of the adverse events that led to discontinuation were Grade 1–2, which might indicate that investigators had a lower threshold for discontinuing treatment in patients with early NSCLC due to treatment-related toxicity compared to what might be observed in the metastatic setting. Overall, more toxicity was observed in atezolizumab compared with BSC, as expected since the latter was comprised of active monitoring only. 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 PD-L1 ≥ 1% Stage II–IIIA population appeared to be favourable. 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.2.13.2 Strengths and limitations of IMpower010

The IMpower010 study was a robust Phase III study that included a large global patient population with well-balanced baselines characteristics between treatment arms, standardised adjuvant chemotherapy, and standardised endpoints powered to show differences between treatment arms.

In terms of limitations, IMpower010 included an open-label design and lack of placebo control. The open-label study design was chosen for safety considerations, in the context of the standard of care at the time. To minimise the potential bias of the open-label design, Good Clinical Practice (GCP), NCCN and ESMO guidelines were adhered to ensure standard patient care. A placebo arm was not included in the adjuvant setting to avoid placing the burden of one year of 3-weekly intravenous treatment visits on patients who had undergone potentially curative resection and adjuvant chemotherapy.

In addition, the SP142 assay was used during screening and enrolment, even though it might be less sensitive on TC in NSCLC than other PD-L1 assays. Therefore, in line with the changing landscape of PD-L1 testing, the SP263 PD-L1 IHC assay was used to define the primary analysis population. However, the proportion of baseline PD-L1 expression by SP263 and baseline characteristics were similar and well-balanced between study arms and within the Stage II–IIIA PD-L1 TC ≥ 1% group (Appendix H). This proves that the analyses 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.3 Cost effectiveness

B.3.1 Published cost effectiveness studies

- **A total of 24 full publications considering interventions for early NSCLC were identified**
- **There was a lack of suitable studies reporting utility values for early NSCLC**
- **In the 14 publications reporting use of an economic model, the model structures were complex and included a variety of health states**

A systematic literature review (SLR) was conducted to identify published cost effectiveness studies in the adjuvant treatment NSCLC patients whose tumours have PD-L1 expression on ≥ 1% TC. Detailed descriptions of the search strategy and extraction methods, as well as an overview of the identified studies are provided in Appendix J.

B.3.1.1 Summary of identified studies and results

A total of 35 publications were identified which met the eligibility criteria of the economic evaluation SLR (full publications, n=24; conference abstracts, n=10; NICE guidelines, n=1). Due to limited reporting and the difficulties associated with meaningful quality assessment, conference abstracts were isolated and tagged; a list of these studies are provided in Appendix J and they are not considered further here. No relevant previous HTA submissions in early NSCLC were identified by the review.

Of the 24 full publications considering interventions for early NSCLC, the majority of studies were cost-utility analyses reporting the cost per quality adjusted life year (QALY) gained for the interventions of interest (n=14). The most commonly cited published sources of utility values across these studies were Doyle et al 2008 (81) and Nafees et al 2008 (82); however,

both of these studies report utilities for health states associated with advanced/metastatic stages of NSCLC. This indicated a lack of suitable utility values specifically for patients with early NSCLC for use in economic evaluations.

A total of 14 published economic evaluations identified in the SLR reported use of a model. A high level of variation was observed across the studies with regard to the selected disease states and pathways used in the models. 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, metastasis/distant recurrence/advanced disease, no evidence of disease (NED), progression free survival, progression, treatment with radiotherapy, and treatment-related adverse events (AEs) (including dysphagia, dyspnoea, pneumonitis, oesophagitis). The remaining 10 studies were trial-based analyses and did not report details of a model.

Further details and results for the identified cost effectiveness studies and abstracts can be found in Appendix J. 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

- **A *de novo* economic model was built which reflects the disease pathway for early NSCLC**
- **The population of interest is adult patients with NSCLC whose tumours have a PD-L1 expression of ≥ 1% TC and whose disease has not progressed following platinum-based adjuvant chemotherapy, following complete resection**
- **A Markov model consisting of five health states was developed: "disease-free survival"; "locoregional 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 were intended to inform the structure for the model used in the economic analysis. However, there is a lack of consensus relating to modelling approaches and model structures/frameworks and no literature were

identified on atezolizumab in the adjuvant setting for patients with Stage II–IIIA NSCLC. Therefore, a *de novo* economic model was built to inform decision making, which reflects the disease pathway in this therapeutic area.

B.3.2.1 Patient population

The cost effectiveness model (CEM) compared the clinical and economic outcomes of atezolizumab versus BSC[2] as [redacted] with the patient population described in the final scope of this appraisal ("adults with fully resected NSCLC after adjuvant cisplatin-based chemotherapy").

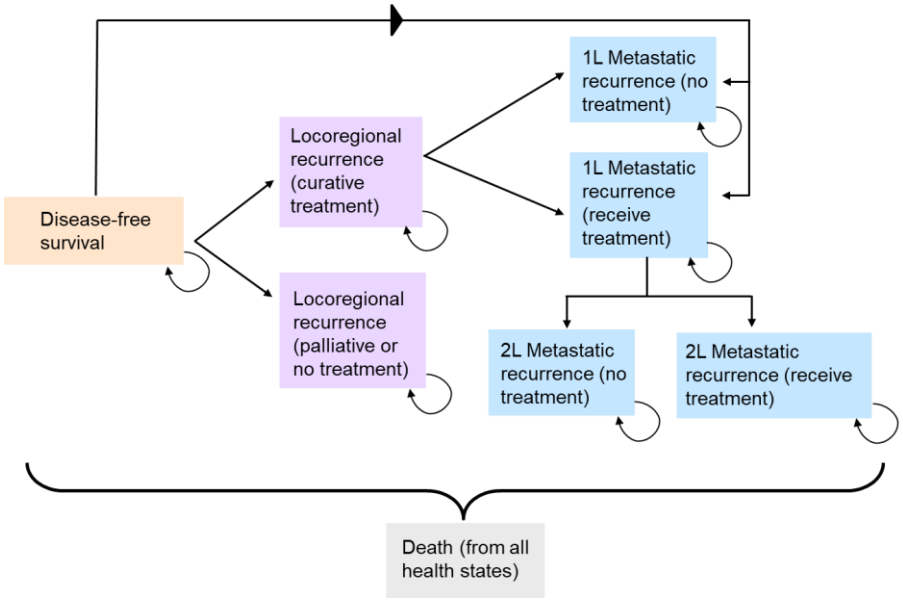
B.3.2.2 Model structure

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[3] and Health Economists[4] provided valuable insights on the model's validity (i.e. model structure, assumptions, and inputs values) during model conceptualisation and post-model build. Their feedback confirmed that the structure of the model accurately represents the disease and treatment pathways of early NSCLC. In addition, the SLR carried out to identify relevant economic evaluations (see Appendix J) noted that the traditional three-state model was not generally used and tended to use more complex structures consisting a variety of alternative health states. Further details on model validation are outlined in Section 3.10.

The five health states in the economic model are "disease-free survival"; "locoregional recurrence"; "first-line metastatic recurrence"; "second-line metastatic recurrence"; "death". Figure 9 presents the model's structure and its five health states.

[2] Also referred to as 'active monitoring'.
[3] Four oncologists were consulted in April 2021
[4] Two health economists were consulted in April 2021

Figure 9: Model structure and health states



B.3.2.2.1 Health states

The possible transitions between each of the health states are described below. Where possible, health state transitions were based on the results of IMpower010. Transitions within progressed health states were based on best available sources of evidence, full details are outlined in Section B.3.3.6.

Disease-free survival

Patients entered the model in the DFS health state. Patients in the intervention arm received atezolizumab for 16 cycles (treatment duration ~1 year) and simultaneously received follow-up care for a maximum length of 5 years, while those in the BSC arm received follow-up care only. Each treatment cycle lasts approximately 3 weeks. Patients who had locoregional or metastatic recurrence, or died, transitioned to the locoregional recurrence, metastatic recurrence or death health states, respectively.

Locoregional recurrence

Patients transitioned to this health state from DFS if they had locoregional recurrence and could either receive treatment with curative intent, palliative intent or no treatment. During 1:1 consultations with UK clinical oncologists[5], they mentioned that some patients might have less reserve and less tolerance for radiotherapy and they would consider whether patients could withstand further treatment. Hence, the model accounted for patients who

[5] Two of the four oncologists who were consulted in April 2021

could not or might not choose to be treated, as this choice would affect the clinical and economic outcomes.

Patients on curative treatment for locoregional recurrence, who then developed metastatic recurrence or died, transitioned to the first line metastatic recurrence or death health states, respectively. Those on palliative treatment or no treatment could only progress to the death health state.

1L metastatic recurrence

Patients transitioned to this health state from DFS and locoregional recurrence if they had metastatic recurrence, 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.

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; when validating the model with UK clinical oncologists[6], 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.

[6] Four oncologists were consulted in April 2021

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 occur 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 ongoing osimertinib appraisal (ID3835) also uses a cycle length of ~4.35 weeks (83). The model applied half-cycle corrections to mitigate bias and assumed transitions across health states occur mid-cycle on average:

$$Survival_t = (survival_t + survival_{t+1})/2$$

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 (84). 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.3.5.2) and utility (Section B.3.4.3) 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 an ongoing appraisal of osimertinib for adjuvant treatment of EGFR mutation-positive NSCLC after complete tumour resection [ID3835] (83). Although focused on EGFR mutation-positive NSCLC, this is the only other NICE appraisal in a similar population for adjuvant treatment of NSCLC after resection. Consequently, we provide an overview of how the economic analysis of atezolizumab compared to the osimertinib for adjuvant treatment following early NSCLC in Table 17.

Table 17: Features of the economic analysis

	Ongoing appraisal	Current appraisal	
Factor	**Osimertinib TA ID3835**	**Chosen values**	**Justification**
Model structure	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	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 month	Aligned with previous NSCLC appraisals
Half-cycle correction	Yes	Yes	Aligned with previous NSCLC appraisals and to mitigate bias
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)	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	Aligned with NICE reference case.
Perspective (NHS/PSS)	Yes	Yes	Aligned with NICE reference case.
Treatment waning effect	Uncertain from the available committee papers	Included in scenario analysis	A five-year treatment effect was chosen as this aligns with previous NSCLC appraisals (TA531 (85), TA428 (86), TA557 (87), TA600 (88).

Source of utilities	EQ-5D-3L estimates from ADAURA37 (mapped from the SF-36), EQ-5D-3L estimates from FLAURA63 (mapped from the EORTC QLQ-C30) and published EQ-5D3L estimates from the literature (Labbé et al (89).	Utility sources identified via an SLR. Disease-free survival: Yang et al. 2014 Locoregional recurrence: Chouaid et al 2013 (curative), Van den Hout et al. 2006 (palliative) 1L metastatic recurrence : IMpower150 2L metastatic recurrence : IMpower150	Aligned with NICE reference case.
Source of costs	NHS reference costs 2018/2019, BNF, eMIT	NHS reference costs 2019/2020, 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 (1200 mg every 21 days; for 16 cycles or ~1 year), and the comparator, BSC (observation and regular scans for disease recurrence), in the IMpower010 trial are consistent with the final NICE scope outlined in Section B.1.1. The NSCLC population of interest is PD-L1 TC ≥ 1% Stage II–IIIA, as aligned with the [redacted]. Osimertinib is not included as a comparator, as this ongoing appraisal is for the Stage IB–IIIA population whose tumours have EGFR exon 19 deletions or exon 21 (L858R) substitution mutations and UK clinical oncologists advised that an immunotherapy is unlikely to be used in the PD-L1 TC ≥ 1% Stage II–IIIA population with EGFR mutations, if osimertinib is available. For this reason, we have included the cost effectiveness results for the PD-L1 TC ≥ 1% Stage II–IIIA, excluding EGFR mutation or ALK-positive population in Appendix N for consideration. Further details regarding the IMpower010 trial design are available in Section B.2.3.

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.3.3.3.5
  - Adjusted curves with five-year "cure" assumption
  - Introduced a ramping-up period to address the unrealistic "kink" in the DFS curve
  - 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 locoregional and metastatic health states, a survey of five UK clinical oncologists was undertaken**
- **Transition probabilities for locoregional and metastatic disease recurrences were obtained from published literature and NSCLC NICE appraisals**
- **As there were no Grade ≥ 3 treatment-related AEs with an incidence of ≥ 2% in the IMpower010 trial, no AEs from this trial were included in the economic model**
- **For the remaining health states, the following sources were used:**
  - **Locoregional recurrence – PACIFIC trial (TA578)**
  - **First-line metastatic recurrence – IMpower150 (TA584)**
  - **Second-line metastatic recurrence – OAK trial (TA520)**

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: 21 January 2021). 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 interim analysis data (CCOD: 21 January 2021) used in this economic model are for the PD-L1 TC ≥ 1% (SP263) subgroup in the Stage II–IIIA population. For health states not captured by the IMpower010 data (i.e. locoregional 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.

The IMpower010 trial is representative of early NSCLC patients who would be suitable for adjuvant atezolizumab therapy. Adjuvant chemotherapy (cisplatin plus vinorelbine, docetaxel, gemcitabine, or pemetrexed; based on investigator choice) within IMpower010 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. The trial median follow-up in the PD-L1 TC ≥ 1% Stage II–IIIA population is 32.8 months, with 35.5% and 46.1% of disease recurrence or death having occurred in the atezolizumab arm and BSC arm, respectively. 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 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 (90). 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

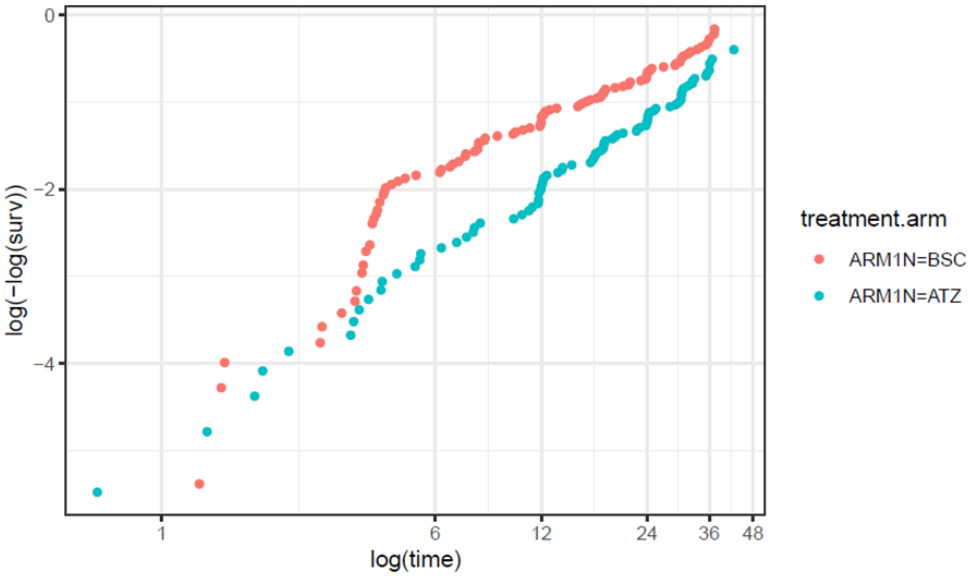
B.3.3.3.1 DFS as a surrogate for OS

Although there is no robust evidence on the correlation between DFS and OS for adjuvant treatment of early NSCLC, UK clinical oncologists noted that in the adjuvant setting, DFS is a suitable surrogate for OS. Meta-analyses by Mauguen et al. 2013 (91) 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 control arm 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 (92). However, Figure 10 shows that the curves separate then converge (the curves do cross over early on but this is not concerning due to the x-axis scale), and for this reason, the proportion hazards assumption does not hold.

Figure 10: Log-cumulative hazard plot (IMpower010, DFS, Stage II–IIIA, PD-L1+, by arm, 21 Jan 2021 data-cut)



NB: log(-log(survival).= log-cumulative hazard

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 (IMpower010, DFS, Stage II–IIIA, PD-L1+, by arm, 21 Jan 2021 data-cut)

Distribution	Atezolizumab arm				BSC arm			
	AIC (Rank)		BIC (Rank)		AIC (Rank)		BIC (Rank)	
Exponential	935.7	6	939.3	1	1028	5	1031	3
Weibull	933.7	2	940.7	3	1030	6	1036	6
Log-logistic	933.9	3	940.9	4	1025	3	1032	4
Log-normal	936.3	7	943.3	6	1019	2	1025	1
Gompertz	935.6	5	946.1	7	1016	1	1026	2
Generalised Gamma	935.1	4	942.1	5	1027	4	1034	5
Gamma	933.6	1	940.6	2	1030	6	1036	6

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.

B.3.3.3.4 Visual fit

Table 18 shows that there was no clearly best fitting distribution statistically. Figure 11 and Figure 12 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 11: Fit of estimated DFS to Kaplan-Meier plot across parametric models (IMpower010, DFS, Stage II–IIIA, PD-L1+, atezolizumab arm, 21 Jan 2021 data-cut)

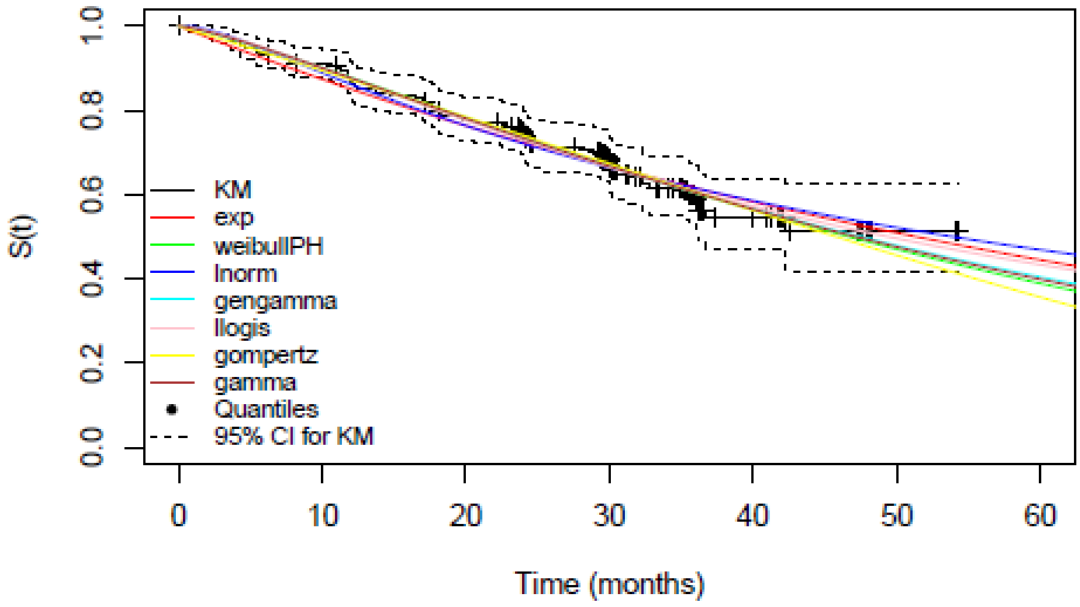


Figure 12: Fit of estimated DFS to Kaplan-Meier plot across parametric models (IMpower010, DFS, Stage II–IIIA, PD-L1+, BSC arm, 21 Jan 2021 data-cut)

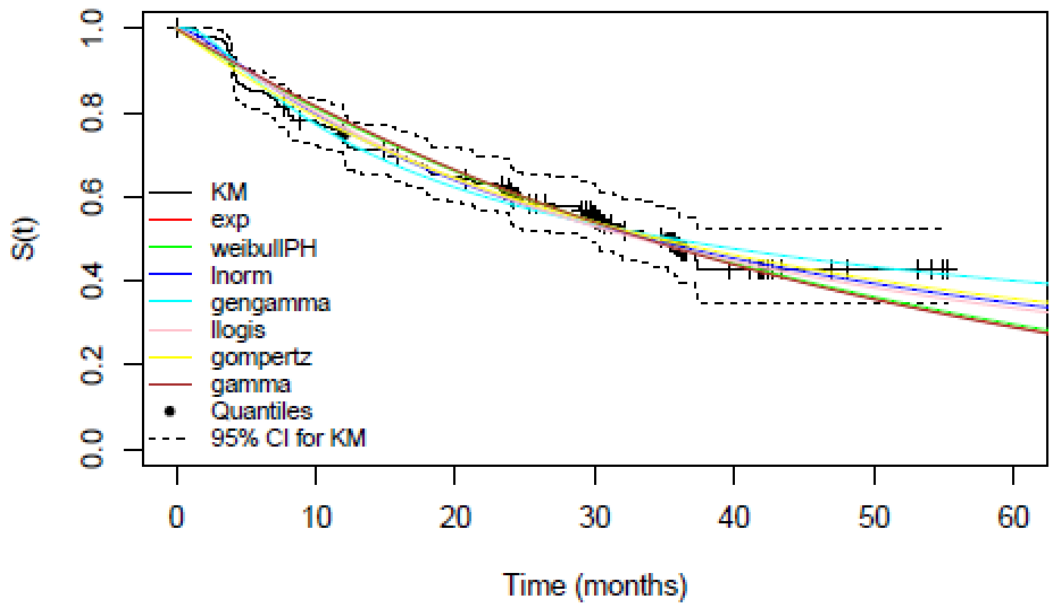


Figure 13 and Figure 14 presents a comparison of the extrapolation of DFS across the different parametric models beyond the follow-up of the trial (trial median follow-up: 32.8 months) (93).

Figure 13: Extrapolation of DFS across Parametric Models (IMpower010, DFS, Stage II–IIIA, PD-L1+, atezolizumab arm, 21 Jan 2021 data-cut)

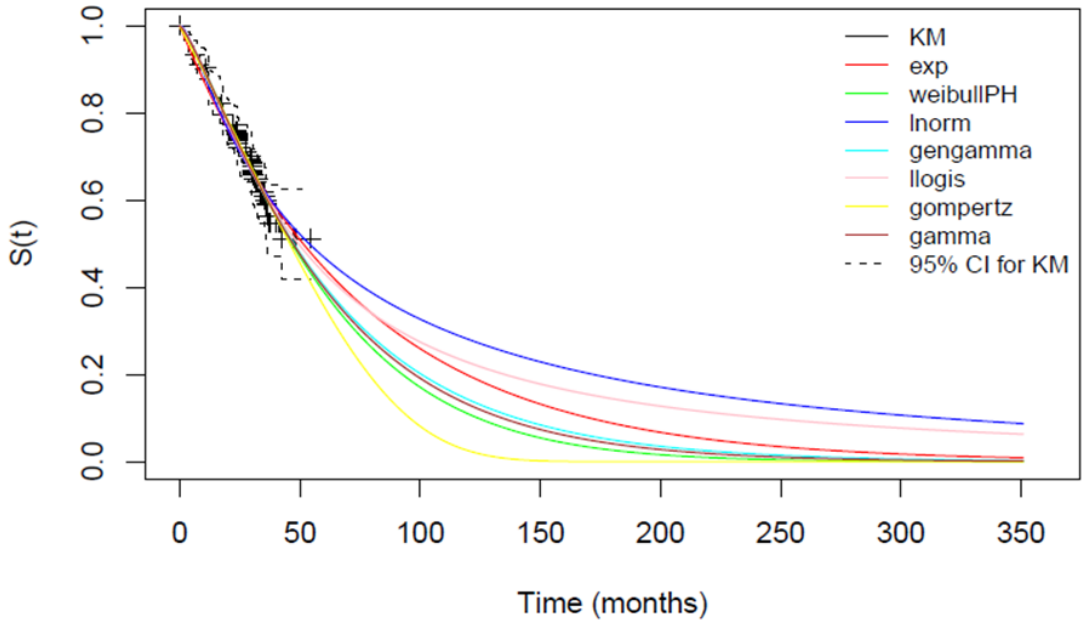
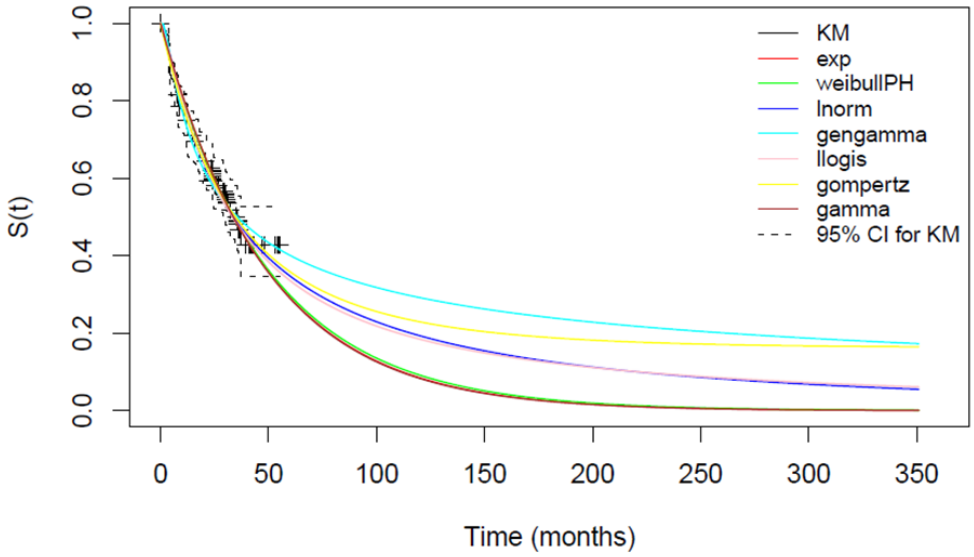


Figure 14: Extrapolation of DFS across parametric models (IMpower010, DFS, Stage II–IIIA, PD-L1+, BSC arm, 21 Jan 2021 data-cut)



A comparison of the DFS events at different time points was carried out. Table 19 presents the proportion of patients who did not experience a DFS event at 10, 20, and 30 years according to the parametric extrapolations of the Kaplan-Meier data. However, as these parametric curves only took into account the available trial data, it was not representative of the benefits of adjuvant chemotherapy and it underestimated DFS, as observed in the literature (explained in Section B.3.3.3.5).

Table 19: Expected proportion (%) patients who are event-free at 10, 20, and 30 years after treatment initiation – BSC arm

Distribution	Proportion (%) patients event-free after treatment initiation		
	10 Years	20 Years	30 Years
Exponential	[redacted]	[redacted]	[redacted]
Weibull	[redacted]	[redacted]	[redacted]
Log-logistic	[redacted]	[redacted]	[redacted]
Log-normal	[redacted]	[redacted]	[redacted]
Gompertz	[redacted]	[redacted]	[redacted]
Generalised-Gamma	[redacted]	[redacted]	[redacted]
Gamma	[redacted]	[redacted]	[redacted]

B.3.3.3.5 Literature and expert clinical opinion

There is a paucity of literature available reporting DFS in patients with early NSCLC. Through focussed literature searching, a handful of studies reporting data on DFS and OS in

the early NSCLC population were identified: Wood et al. 2021 (94), Chi et al. 2019 (95), Pignon et al. 2008 (33), and Non-Small Cell Lung Cancer Collaborative Group 1995 (96). One study, Pignon et al. 2008, was identified which reported DFS in patients with resected NSCLC. This was a pooled analysis of large trials of cisplatin-based adjuvant chemotherapy in patients with NSCLC and they estimated a 5-year DFS of approximately 40% for patients who received adjuvant chemotherapy. It also reported a 5-year OS of approximately 55% (33).

Chi et al. 2019 compared long-term OS of patients with early NSCLC after surgery versus stereotactic body radiotherapy (a cohort study of 104,709 patients in the US National Cancer Database). This reported a 5-year OS of 65% (in the 'with lymph node examination' population, which more closely represents the BSC arm of the IMpower010 trial than the 'without lymph node examination' population, according to the inclusion criteria of the IMpower010 trial). These literature were presented to clinical oncologists during 1:1 interviews and overall, they agreed with the lower overall survival estimates of around 50% at 5 years and 30% at 10 years, due to the IMpower010 population being stage II-IIIA patients[7]. Wood et al. 2021 was not considered as the patients have medically inoperable NSCLC, and would therefore have a worse outcome than the target patient population. In addition, Non-small Cell Lung Cancer Collaborative Group 1995 was ruled out, as this was considered out of date in terms of clinical practice (commented by a UK clinical oncologist).

UK clinical oncologists were consulted regarding the identified studies, Pignon et al. 2008, (five-year OS of approximately 55%) and Chi et al. 2019 (five-year OS of approximately 65%). They considered the Chi et al. figure to be an over-estimation.

In addition, Sonoda et al. 2019 (97) showed that approximately 6% of recurrences occurred after five years; this evidence was validated with clinical oncologists during 1:1 interviews[8]. The study also reported that an additional 2.5% patients developed a recurrence after 10 years ("ultra-late recurrences"). This suggests that the cure probability is approximately 91.5% and, therefore, an adjustment could be made to the parametric curves to assume that 91.5% of modelled patients are no longer at risk of cancer recurrence or cancer-related mortality after 5 years from treatment initiation. With this adjustment, only a small proportion of patients would progress from the DFS health state to locoregional or metastatic

[7] Three clinical oncologists were interviewed in August 2021 in 1:1 video calls
[8] Four clinical oncologists were interviewed in April 2021 in 1:1 video calls

recurrence every cycle after 5 years. The adjustment to the DFS curves is further discussed in Section B.3.3.4.

In summary, the literature identified, along with UK clinical expert opinion, support a five-year DFS for the BSC arm of around 40–50% and a five-year OS of around 55%. These were used to validate the model predictions and aid curve selection. DFS was used as a surrogate for OS in the economic model, which was validated with UK clinical experts as appropriate for early NSCLC. Therefore, the DFS curves were adjusted by anchoring the OS values to literature-reported OS.

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**
4. **Introduced a ramping-up period to address the unrealistic "kink" in the DFS curve**
5. **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 March and April 2021, which was used to inform the inputs of the model. The full report is provided in Appendix M.

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:

1. Cure Adjustment: the model used IMpower010 data for a time-period where recurrences occurred more frequently, due to the short follow-up. This could lead to the model overestimating the proportion of patients who have recurrences for time points beyond the trial follow-up. Therefore, the model allowed the proportion of patients who were not at risk of a DFS event to linearly increase from year 3 and reach a maximum of 91.5% at

year 6 to prevent this from occurring[9]. These estimates came from Sonoda et al. as mentioned in Section B.3.3.3.5

2. Mortality Adjustment: the model calculated the probability of death in each cycle using IMpower010 data on the number of patients who had death as their first event and median follow-up of patients. Patients in the model who were not considered cured confront this probability of death. However, the probability is time-invariant which leads to a point in the cycle at which its value was smaller than the probability of death in the general population. The model does not allow the probability of an uncured patient dying to be smaller than that of an individual from the general population (refer to Section 3.3.5 for more details on implementation)[10]. Patients in the model considered cured were not at risk of cancer-related death and, therefore, revert to the general population probability of death. However, 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)[11] 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) (98) and validated by UK clinicians[12].
3. Treatment Effect: the model allows the treatment effect of atezolizumab to decrease over time. The probability of a patient in the atezolizumab arm experiencing an event equalled the probability of a patient in the BSC arm experiencing an event if the model allowed this to occur. There is currently lack of data from IMpower010 and external evidence to inform at what 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 (85), TA428 (99), TA557 (87), TA600 (100).

Figure 15 and Figure 16 shows that without these adjustments, the proportion of patients in DFS is lower.

[9] Clinical oncologists confirmed that they might consider patients cured if they have been disease-free for 5 years in 1:1 interviews held April 2021.
[10] The model used results from the general population UK lifetable.
[11] 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 M).
[12] Three clinical oncologists were interviewed in August 2021 in 1:1 video calls.

Figure 15: DFS curve extrapolations for BSC arm – left) unadjusted; right) adjusted

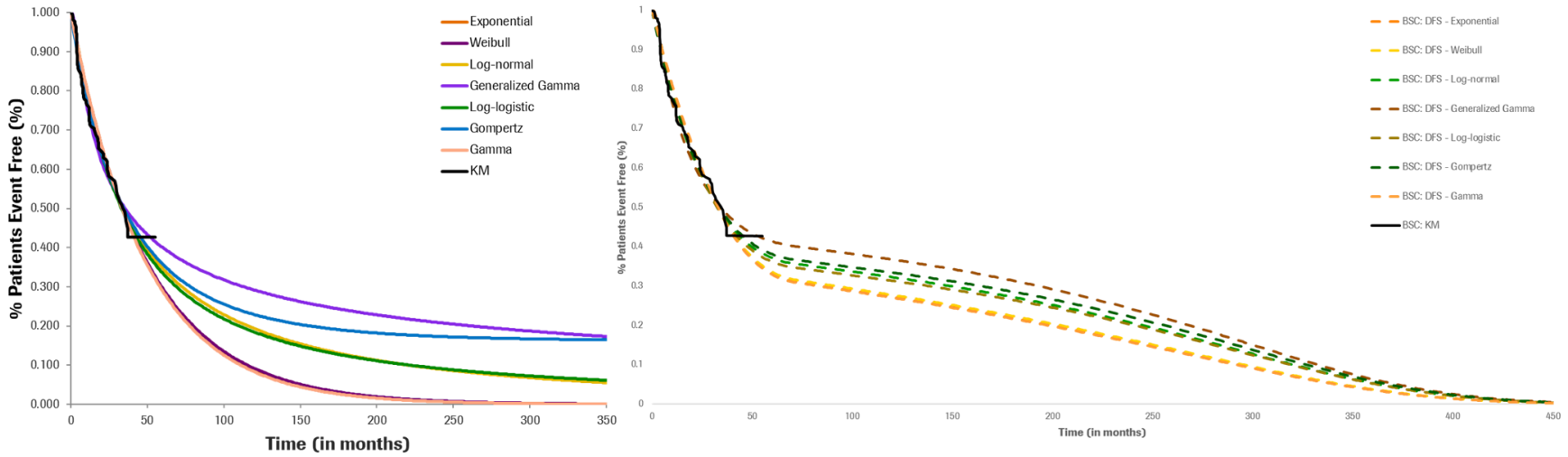
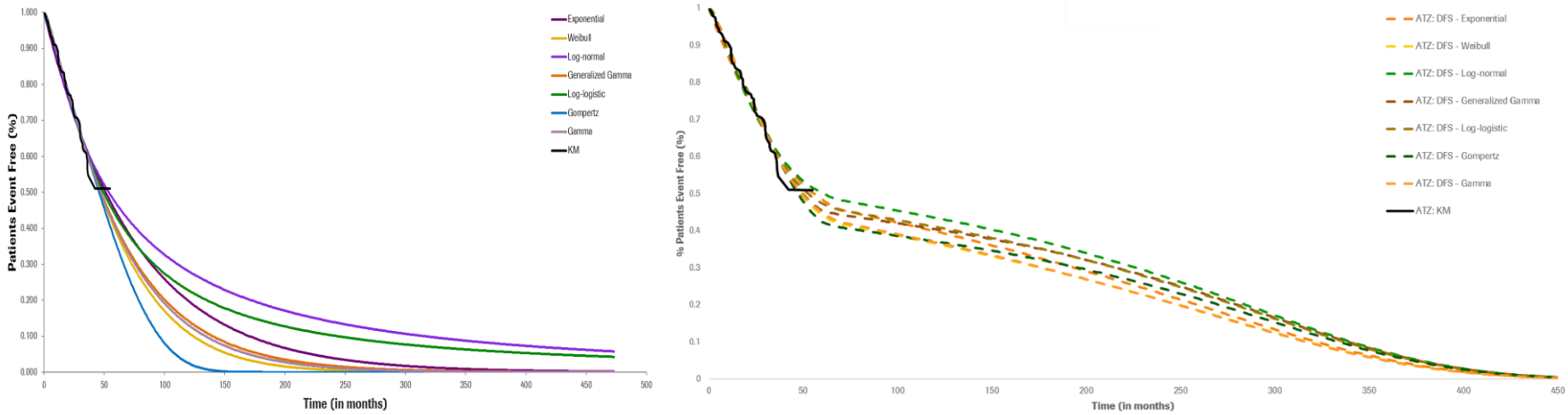


Figure 16: DFS curve extrapolations for atezolizumab arm – left) unadjusted; right) adjusted



B.3.3.4.1 Clinical expert opinion

Figure 17 and Figure 18 shows the DFS curve extrapolations in the BSC arm and atezolizumab arm, respectively.

Figure 17: DFS curve extrapolations for the BSC arm – adjusted

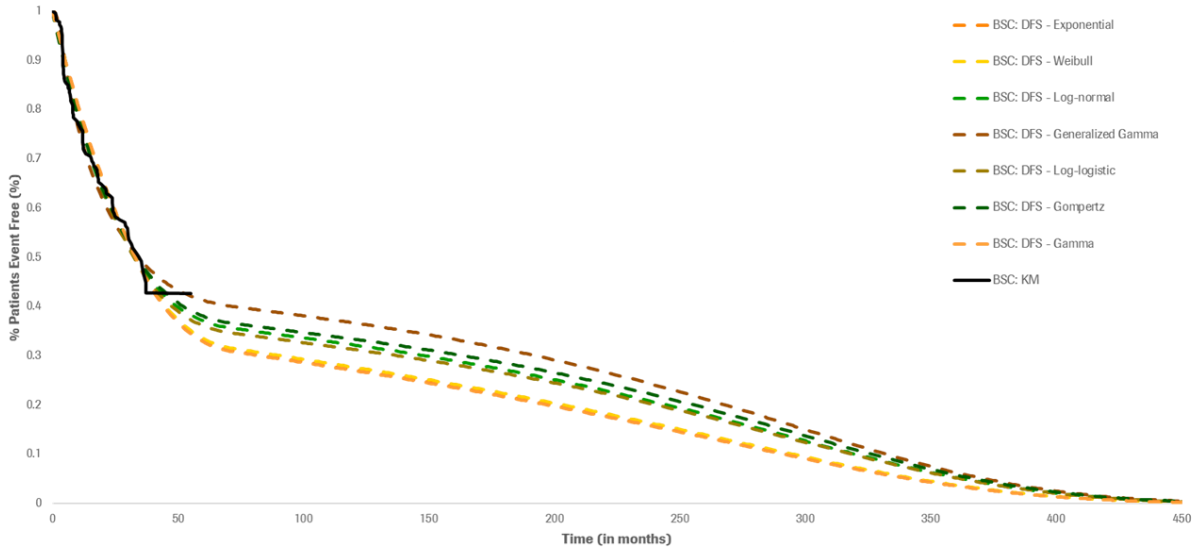


Figure 18: DFS curve extrapolations for the atezolizumab arm – adjusted

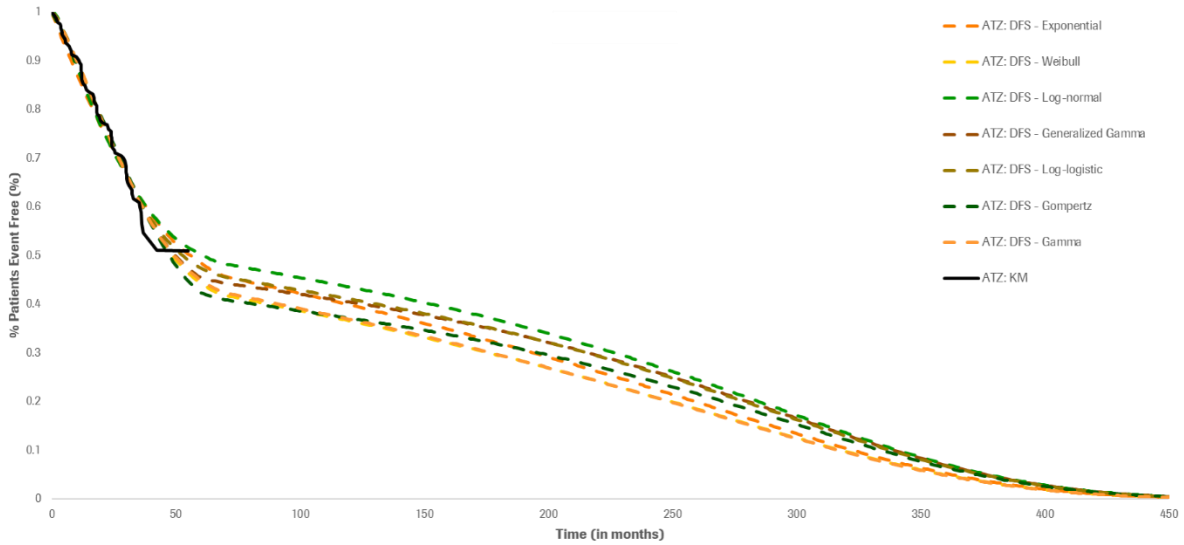


Table 20 presents the information shown in these figures numerically via the proportion of patients that the models estimated to be event-free at 5, 10, 20 and 30 years in both the atezolizumab and BSC arms. The views of the UK clinical oncologists were that it was easier to look at the OS curve extrapolations as this is more familiar (see Section 3.3.5), however they would agree with the estimates from the Pignon et al 2008 study of 40% DFS at 5 years (and not much higher than 40% due to the patients in IMpower010 having Stage II–IIIA disease) (33).

Table 20: Expected proportion patients event free at 10-30 years after treatment initiation across parametric models (by arm)

Distribution	5 years		10 Years		20 Years		30 Years	
	Atezolizumab	BSC	Atezolizumab	BSC	Atezolizumab	BSC	Atezolizumab	BSC
Exponential	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Weibull	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Log-normal	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Generalized Gamma	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Log-logistic	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Gompertz	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Gamma	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

From the Pignon et al 2008 paper (33) and UK clinical opinion, the survival models using the Exponential, Weibull and Gamma distributions may underestimate the proportion of patients at 5 years onwards who are in the DFS health state. This is based on the BSC data, where at five years, the Exponential, Weibull, and Gamma distributions all estimate 33% are event-free at five years, compared with the Pignon et al. estimation of 40% event-free at 5 years.

B.3.3.5 Overall survival

The model switched to the use of age-adjusted probabilities of death from the general population to calculate the proportion of patients who transition to death, if the model estimates were greater than the probabilities from the literature or trial data. This was irrespective of the health state. The formula below was used, where *A* and *B* equalled the health state specific death probability and age-adjusted general population death probability:

$$Death\ Probability_{(health\ state, treatment\ status)} = \begin{cases} A_{(health\ state, treatment\ status)}, A_{(health\ state, treatment\ status)} \leq B_{(general\ population)} \\ B_{(general\ population)}, A_{(health\ state, treatment\ status)} > B_{(general\ population)} \end{cases}$$

Without this adjustment the analysis would be biased as the probability of death in certain cycles would be less than or equal to the age-adjusted probabilities from the general population.

Figure 19 shows that the probability of death in the model was always higher than the age-adjusted probability of death from the general population to account for the higher probability of death that patients with lung cancer confront compared to the general population. Figure 20 and Figure 21 shows the adjusted OS curves for the BSC and atezolizumab arm, respectively.

Figure 19: Estimated probability of death vs. age-adjusted probability of death from general population

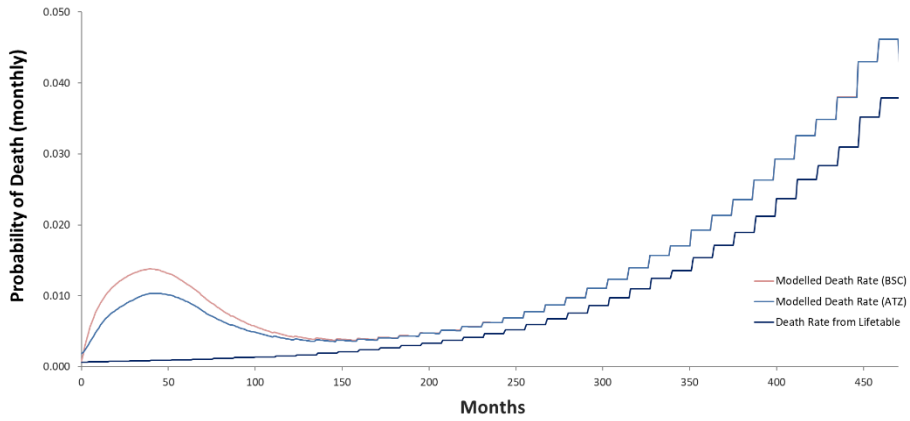


Figure 20: OS curve extrapolations (solid line) for the BSC arm (overlaid with DFS curve extrapolations, dotted line) – adjusted

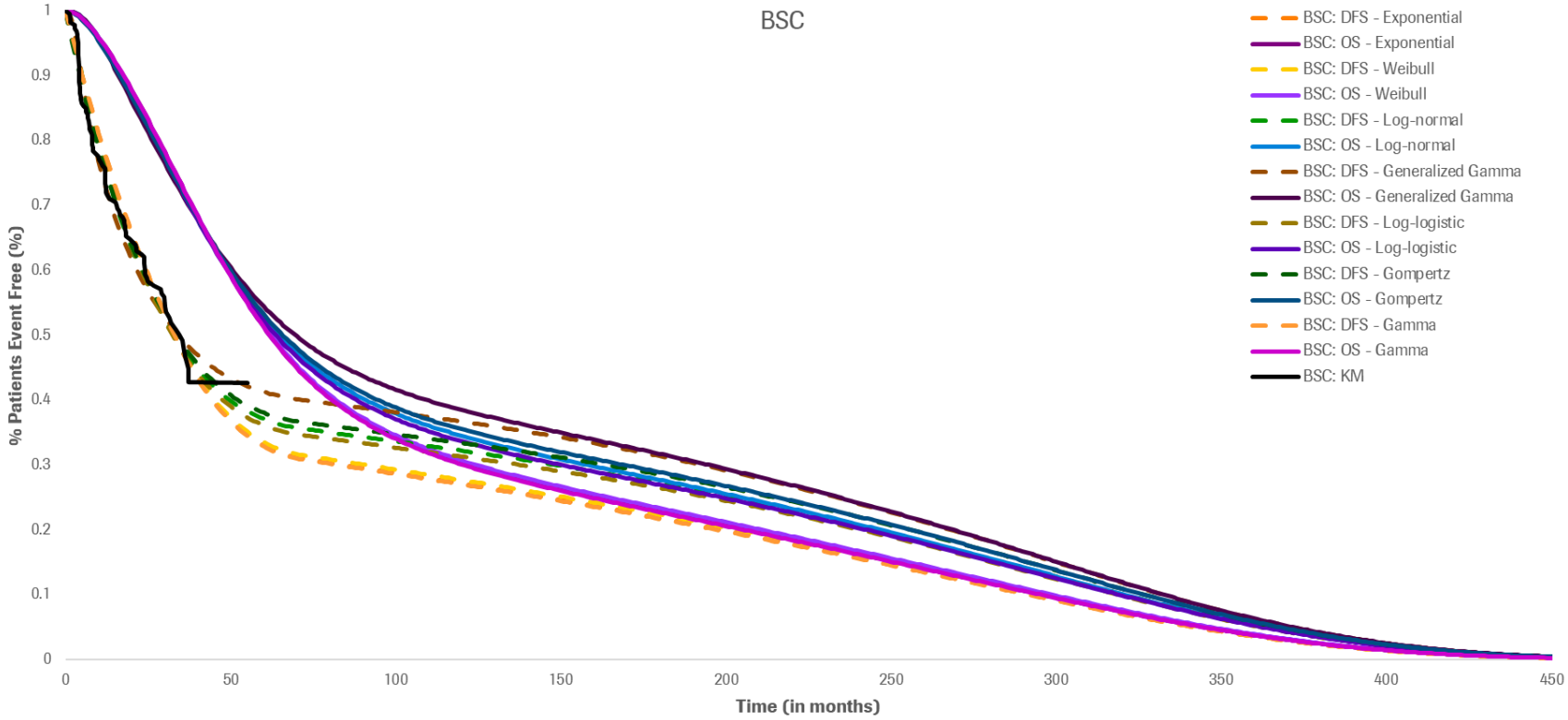


Figure 21: OS curve extrapolations (solid line) for the atezolizumab arm (overlaid with DFS curve extrapolations, dotted line) – adjusted

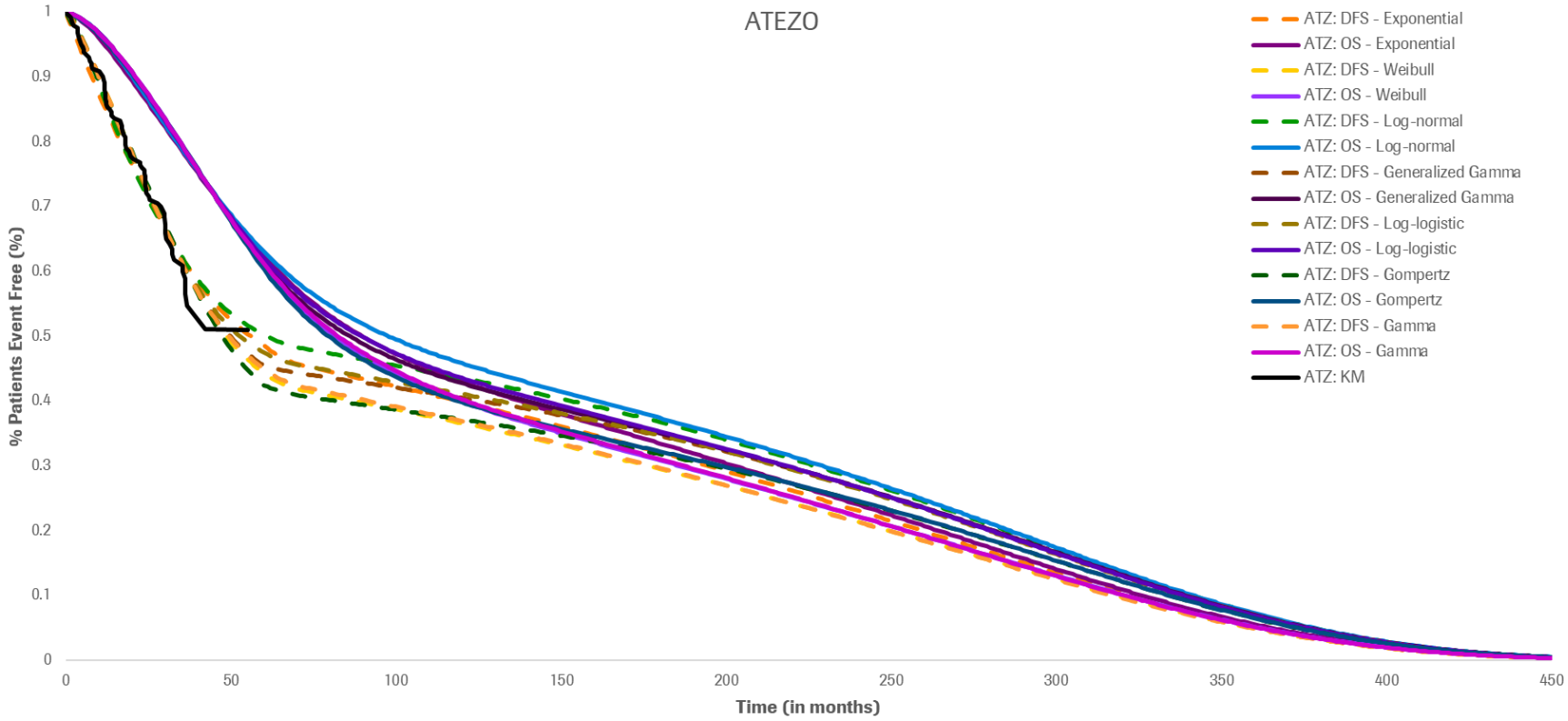


Table 21 presents the information shown in the Figure 20 and Figure 21 numerically, via the proportion of patients that the models estimated to be alive at 5, 10, 20 and 30 years for both the atezolizumab and BSC arms. As previously mentioned, the clinical oncologists were more familiar with the OS curve extrapolations, and when looking at these extrapolations, commented that the BSC curves which aligned with the lower estimates from literature were more reflective of clinical reality, i.e.~50% for 5-years OS and ~30% for 10-year OS. From Table 21, Generalised Gamma and Gompertz appears to overestimate OS, with a 5-year OS of [redacted] and [redacted] and a 10-year OS of [redacted] and [redacted], respectively.

Table 21: Expected proportion patients alive at 5–30 years after treatment initiation across parametric models (by arm)

Distribution	5 Years		10 Years		20 Years		30 Years	
	Atezolizumab	BSC	Atezolizumab	BSC	Atezolizumab	BSC	Atezolizumab	BSC
Exponential*	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Weibull*	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Log-normal	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Generalised Gamma	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Log-logistic	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Gompertz	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Gamma*	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

*In Table 20 (section B.3.3.4.1), these distributions were dismissed due to underestimation of DFS at 5 years.

B.3.3.5.1 Base case DFS extrapolation

Based on the assessment above, the Exponential, Weibull and Gamma distributions appears to underestimate the proportion of patients at five years onwards who are event-free and the Generalised Gamma and Gompertz appears to overestimate OS at five years. Therefore, the Log-normal and Log-Logistic distribution are clinically plausible options for DFS extrapolation. The distribution used for the base case in both the atezolizumab and BSC arms was Log-Logistic as it estimated a more conservative cost per QALY than the Log-Normal distribution.

This gives a five-year OS estimate for the BSC arm in the model of [redacted] which is close to the Pignon et al. 2008 value of 55%. It should be noted that the removal of the cure probability caused a small reduction in five-year OS but the model estimates were still around [redacted]. Therefore, this analysis indicated that the model slightly underestimates shorter-term OS, particularly in the BSC arm.

These results using the Log-Logistic distribution and curve adjustments were within the clinically plausible DFS ranges [redacted] five-year DFS in the BSC arm) and therefore the model appears to align with the available published data and UK clinical expert validation.

B.3.3.6 Types of disease recurrences

The model calculated the probability of a DFS event in each cycle with the following formula:

$$Event\ Probability\ (t) = \frac{Proportion\ of\ Patients\ in\ DFS_{Distribution,t}}{Proportion\ of\ Patients\ in\ DFS_{Distribution,t-1}}$$

The model first accounted for the patients who died (i.e. event probability – probability of patients who died), and then assigned the remainder of the event probability as locoregional and metastatic recurrences, applying IMpower010 results to calculate the proportion of patients who had either locoregional or metastatic as a first event.

The model assigned [redacted] and [redacted] of recurrences as locoregional and metastatic recurrences for the atezolizumab arm and [redacted] and [redacted] as locoregional and metastatic recurrences for the BSC arm (presented in Table 22).

Table 22: Efficacy inputs, DFS events (IMpower010, Stage II–IIIA, PD-L1+, 21 Jan 2021 data-cut)

DFS event	Atezolizumab arm	BSC arm
First event occurrence by type – proportion of patients with locoregional recurrence	[redacted]	[redacted]
First event occurrence by type – proportion of patients with first line metastatic recurrence	[redacted]	[redacted]
First event occurrence by type – transition probability to death (monthly)	[redacted]	[redacted]

Table 23 outlines the number and proportion of patients who had each type of recurrence and death. The model assumes that these proportions would remain the same until the end of the model's time horizon. Although this may not be clinically plausible, it made this assumption as the IMpower010 data were too immature to analyse how the proportion of recurrences evolved over time.

Table 23: DFS events (IMpower010, Stage II–IIIA, PD-L1+, 21 Jan 2021 data-cut)

DFS events	Atezolizumab arm	BSC arm	Pooled across arms
Total events	[redacted]	[redacted]	[redacted]
Death	[redacted]	[redacted]	[redacted]
Second primary lung cancer*	1 (~0%)	3 (3%)	4 (2%)
Recurrence events*	72	99	171
Locoregional recurrence*	35 (49%)	42 (42%)	77 (45%)
Metastatic recurrence*	37 (51%)	57 (58%)	94 (55%)

*Data presented in ESMO 2021 (70)

UK clinical oncologists survey

In August 2021, a survey of five UK clinical oncologists was undertaken to determine what treatments patients within each of the different health states receive and estimates of proportions of patients on different treatments. In addition, literature identified via the structured review (see Appendix M) were also used to inform the inputs described in Sections B.3.3.6.1 to B.3.3.6.3.

B.3.3.6.1 Locoregional recurrence

Patients who have locoregional recurrence could either be treated with curative intent, palliative intent, or not treated after locoregional recurrence. The model included this separation to account for the fact that some patients cannot or choose not to be treated and

the following proportions by treatment intent was applied (estimate from Sonoda et al. 2019 (97):

- Curative treatment: 80%
- Palliative treatment: 20%
- No treatment: 0%

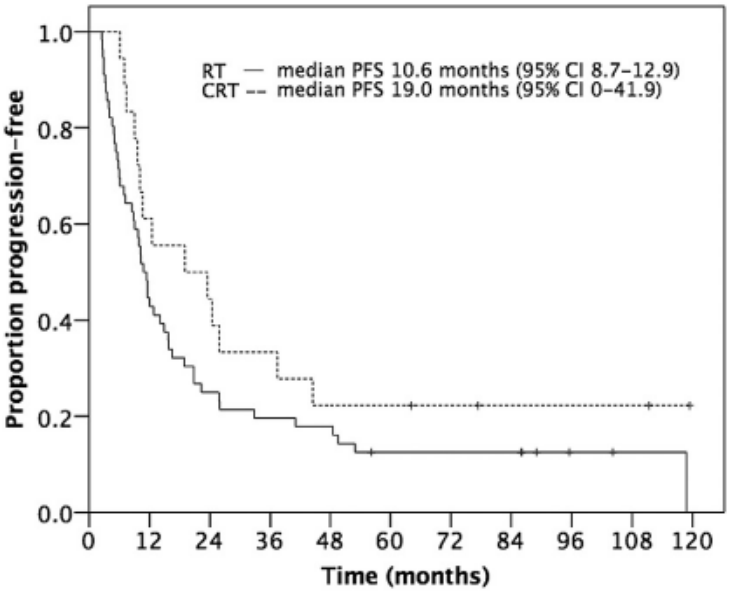
Curative treatment

Patients who received curative treatment remained in this health state while they were alive and progression-free. The model allowed patients to receive chemotherapy and/or radiotherapy (mono- or combined therapy) and in the base case settings, patients received combined therapy, as informed by Prewett et al. 2012 (101) and confirmed by UK clinical oncologists. The duration of treatment depended on the chosen regimen, which was capped at a maximum of 6 months (the tunnel state in the model only allows for a maximum of 6 months treatment, this was validated with UK clinical oncologists).

IMpower010 did not collect the information necessary to calculate probabilities of the progression-free survival of patients who had locoregional recurrence after treatment for early NSCLC. Therefore, published literature was used to calculate the probabilities of transitioning to first-line metastatic recurrence and death health states.

Evidence from Nakamichi et al. 2017 (102), identified from the structured review (Appendix M) was used to calculate the transition probabilities. This study analysed the PFS and OS of 74 patients who experienced locoregional recurrence after surgery for Stages I-III NSCLC, and who treated with chemoradiotherapy or radiotherapy - median PFS was 19 and 10 months. Figure 22 presents the Kaplan-Meier plot.

Figure 22: Kaplan-Meier Plot – PFS (Nakamichi, et al., 2017)



The data from the digitised Kaplan-Meier plot was analysed with a parametric survival model (exponential[13]). The model used the results to calculate the transition probability of progressing from locoregional recurrence to metastatic recurrence or death. The probability equalled 0.018 and 0.034, if the model assumed all patients treated locoregional recurrence with chemoradiotherapy and radiotherapy alone (see 'LR Survival Analysis' tab of the model). Chemoradiotherapy is used in the base case based on the median results from the Nakamichi study due to the uncertainty from using the analysis of the digitised Kaplan-Meier plot.

The model sourced evidence from the PACIFIC trial (TA578) (40) to support the assumption that 81% and 19% of patients who had a progression-free event, transitioned to the first-line metastatic recurrence and death health states, respectively ('Efficacy Inputs' tab of the model, cell F115).

If the modelled proportion of patients who died were smaller than age-adjusted probability of death from the general population, the model would switch to calculating the proportion of patients who died using the age-adjusted probability of death from the general population (see Section B.3.3.5 for more details on implementation).

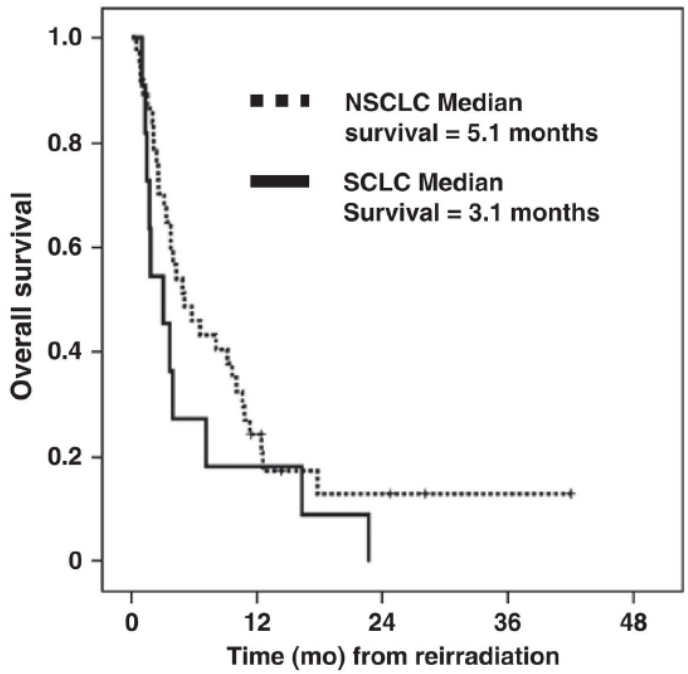
[13] This was a simplifying assumption as using a different parametric distribution would make it time varying. As seen in Section B.3.8.2, testing a range of transition probabilities had a small impact on the ICER.

Palliative or no treatment

Patients who received palliative treatment or no treatment remained in this health state while they were alive.

IMpower010 did not collect the information necessary to calculate probabilities on the survival of patients who had locoregional recurrence after treatment for early NSCLC. Therefore, published literature was used to calculate the probabilities of transitioning to death. Evidence from Kruser et al. 2014 (103), identified via a focussed literature search, was used to calculate the transition probability. The study analysed the overall survival of 37 patients who had locoregional recurrence after radiotherapy for Stages I–IV NSCLC, and who were re-treated with either palliative or curative radiotherapy – the median overall survival for all patients was 5.1 months. Figure 23 presents the Kaplan-Meier plot.

Figure 23: Kaplan Meier – OS (104)



The data from the digitised Kaplan-Meier Plot was analysed with a parametric survival model (exponential[14]). The model used the results of the analysis to calculate the transition probability of progression from locoregional recurrence to death. The probability equals 0.076, which is greater than the figures used for curative treatment intent. In the base case,

[14] This was a simplifying assumption as using a different parametric distribution would make it time varying. As seen in Section B.3.8.2, testing a range of transition probabilities had a small impact on the ICER.

the median results from the Kruser study is used due to the uncertainty from using the analysis of the digitised Kaplan-Meier plot.

If the modelled proportion of patients who died was smaller than what it would equal if the model used age-adjusted probability of death from the general population, the model switches to calculating the proportion of patients who died using the age-adjusted probability of death from the general population (See Section B.3.3.5 for more details on implementation).

B.3.3.6.2 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 (via the survey carried out in August 2021):

- Treatment: [redacted]
- No treatment: [redacted]

Treatment

Patients who received treatment remained in this health state while they were alive and progression-free. The model includes up to four treatment options, capturing differing market shares for patients in the atezolizumab and BSC arms (see Section B.3.5 for more details). The model capped the duration of treatment to 24 months to reflect the recommendation of guidelines on the use of innovative immunotherapies[15] (105, 106).

IMpower010 did not collect the information necessary to calculate probabilities on the progression-free and overall survival of patients who had metastatic recurrence after treatment for early NSCLC. Therefore, other sources were explored to calculate the probabilities of transitioning to second-line metastatic recurrence and death health states. The IMpower150 trial compared the effect of atezolizumab in combination with carboplatin and paclitaxel with or without bevacizumab to carboplatin, paclitaxel and bevacizumab in patients with Stage IV non-squamous NSCLC (107). The IMpower110 trial compared the effect of atezolizumab monotherapy to cisplatin/carboplatin and pemetrexed/gemcitabine in

[15] Atezolizumab (combination therapy) and pembrolizumab (mono/combination therapy) can be used for a maximum of 2 years while there appear to be no time restrictions on the use of atezolizumab (monotherapy) or chemotherapy.

patients with stage IV non-squamous or squamous NSCLC[16] (105). The IMpower150 trial was deemed the most appropriate source of evidence for these transitions in the base case as this combination was reimbursed in 2019, whereas atezolizumab monotherapy for first-line NSCLC was only approved in June 2021. However, both IMpower110 and IMpower150 are included in the scenario analyses (B.3.8.3).

The analysis used data from these trials to run two parametric survival models separately for each of the trial arms and assumed that progression-free survival follows an exponential distribution[17]. Specifically, it used the intent-to-treat, wild type, PD-L1+, B and C arm patients from the IMpower150 trial and the intent-to-treat, wild type, PD-L1 high (expression ≥ 50% of cancer cells) from the IMpower110 trial. The model then calculated the monthly probability of either having a progression-free survival event (disease progression or death) or death alone. The model uses the IMpower110 transition probability if second-line metastatic treatment is not considered as an option. Table 24 summarises the probabilities, with IMpower150 used in the base case and IMpower110 explored through scenario analyses. However, it should be noted that probabilities generated from IMpower150 and Impower110 are comparably similar.

[16] The median progression-free survival of patients in the intervention and control arms (chemotherapy) of IMpower150 (PD-L1+, wild-type) and IMpower110 (PD-L1 high, wild-type) are ~11.1/6.7 and ~8.2/5.1 months. While we can expect that these results on this are driven by factors such as the average age and health status of the cohort, they appeared comparable to the results in the literature (refer to Reck et al. 2016 [10.3 months - pembrolizumab/KEYNOTE-024] Reck M, Rodríguez-Abreu D, Robinson A, Hui R, et al. Pembrolizumab versus Chemotherapy for PD-L1-Positive Non-Small-Cell Lung Cancer. New England journal of medicine. 2016;375(19):1823-33, Mok et al. 2019 [7.1 months - pembrolizumab/KEYNOTE-042] Mok TSK, Wu YL, Kudaba I, Kowalski DM, Cho BC, Turna HZ, et al. Pembrolizumab versus chemotherapy for previously untreated, PD-L1-expressing, locally advanced or metastatic non-small-cell lung cancer (KEYNOTE-042): a randomised, open-label, controlled, phase 3 trial. The Lancet. 2019;393(10183):1819-30, Paz-Ares et al. 2015 [5.6 months – pemetrexed + cisplatin] Paz-Ares L, Mezger J, Ciuleanu TE, Fischer JR, von Pawel J, Provencio M, et al. Necitumumab plus pemetrexed and cisplatin as first-line therapy in patients with stage IV non-squamous non-small-cell lung cancer (INSPIRE): an open-label, randomised, controlled phase 3 study. The Lancet Oncology. 2015;16(3):328-37, and Novello et al. 2017 [5.2 months - pemetrexed and cisplatin]) Novello S, Scagliotti G, de Castro G, Jr., Kiyik M, Kowalyszyn R, Deppermann KM, et al. An Open-Label, Multicenter, Randomized, Phase II Study of Cisplatin and Pemetrexed With or Without Cixutumumab (IMC-A12) as a First-Line Therapy in Patients With Advanced Nonsquamous Non-Small Cell Lung Cancer. Journal of thoracic oncology: official publication of the International Association for the Study of Lung Cancer. 2017;12(2):383-9. Moreover, a recent network meta-analysis showed that atezolizumab and pembrolizumab may lead to comparable outcomes compared to chemotherapy alone in patients with PD-L1 ≥ 50%.

[17] This was a simplifying assumption as using a different parametric distribution would make it time varying. As seen in Section B.3.8.2, testing a range of transition probabilities had a small impact on the ICER.

Table 24: Transition probabilities (first-line metastatic treatment to latter health states)

Transition probability	IMpower150 (base case)	IMpower110
Atezolizumab – PFS event	0.052	0.056
Atezolizumab – Death	0.028	0.030
Chemotherapy – PFS event	0.108	0.116
Chemotherapy - Death	0.038	0.041

Note: These transition probabilities can be found in the 'Efficacy Inputs' tab in the model, rows 174 to 184 - Transition probability to death is shown when 'Allow Metastatic Recurrence (2L) is set to 'No'.

As the model included four different first line metastatic treatments, a weighted average transition probability was calculated based on the proportion of patients who receive either an immunotherapy or chemotherapy treatment option (using IMpower150 and allowing transition to second-line metastatic treatment as the base case). The probabilities differed across the arms of the model if there were differences in the proportion of patients who were treated with the different options (please refer to Section B.3.5 for more details on the proportions). In the model, the atezolizumab arm only had chemotherapy (pemetrexed and cisplatin) as an option for first-line metastatic treatment, as UK clinical oncologists did not think that re-challenging with immunotherapy would be reimbursed; re-challenging is explored as part of scenario analyses. Below are the weighted average transition probabilities:

- Atezolizumab arm: 0.108
- BSC arm: 0.065

The model also included second-line metastatic treatment 77% of all PFS events lead to disease progression, with the remaining 23% leading to death. These proportions were based on IMpower150 – data-cut 15 September 2017, pooled across three trial cohort arms and verified by UK clinical experts.

If the modelled proportion of patients who died was smaller than what it would equal if the model used age-adjusted probability of death from the general population, the model switches to calculating the proportion of patients who died using the age-adjusted probability of death from the general population (see Section B.3.3.5 for more details on implementation).

Palliative or no treatment

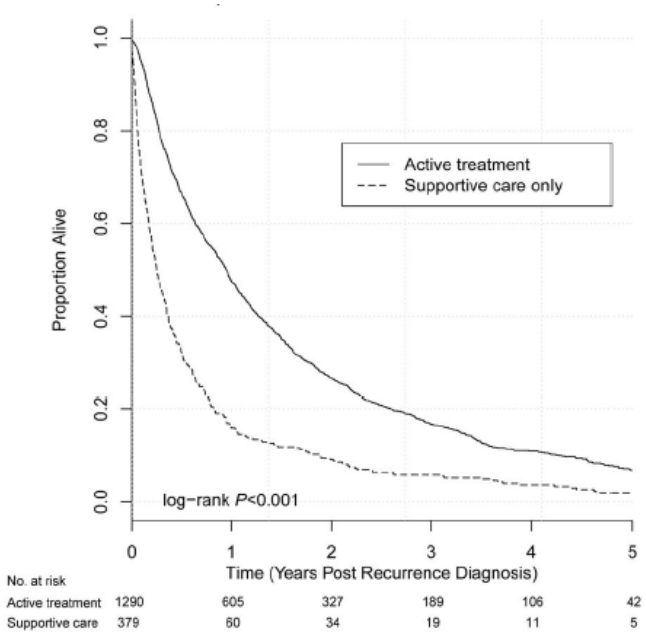
Patients not receiving treatment remained in this health state while alive and could only transition to death. IMpower010 did not collect the information necessary to calculate

probabilities on the overall survival of patients who had metastatic recurrence after treatment for early NSCLC. Therefore, other sources were explored to calculate the probabilities of transitioning to first line metastatic recurrence and death health states. Wong et al. (2016) was identified in a focussed literature search to calculate the transition probability. This study analysed the OS of patients who had metastatic recurrence after surgery for stages I-III NSCLC – median OS was 3 months for patients on no treatment. Figure 24 presents the Kaplan-Meier plot.

The data from the digitised Kaplan-Meier Plot was analysed with a parametric survival model (exponential[18]). The model used the results of the analysis to calculate the transition probability of progression from first-line metastatic recurrence, when receiving no treatment, to death. The probability equalled 0.104, which is greater than those receiving curative treatment intent.

If the modelled proportion of patients who died was smaller than what it would equal if the model used age-adjusted probability of death from the general population, the model switches to calculating the proportion of patients who died using the age-adjusted probability of death from the general population (See Section B.3.3.5 for more details on implementation).

Figure 24: Kaplan Meier – OS (108)



[18] This was a simplifying assumption as using a different parametric distribution would make it time varying. As seen in Section B.3.8.2, testing a range of transition probabilities had a small impact on the ICER.

B.3.3.6.3 Second-line metastatic recurrence

Patients could be treated or not treated after metastatic progression as evidence showed that not all patients proceeded to second-line metastatic treatment after metastases occured (109). UK clinical experts noted that the proportion of patients who proceeded to later lines of treatment depended on the treatment efficacy and that metastatic treatment options may fluctuate over time as clinical practice evolve and change. The following validated proportions were used in the model:

- Treatment: [redacted]
- No treatment: [redacted]

Treatment

Patients who received treatment remained in this health state while they were alive and from there they could only transition to the death health state. IMpower010 did not collect the information necessary to calculate probabilities on the overall survival of patients who had metastatic recurrence after treatment for early NSCLC. Therefore, other sources were explored to calculate the probabilities of transitioning to first-line metastatic recurrence and death health states. The OAK trial (a Roche-Led trial) was identified via the structured literature search carried out in June 2021 as the best source of evidence for second-line metastatic overall survival and was also used in the NICE submission for atezolizumab in second-line metastatic NSCLC (TA520) (78). This trial compared the effect of atezolizumab to docetaxel in patients with locally advanced or metastatic NSCLC who had failed platinum-containing therapy.

The analysis used data from the trial to run two parametric survival models separately for each trial arm and assumed that OS had an exponential distribution[19]. This allowed the model to calculate the monthly probability of transitioning to death. Table 25 presents these transition probabilities.

[19] This was a simplifying assumption as using a different parametric distribution would make it time varying. As seen in Section B.3.8.2, testing a range of transition probabilities had a small impact on the ICER.

Table 25: Transition probabilities (second-line metastatic treatment to death)

Transition probability	OAK
Atezolizumab	0.050
Chemotherapy	0.068

As the model included four different first-line metastatic treatments, a weighted average transition probability was calculated based on the proportion of patients who received either immunotherapy or chemotherapy treatment option. The probabilities differed across the arms of the model if there were differences in the proportion of patients who were treated with the different options (refer to Section B.3.5 for more details on the proportions). In the model, patients who were initially treated with atezolizumab could not be re-challenged with immunotherapy; re-challenging was explored in scenario analyses (Section B.3.8.3):

- Atezolizumab arm: 0.068
- BSC arm: 0.063

If the modelled proportion of patients who died was smaller than age-adjusted probability of death from the general population, the model switches to calculating the proportion of patients who died using the age-adjusted probability of death from the general population (see Section B.3.3.5 for more details on implementation).

Palliative or no treatment

Patients not receiving treatment remained in this health state while alive and could only transition to death. IMpower010 did not collect the information necessary to calculate probabilities on the overall survival of patients who had metastatic recurrence after treatment for early NSCLC. Therefore, other sources were explored to calculate the probabilities of transitioning to second-line metastatic recurrence and death health states. The model therefore used the same source (first-line metastatic recurrence (Wong et al. 2016 (108) and method to model the OS for these patients as patients receiving no treatment in the first-line metastatic recurrence health state (refer to Section B.3.3.6.2 for details on Wong et al. 2016).

B.3.3.7 Adverse events

B.3.3.7.1 Disease-free survival

AEs of any grade occurred in 93% of patients who received atezolizumab in the IMpower010 study versus 71% in the BSC arm (93). The safety profile for adjuvant atezolizumab was

tolerable and consistent with the previously reported profile for atezolizumab monotherapy across multiple indications and lines of therapy (93).

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 (85), TA428 (99), TA520 (78), TA584 (110). The treatment-related AEs are presented in Table 14.

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 [redacted] (in the atezolizumab arm, as BSC arm was active monitoring only).

B.3.3.7.2 Locoregional recurrence

AE event rates for the locoregional recurrence health state in both arms were taken from the SoC arm of the PACIFIC trial using the TA578 NICE committee papers (durvalumab for treating locally advanced unresectable NSCLC after platinum-based chemoradiation (40). This PACIFIC AE data are presented in Table 26.

Table 26: Adverse event rates from the PACIFIC trial (40)

AE	Bi-weekly probability of event
Anaemia	0.002
Haemoptysis	0.001
Hypokalaemia	0.003
Pneumonia	0.003
Pneumonitis	0.001
Radiation pneumonitis	0.002
Endocrinopathy	0.001

B.3.3.7.3 First-line metastatic recurrence

AE event rates for the first-line metastatic recurrence health state were taken from the IMpower150 trial using the TA584 NICE committee papers (atezolizumab in combination for treating metastatic non-squamous non-small-cell lung cancer (110). This is presented in Table 27.

Table 27: Adverse event rates from the IMpower150 trial (110)

AE	Weekly probability of event	
	Atezolizumab + bevacizumab + carboplatin + paclitaxel	Active comparator (pemetrexed in combination with a platinum drug (carboplatin or cisplatin), and pemetrexed plus a platinum drug with pemetrexed maintenance)
Anaemia	0.001	0.006
Fatigue	0.001	0.000
Febrile neutropenia	0.002	0.000
Leukopenia	0.000	0.000
Neutropenia	0.003	0.007
Decreased appetite	0.001	0.000
Dehydration	0.000	0.000
Diarrhoea	0.001	0.000
Respiratory tract infection	0.002	0.000
Hypertension	0.000	0.000
Hypokalaemia	0.000	0.000
Nausea	0.001	0.000
Neutrophil count decreased	0.003	0.000
Platelet count decreased	0.001	0.000
Proteinuria	0.001	0.000
Thrombocytopenia	0.001	0.007
White blood cell count decreased	0.001	0.000

B.3.3.7.4 Second-line metastatic recurrence

AE event rates for the second-line metastatic recurrence health state were taken from the OAK trial using the TA520 NICE committee papers (atezolizumab for treating NSCLC after platinum-based chemotherapy (78). This is presented in Table 28.

Table 28: Adverse event rates from the OAK trial (78)

AE	Weekly probability of event	
	Atezolizumab	Docetaxel
Anaemia	0.000	0.003
Fatigue	0.001	0.003
Febrile neutropenia	0.000	0.008
Leukopenia	0.000	0.003
Neutropenia	0.000	0.013
Neutropenic sepsis	0.000	0.000
Neutrophil count decreased	0.000	0.023
Pneumonia	0.000	0.002
Respiratory tract infection	0.000	0.000
White blood cell count decreased	0.000	0.004

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 and NSCLC NICE appraisals**
- **Disutilities associated with AEs were not included to avoid double-counting**
- **The HRQoL SLR identified 5 full publications which had utility values which were deemed appropriate to be used for the DFS health state in the model. Jang et al. 2010 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:**
  - **Locoregional recurrence, curative treatment – Chouaid et al. 2013**
  - **Locoregional recurrence, palliative or no treatment – Van den Hout et al. 2006**
  - **First-line metastatic recurrence, treatment – IMpower150**
  - **First-line metastatic recurrence, no treatment – Van den Hout et al. 2006**
  - **Second-line metastatic recurrence, treatment – IMpower150**
  - **Second-line metastatic recurrence, no treatment – Van den Hout et al. 2006**

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 and other trials. 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. Utility values also need to be considerate of the values used within all other health states within the model; for example, utility values are expected to decrease with each progressive health state (DFS to locoregional recurrence to metastatic recurrence, as validated by UK clinical oncologists). Therefore, a number of sources have been identified and included within the analysis through scenario analyses.

The model incorporates health-related quality of life via utility values, with a unique value for each health state and treatment intent that alive patients realise in each cycle. The sources used and including utility decrements (disutilities) based on age and gender for each source used is further described in Section B.3.4.2 and B.3.4.3, respectively. 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. However, this is expected to only have a minor impact as adverse events were only included for progressed states. With this, it is assumed that:

- 0 = death
- 1 = perfect health

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

Overall, 27 publications reporting health state utility values (HSUV) for patients with early NSCLC were identified in the SLR for final inclusion (full publications, N=25; conference abstracts, N=2). In addition, 140 studies reporting generic and/or disease-specific HRQOL data were tagged and are listed in Appendix H.

Across the 25 studies presented as full publications, utility data were primarily derived from the US, Canada, and Europe (including Denmark, Finland, France, Germany, Italy, the Netherlands, and the UK). Fifteen studies reported intervention-specific utilities, but data were also reported for a range of different patient- and disease-related health states, including disease stage/status, time since diagnosis, and resectability status. A summary of the 25 identified studies is provided in Appendix H.

Table 29 outlines rationale for exclusion of studies from the analysis. Five studies were deemed appropriate sources for utility values for the model – Manser et al. 2006 (111), Grutters et al. 2010 (112), Jang et al. 2010 (113), Black, Keeler and Soneji 2014 (114), Yang et al. 2014 (115). A summary of the utility values for the cost effectiveness analysis are provided by health state below in Sections B.3.4.2.1 to B.3.4.2.4.

Table 29: Exclusion of Studies (from HRQoL SLR)

Criteria	Number of studies
Combine patients with NSCLC and SCLC	3
Do not specifically show values for stage II-IIIA (e.g. combine stage II-IIIA patients with stage I or IV)	14
Do not consider patients who did not receive surgery (e.g. received radiotherapy for inoperable NSCLC)	2
Follow-up time period after resection too short	1

B.3.4.2.1 Disease-free survival

As outlined above, five studies were identified for consideration to inform disease-free health state utility. Values are summarised below in Table 30.

Table 30: Summary of utility values for DFS

Study	Population	Utility values
Manser et al. (2006)	Stage II–III, 6 months post-surgery	0.55
Grutters et al. (2010)	Stage II	0.74
	Stage III	0.70
Jang et al. (2010)	Stage II	0.78
	Stage III	0.73
Black, Keeler and Soneji (2014)	Stage II, 12 months post-diagnosis	0.68
	Stage III, 12 months post-diagnosis	0.72
Yang et al. (2014)	PS 0–4, stage II–III	0.83

B.3.4.2.2 Locoregional recurrence

The HRQoL SLR revealed a lack of studies on the health state utility value of locoregional recurrence, thus the model includes utility values from Chouaid et al. 2013[20] (116), as a

[20] Chouaid et al. 2013 was identified as a utility source in the NICE appraisal for Atezolizumab monotherapy in untreated PD-L1 positive metastatic non-small-cell lung cancer (TA705)

regression analysis allowed the model to isolate the effect that disease severity of this health state has on utility for patients who were treated with curative intent. The study was prospective in nature and considered a sample of 319 patients with locally advanced and metastatic NSCLC across 25 centres. Table 35 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 locoregional recurrent health state was 0.73 (intercept + 1L progressive disease variables).

Table 31: Multivariate regression - utility values (116)

Variable	Estimate	Standard error	p-value
Intercept	0.77	0.03	<0.01
Stage IV	-0.07	0.04	0.029
1L progression free	0.00	NA	NA
1L progressive disease	-0.04	0.04	0.41
2L progression free	0.03	0.04	0.47
2L progressive disease	-0.11	0.08	0.18

The model included utility values from van den Hout et al. 2006 (117) for patients who treat with palliative intent. This was identified through a supplementary search of previous NSCLC appraisals (it was referenced in a nivolumab NICE appraisal for advanced non-squamous non-small-cell lung cancer after chemotherapy [TA713] (118). The study conducted a cost-utility analysis comparing radiotherapy schedules consisting of 10 fractions of 3Gy versus two fractions of 8Gy in poor prognosis patients with stage IIIA-IV NSCLC. The study calculated a median utility value equal to 0.62 and 0.52 for patients on the 10 and 2 fraction schedules and used the former value as the utility of these patients may converge to the higher value some weeks after randomisation.

B.3.4.2.3 First-line metastatic recurrence

The model included utility values from Chouaid et al. 2013 (116) for patients who received first-line metastatic treatment. In addition, the model included health state utility values estimated from the IMpower150 and IMpower110 data. The utility values from the clinical trials came from statistical models that stratified patients by progression. The model again included utility values from van den Hout et al. (2006) for patients who were not treated (117). Table 37 provides an overview of the utility values.

Table 32: Progression-free health state utility values – first-line metastatic treatment

Treated			Not treated
Chouaid et al. (2013)*	IMpower150	IMpower110	van den Hout et al. (2006)
0.70	0.71	0.76	0.62

*The model uses the parameters *Intercept* and *Stage IV* from Table 35.

B.3.4.2.4 Second-line metastatic recurrence

The model included utility values from Chouaid et al. 2013 (116) for patients who received second-line metastatic treatment. In addition, the model included health state utility values from Nafees et al. 2008 (119) and from the IMpower150 and IMpower110 data. The utility values from the clinical trials came from statistical models that stratified patients by progression. Table 33 provides an overview of the utility values.

Table 33: Progression health state utility values – second-line metastatic treatment

Treated				Not treated
Chouaid et al. (2013)*	Nafees et al. (2008)	IMpower150	IMpower110	van den Hout et al. (2006)
0.59	0.65	0.69	0.69	0.62

*The model uses the parameters *Intercept*, *Stage IV*, and *Progressive Disease (second line)* from Table 35.

B.3.4.3 Health-related quality-of-life data used in the cost effectiveness analysis

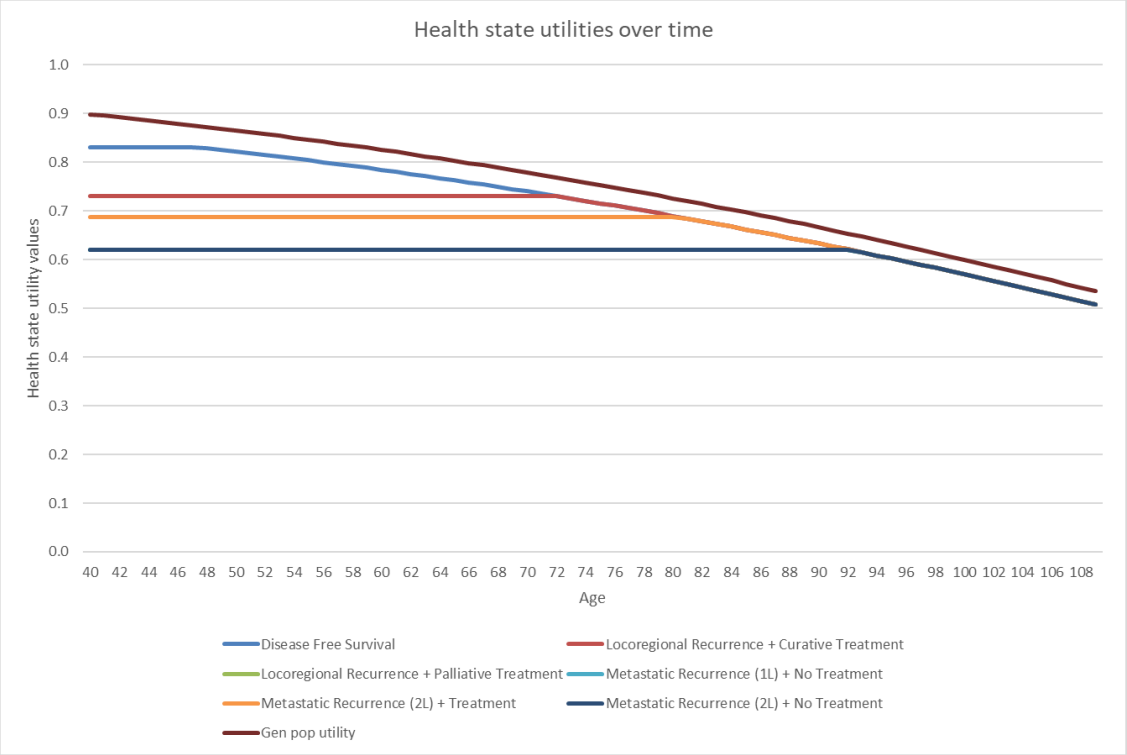
B.3.4.3.1 Adjusting utility values

Sourced utility values were based on a static period. As these utility values were extrapolated over longer time horizons 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 from increasing comorbidities as the population aged (120). Even with age adjustment to utilities, the utility values used within the model are based on a number of sources. As a result, there is likely to be heterogeneity between study sources. Using an age-adjusted utility approach would not address this heterogeneity and without additional adjustments would see utility values within each health state converge in line with general population.

Two approaches were explored to address this. Applying a 95% adjustment factor and applying a utility decrement (disutilities) based on age and gender for each study used. These are described in more detail as follows:

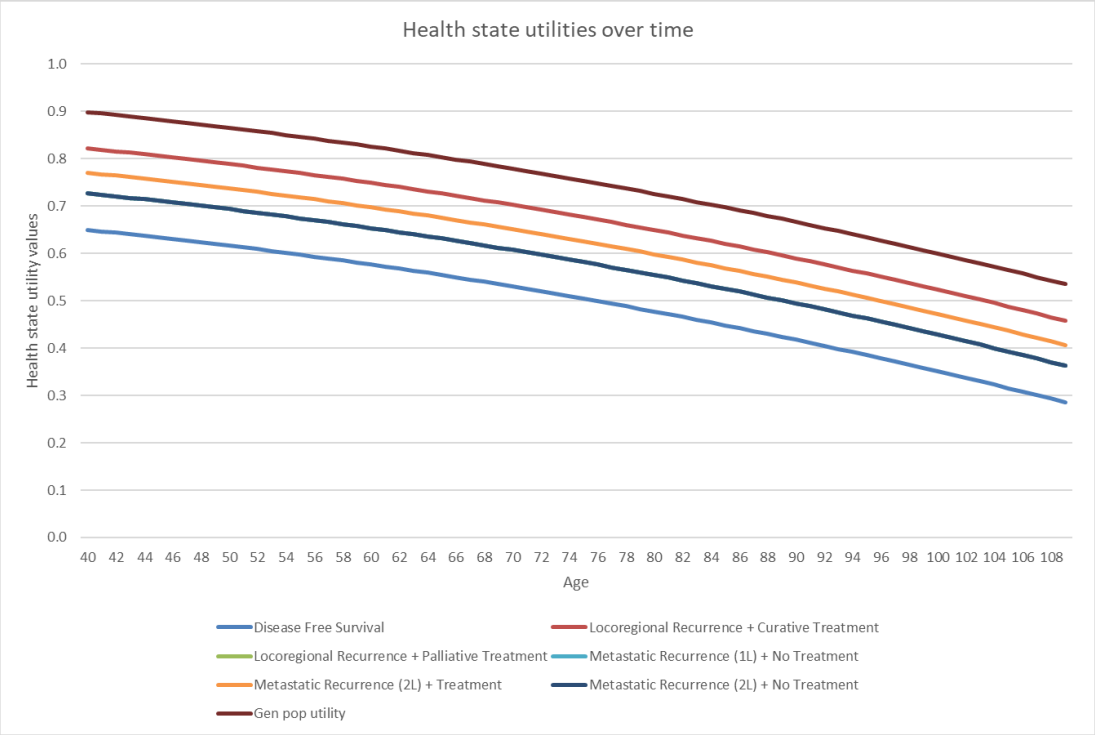
- In order to maintain a lower utility value than general population, an adjustment factor of 95% was used to estimate the difference in utility between a patient in the DFS health state and the general population. This was informed by Grutters et al. 2010 where the EQ-5D utility value for a lung cancer survivor was 0.74 versus 0.78 for the general population (112). Therefore the DFS health state utility, adjusted by age and gender, was assumed to be 5% lower than the general population (adjusted from the point at which the chosen utility became higher than the general population utility).
- The model included the functionality to apply an adjustment factor for each alternative health state to be applied to the estimated DFS utility value; this DFS utility value was used as the 'reference case' and a percentage reduction from DFS could be estimated for each alternative health state. However, no evidence was identified to inform these adjustment factors. The approach was not robust given the heterogeneity of the sources used and the different patient characteristics across the trials, so a different method was required to account for this. As seen in Figure 25, the model did not allow the utility value of the trial population to exceed the general population utility, leading to a time point where all patients eventually had the same utility as the general population (with the adjustment factor for the DFS health state), which is not clinically valid. It did, however, lead to all health state utility values eventually converging (without any additional adjustment factors for subsequent health states).

Figure 25: Health state utilities over time using the 95% adjustment approach



A disutility approach was explored to control for some of this heterogeneity, creating a disutility versus general population matched by study age and gender, where possible. For each study, a comparable general population utility was estimated using the age and gender distribution reported (121). The utility value reported in each study was then subtracted from the general population utility, to estimate the disutility associated with each health state. These disutility values were then subtracted from the population norms. This approach ensured that all health state utility values remained below the general population utility and the progressed states aligned over time, as seen in Figure 26.

Figure 26: Health state utilities over time using the disutility approach



In the company base case, the second approach was used; applying a utility decrement associated with increasing age and gender, sourced from the UK-EQ-5D-3L age-adjusted population norms (121, 122). Further details, rationale and calculations for the values used in the base case are provided split by health state below, in Sections B.3.4.3.2 to B.3.4.3.5.

B.3.4.3.2 Disease-free survival

While the model considered all five studies, evidence from Manser et al. (2006), Grutters et al. (2010) and Black, Keeler and Soneji (2014) could lead to the use of lower utility values for patients in the DFS than in the locoregional recurrence health state, which is clinically implausible. In addition, Yang et al. (2014) reported a higher utility value than the population

norm. Therefore, the base case uses the values from Jang et al. (2010) as it provided the most clinically plausible values. Other sources were explored within scenario analyses.

Table 34: Disutility values sourced for DFS

Study	Population	Age	% Male	General population utility	Health state utility value	Disutility value
Manser et al. 2006 (111)	Stage II–III, 6 months post-surgery	67	69	0.7990	0.55	0.25
Grutters et al. 2010 (112)	Stage II	68	67	0.7940	0.74	0.05
	Stage III	68	67	0.7940	0.70	0.09
Jang et al. 2010 (113)	Stage II	66.00	47%	0.7990	0.78	0.02
	Stage III	66.00	47%	0.7990	0.73	0.07
Black, Keeler and Soneji 2014 (114)	Stage II, 12 months post-diagnosis	61.00	50%	0.8221	0.68	0.14
	Stage III, 12 months post-diagnosis	61.00	50%	0.8221	0.72	0.10
Yang et al. 2014 (115)	PS 0–4, stage II–III	63.00	54%	0.8143	0.83	-0.02

B.3.4.3.3 Locoregional recurrence

Chouaid et al. (2013) is the only source available to inform the utility of patients within the locoregional recurrence health state (Table 35). Focusing on the most appropriate regression values (intercept + 1L progressive disease variables), gives a disutility of 0.08 when age and gender are considered (Table 36). A disutility of 0.17 was applied to patients receiving palliative or no treatment, based on van den Hout et al. 2006 (117).

Table 35: Multivariate regression - utility values (116)

Variable	Estimate	Standard error	p-value
Intercept	0.77	0.03	<0.01
Stage IV	-0.07	0.04	0.029
1L progression free	0.00	NA	NA
1L progressive disease	-0.04	0.04	0.41
2L progression free	0.03	0.04	0.47
2L progressive disease	-0.11	0.08	0.18

Table 36: Disutility values sourced for locoregional recurrence

Study	Population	Age	% Male	General population utility	Disutility value
Chouaid et al. 2013 (116)	Intercept + 1L progressive disease	65.00	61%	0.8068	0.08

B.3.4.3.4 First-line metastatic recurrence

The model sourced utility values estimated from IMpower150 for patients who received first-line metastatic treatment. In addition, the model sourced health state utility values estimated from the IMpower110 data and Chouaid et al. 2013 (116). The utility values from the clinical trials were obtained from statistical models that stratified patients by progression. The model also sourced utility values from Van den Hout et al. (2006) for patients who were not treated (117). As previously mentioned, this was identified through a supplementary search of previous NSCLC appraisals and was referenced in a nivolumab NICE appraisal for NSCLC (TA713 (123)). Table 37 provides an overview of the utility values. The model uses the 0.71 utility value from IMpower150 for the base case, with a disutility of 0.11 applied (see Table 38 for disutilities). This was due to the trial population aligning with the population of interest, first-line metastatic, and having a greater disutility value than the other sources (i.e. more conservative).

Table 37: Health state utility values – first-line metastatic treatment

Treated			Not treated
Chouaid et al. 2013* (116)	IMpower150	IMpower110	van den Hout et al. 2006 (117)
0.70	0.71	0.76	0.62

*The model uses the parameters *Intercept* and *Stage IV* from Table 35.

Table 38: Disutility values sourced for first line metastatic treatment

Study	Population	Age	% Male	General population utility	Health state utility value	Disutility Value
IMpower150 (124)	Progression-free	63.00	60%	0.8155	0.71	0.11
IMpower110 (125)	Progression-free	65.00	70%	0.8086	0.76	0.05
Chouaid et al. 2013 (116)	Intercept + 1L progressive disease	65.00	61%	0.8067	0.70	0.11

van den Hout et al. 2006 (117)	Utility (30 Gy RT)	69.00	80%	0.7919	0.62	0.17

B.3.4.3.5 Second-line metastatic recurrence

The model sourced utility values estimated from IMpower150 for patients who received second-line metastatic treatment. In addition, the model sourced health state utility values from Nafees et al. 2008 (119), Chouaid et al. 2013 (116) and from IMpower110 data. The utility values from the clinical trials were obtained from statistical models that stratified patients by progression. The model also sourced utility values from van den Hout et al. (2006) for patients who were not treated (117). Table 39 provides an overview of the utility values. The model uses the 0.69 utility value from IMpower150 for the base case, with a disutility of 0.13 applied (see Table 40 for disutilities). Again, this was due to the trial population aligning with the population of interest, first-line metastatic, and having a greater disutility value then the other sources (i.e. more conservative).

Table 39: Health state utility values – second-line metastatic treatment

Treated				Not treated
IMpower150	Nafees et al. 2008 (119)	Chouaid et al. 2013* (116)	IMpower110	van den Hout et al. 2006 (117)
0.69	0.65	0.59	0.69	0.62

*The model uses the parameters *Intercept*, *Stage IV*, and *Progressive Disease (second line)* from Table 35.

Table 40: Disutility values sourced for second-line metastatic treatment

Study	Population	Age	% Male	General population utility	Health state utility value	Disutility value
IMpower150	Progression	63.00	60%	0.8155	0.69	0.13
IMpower110	Progression	65.00	70%	0.8086	0.69	0.11
Nafees et al. 2008 (119)	Intercept	40.51	49%	0.8824	0.65	0.23
Chouaid et al. 2013 (116)	Intercept, Stage IV, and progressive disease (second-line)	65.00	61%	0.8067	0.59	0.22
van den Hout et al. 2006 (117)	Utility (30 Gy RT)	69.00	80%	0.7919	0.62	0.17

B.3.4.3.6 Utility values in the base case analysis

The health state utility values used for the base case analysis are presented in Table 41, including the disutilities applied from the corresponding sources.

Table 41: Summary of utility and disutility values for cost effectiveness analysis

Health state	Population	Utility value: mean (standard error)	Disutility value	Reference in submission	Justification
Disease-free survival	Stage II	0.78 (0.06)	0.02	Section B.3.4.2	Jang et al. 2010 identified from HRQoL SLR as clinically plausible and a conservative value
	Stage III	0.73 (0.04)	0.07		
Locoregional recurrence	Curative treatment	0.77 (0.03)	0.08		Regression analysis of Chouaid et al 2013 data allowed the model to isolate the effect the disease severity this health state had on utility
	Palliative treatment	0.62 (0.03)	0.17		Utility values from Van den Hout et al. 2006 for patients who were treated with palliative intent
	No treatment	0.62 (0.03)	0.17		
Metastatic recurrence (1L)	Treatment	0.71 (0.01)	0.11		IMpower150 provided a more conservative value compared to IMpower110 and Chouaid et al. 2013. Accepted in NICE TA584.
	No treatment	0.62 (0.03)	0.17		Utility values from Van den Hout et al. 2006 for patients who were treated with palliative intent
Metastatic recurrence (2L)	Treatment	0.69 (0.02)	0.13		IMpower150 provided a more conservative value compared to IMpower110 and Chouaid et al. 2013. Accepted in NICE TA584.
	No treatment	0.62 (0.03)	0.17		Utility values from Van den Hout et al. 2006 for patients who were treated with palliative intent

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**
- **It was assumed that patients on the atezolizumab arm did not receive subsequent immunotherapy treatment, only chemotherapy. Patients on the BSC arm could receive subsequent immunotherapy**
- **Estimation of subsequent treatment use was obtained from a survey of five UK clinical oncologists**

An SLR was conducted 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 adjuvant cisplatin-based chemotherapy.

The majority of studies reported direct medical cost data and consistently demonstrated that the economic burden of early NSCLC is substantial (N=32). (126-157) (123, 124, 133-162) The identified studies are listed in detail in Appendix I. Overall, studies showed that costs grow with increasing pathological stage of disease. Additionally, patients with advanced disease incur higher costs than those with early stage disease. Cost drivers also vary according to disease stage, with surgery being the predominant contributor to costs in the early stages of disease, and radiotherapy, medical therapy, treatment for progression, and supportive care becoming increasingly important with more advanced disease stages.

A summary of studies with UK-specific costs are provided in Table 42.

Table 42: UK costs related to adjuvant treatment of resectable NSCLC identified from the SLR

Study, country, currency (yr.), follow up period	Study design & objective(s)	Population (sample size)	Direct medical costs	Resource use
Andreas, 2018 Multi-national (France, Germany, UK) EUR (2013) – follow up >1 year	Study design: cost analysis Objective(s): to estimate the burden and cost-of-illness associated with completely resected stage IB-IIIA NSCLC in France, Germany and the UK	Patients aged ≥18 years who had undergone complete resection (no residual disease) of stage IB-IIIA NSCLC (N=306)	Mean total direct costs per patient over follow up period (95% CI): UK: €8,377 (€7,310, €9,518) Mean total community care direct costs per patient (95% CI): UK: €794 (€415, €1,231) Mean monthly direct cost per patient (95% CI): UK: €492 (€405, €587) Mean monthly community care direct cost per patient (95%CI): UK: €71 (€35, €120)	Mean number of episodes per patient over follow up period (SD): Oncologist visits: 5.3 (4.1) Surgeon visits: 2.6 (2.2) Pulmonologist/respiratory physician: 4.6 (3.5) Palliative care physician (Germany & UK): 0 Other specialist visit: 3.2 (3.3) Nurse visits (UK): 1.6 (0.8) Hospitalisations: 1.8 (1.4) ED visits: 1.2 (0.6) CT scans: 3.5 (2.3) MRI: 1.4 (1.1) PET scans: 1.2 (0.4) PET-CT combination: 2.4 (2.2) Ultrasound: 2.5 (2.4) Gamma-knife procedure: 1.0 (-) Nuclear medicine scans: 1.4 (0.8) Ambulance transports: 1.7 (1.8) Other paid transport services: 6.9 (8.0) Radiotherapy courses: 9.8 (12.1) Radiotherapy fractions: 44.2 (15.6) Mean duration of hospitalisation, days (SD): 12.3 (15.2)
Kennedy, 2016 UK GBP (2013/ 2014) – follow up ≤1 year	Study design: retrospective cohort (January 2008 to October 2014; follow up period, 12 months) Objective(s): to evaluate the direct	Patients with a diagnosis of lung cancer (N=1,883)	The total direct cost of hospital care over 12 months for the 3,274 patients included in the study was £32,768,229. The mean	NR

	costs of hospital care in the diagnosis and management of lung cancer in a single large UK teaching hospital using routine NHS data, and to identify factors that were predictive of high costs		cumulative costs at 90 days and one year were £5,852 (95% CI: £5,694, £6,027) and £10,009 (95% CI: £9,717 to £10,278), respectively.	
Rintoul, 2014 Multi-national (UK, Belgium, Netherlands) EUR (2010) – follow up ≤1 year	Study design: economic evaluation (time horizon, 6 months) Objective(s): to report survival, HRQOL, and resource use during the ASTER trial of endosonography versus surgical staging in potentially resectable lung cancer, together with trial-based, country-specific, cost effectiveness analyses	Patients with confirmed or suspected potentially resectable NSCLC requiring mediastinal staging based on CT and PET-CT (N=241)	Incremental mean UK costs for patients who had complete information for all resource use items: EBUS/EUS procedure: €1,651 Surgical staging procedure: -€1,793 Thoracotomy with lymph node dissection: -€997 Total chemotherapy costs in first 2 months: €169 Total radiotherapy cost in first 2 months: -€89 Total hospital admission costs in the first 2 months: -€19 Hospice admission in the first 2 months: €0 Surgery between months 2 and 6: -€116 Total chemotherapy cost between months 2 and 6: -€108 Total radiotherapy cost between months 2 and 6: €264	Number of patients using each resource use item in the UK, n (%): (a) EBUS/EUS (N=11): EBUS/EUS procedure: 11 (100) Surgical staging procedure: 5 (45) Thoracotomy with lymph node dissection: 6 (55) Chemotherapy in first 2 months: 4 (36) Radiotherapy in first 2 months: 0 (0) Hospital admission in first 2 months: 2 (18) Hospice admission in first 2 months: 0 (0) Surgery between months 2 and 6: 1 (9) Chemotherapy between months 2 and 6: 6 (55) Radiotherapy between months 2 and 6: 6 (55) Hospital admission between months 2 and 6: 5 (45) Hospice admission between months 2 and 6: 1 (9) (b) Surgical staging (N=10): EBUS/EUS procedure: 0 (0) Surgical staging procedure: 10 (100) Thoracotomy with lymph node dissection: 7 (70) Chemotherapy in first 2 months: 5 (50)

			Total hospital admission costs between months 2 and 6: €25 Hospice admission between months 2 and 6: €12	Radiotherapy in first 2 months: 0 (0) Hospital admission in first 2 months: 2 (20) Hospice admission in first 2 months: 0 (0) Surgery between months 2 and 6: 1 (10) Chemotherapy between months 2 and 6: 6 (60) Radiotherapy between months 2 and 6: 3 (30) Hospital admission between months 2 and 6: 2 (20) Hospice admission between months 2 and 6: 0 (0) Median hospital LOS following thoracotomy, days (IQR): Belgium: 13 (9-13) Netherlands: 8 (7-11) UK: 10 (8-15)

EBUS, endobronchial ultrasound; IQR, interquartile range

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 43. Prices for generic medicines were taken from the 2021 electronic market information tool (eMIT) (158), 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 2021 British National Formulary (BNF (159). Follow-up costs were taken from NHS Reference Costs 2019-2020 and the Personal Social Services Research Unit 2020 and unit costs were inflated to 2020, if applicable. 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 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 kg and 1.85 m^2) were used to estimate the average cost per dose per patient for the treatments with dosing according to weight or BSA.

As a conservative assumption, the base case of the economic model assumes full vial sharing (i.e., no wastage) for the administration of all weight-based drugs in the model. The proportion of the new vial that should be used to justify opening is 2%. For completeness, a scenario analysis is provided assuming drug wastage of weight-based drugs.

Table 43: Drug acquisition unit costs

Drug	Dose per vial/pack (large vial, mg)	Cost per vial/pack (£)	Cost per mg (£)	Source
Atezolizumab	1200	£3,807.69 (list price) [redacted] (PAS price)	£3.17 (list price) [redacted] (PAS price)	BNF
	840	£2,665.38 (list price) [redacted] (PAS price)		
Cisplatin	100	£8.97	£0.09	eMIT 2021DHA010 and DHA011
Vinorelbine	50	£159.46	£3.19	eMIT 2021 DHA220 and DHA221
Gemcitabine	2,200	£45.29	£0.02	
Pembrolizumab	100	£2,630.00	£26.30	BNF
Pemetrexed	500	£450.00	£0.90	BNF
Bevacizumab	400	£924.40	£2.31	
Carboplatin	600	£20.28	£0.03	eMIT 2021 DHE003 DHA162
Paclitaxel	300	£15.97	£0.05	
Docetaxel	160	£17.38	£0.11	eMIT 2021 DHC025 and DHC046
Nintedanib	150	£2,151.10	£14.34	BNF
Nivolumab	240	£2,633.00	£10.97	BNF

Table 44: Drug cost per treatment cycle for interventions used in the cost effectiveness model

Intervention	Method and frequency of administration	Total drug cost per cycle (with vial sharing)	Drug cost per combination partner per cycle
Cisplatin and vinorelbine	IV, Q3W	£366.44	Cispltain: £12.89 Vinorelbine: £349.28
Pembrolizumab and pemetrexed	IV, Q3W	£6,090.61	Pembrolizumab: £5,260.00 Pemetrexed: £830.61
Pemetrexed and cisplatin	IV, Q3W	£843.02	Pemetrexed: £830.61 Cisplatin: £12.09
Pembrolizumab	IV, Q3W	£5,260.00	Pembrolizumab: £5,260.00
Pembrolizumab plus carboplatin	IV, Q3W	£5,290.42	Pembrolizumab: £5,260.00 Carboplatin: £36.17
Nintedanib plus docetaxel	Oral and IV, Q3W	£2,166.14	Nintedanib: £2,151.10 Docetaxel: £15.53
Docetaxel	IV, Q3W	£15.04	N/A
Atezolizumab	IV, Q3W	£3,807.69 (list price) [redacted](PAS price)	N/A

NB: Cost per cycle can be found in the 'Tx Schedule' tabs of the model

B.3.5.1.2 Administration costs

The administration costs for all therapies apart from nintedanib are sourced from the NHS reference costs and assumed to be for delivering simple parenteral chemotherapy at first attendance (Table 45) (160). Nintedanib is an oral therapy where an assumption of zero administration cost has been made as per the nintedanib NICE appraisal for locally advanced, metastatic or recurrent NSCLC of adenocarcinoma tumour histology after first-line chemotherapy (TA347) (161).

Table 45: Drug administration costs

Drug	Type of administration		NHS reference code	Cost per administration	Source
All therapies (apart from nintedanib*)	Deliver simple parenteral chemotherapy at first attendance	Daycase and Reg day/night	SB12Z	£299.61	NHS reference costs 2019-2020

*In line with the nintedanib appraisal (TA347) (161), zero administration cost is assumed

B.3.5.2 Health-state unit costs and resource use

B.3.5.2.1 Disease-free survival

Treatment cost

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. The safety-evaluable population of IMpower010 showed that [redacted] of patients completed the planned one year of treatment, whereas [redacted] discontinued due to AEs, relapse or other reasons, respectively. In the base case, treatment duration for atezolizumab is based on time-to-off treatment (TTOT) from IMpower010. Table 46 shows the TTOT data; proportion of patients on atezolizumab in each cycle and Table 47 shows the cost of atezolizumab each month (11 months in total). A scenario aligning treatment duration to DFS (treat to progress) has also been explored (see Section B.3.8.3).

Table 46: TTOT (IMpower010, TTOT, Stage II–III, PD-L1+, ATZ arm, 21 Jan 2021 data-cut)

Cycle	Proportion of patients on treatment
1	[redacted]
2	[redacted]
3	[redacted]
4	[redacted]
5	[redacted]
6	[redacted]
7	[redacted]
8	[redacted]
9	[redacted]
10	[redacted]
11	[redacted]
12	[redacted]
13	[redacted]
14	[redacted]
15	[redacted]
16	[redacted]

Table 47: Treatment acquisition costs – DFS health state

Month	Cost per month, PAS price (£)	Cost per month, list price (£)
0	[redacted]	£7,978.84
1	[redacted]	£3,736.82
2	[redacted]	£7,153.68
3	[redacted]	£3,450.54
4	[redacted]	£6,631.65
5	[redacted]	£3,214.78
6	[redacted]	£6,278.42
7	[redacted]	£3,046.80
8	[redacted]	£5,925.19
9	[redacted]	£2,878.40
10	[redacted]	£2,844.72

Follow-up costs

Patients in both the 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.

Table 48: 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)	32.73	NHS reference costs 2019-2020, DAPF
Outpatient visit	1.4 visits	Clinical expert opinion (UK) – matched to CT scans	192.85	Per visit. NHS Reference Costs 2019-20: Code 370 outpatient medical oncology
Community nurse	1.18 visits	Clinical expert opinion (UK)	64.00	Band 8a, Cost per hour. Personal Social Service Research Unit in UK, 2020
Clinical nurse specialist	1.7 visits	Clinical expert opinion (UK)	81.00	Band 8b, Cost per hour. Personal Social Service

				Research Unit in UK, 2020
GP surgery	2.8 visits	Clinical expert opinion (UK)	39.00	Cost per hour. Personal Social Service Research Unit in UK, 2020.
Total monthly cost (per cycle)	£53.19			

B.3.5.2.2 Locoregional recurrence

Treatment cost

The model allowed the choice of different treatment options for the curative and palliative treatments. From UK clinical expert opinion[21], curative treatment consists of chemoradiation therapy with cisplatin and vinorelbine and for palliative treatment, no active treatment would be provided. The model set no active treatment as the palliative treatment option as per the study by Sonoda et al. 2020 (97), where patients either received chemotherapy or best supportive care. Information on the radiotherapy regimen were from Prewett et al. 2012 (101) and confirmed by UK clinical experts.

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 49. Table 50 presents the cost of chemoradiation each month (3 months in total).

Table 49: Treatment Options (Locoregional Recurrence)

Option	Curative treatment
Chemotherapy inclusion	Yes
Drug 1	Cisplatin
Dose size	80mg/m^2
# Of cycles	4
Doses per cycle	1
Weeks between cycles	3
Drug 2	Vinorelbine
Dose size	60mg/m^2
# Of cycles	4

[21] Three UK clinical oncoglists were consulted in 1:1 video calls in August 2021.

Doses per cycle	1
Weeks between cycles	3
Radiotherapy inclusion	Yes
Total dose	66 grays
Dose per fraction	2 grays
Fractions per week	5

Table 50: Treatment acquisition costs – locoregional health state

Month	Cost per month (per cycle)
1	£5,544.82
2	£2,121.98
3	£965.66

Follow-up costs

Patients who have locoregional recurrence receive follow-up healthcare regardless of treatment status. However, the model assumed that patients who received palliative treatment or no treatment at all did not utilise CT chest scans intended to detect disease progression.

Table 51 summarises follow-up healthcare resource use. The model did not allow the use of these resources to be finite in time to account for the fact that the majority of patients who had locoregional recurrence eventually experienced metastatic recurrence. Therefore, it could be plausible to assume that they would continue to use these resources until disease progression.

The model sourced information on the use of the resources from UK clinical oncologists and the results of the PACIFIC trial (TA578) (40) - maintenance of unresectable Stage III NSCLC after platinum-based chemoradiatation.

Table 51: Other healthcare resource use after locoregional recurrence

Healthcare resource	Curative treatment and palliative treatment or no treatment – use (yearly)	Palliative treatment or no treatment – use (yearly)	Resource use reference	Unit costs (£)	Unit cost reference
Ct chest scan	4.00 scans	0 scans	UK clinical expert opinion	119.01	NHS Reference Costs 2019-2020, Diagnostic Imaging, Outpatient, HRG code RD24Z (two areas with contrast) – aligned with TA705 (IMpower110)
Chest radiography	1.20 scans	1.20 scans	UK clinical expert opinion	32.73	Per visit. NHS Reference Costs 2019-20: Code 370 outpatient medical oncology
Outpatient visit	4.76 visits*	4.76 visits*	UK clinical expert opinion	192.85	Band 8a, Cost per hour. Personal Social Service Research Unit in UK, 2020
Community nurse	1.96 visits*	1.96 visits*	UK clinical expert opinion	64.00	Band 8b, Cost per hour. Personal Social Service Research Unit in UK, 2020
Clinical nurse specialist	8.50 visits*	8.50 visits*	UK clinical expert opinion	81.00	Cost per hour. Personal Social Service Research Unit in UK, 2020.
GP surgery	4.3 visits	4.3 visits	UK clinical expert opinion	39.00	Per visit. NHS Reference Costs 2019-20: Code 370 outpatient medical oncology
Total monthly cost (per cycle)	£201.24	£161.57	-	-	-

*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

The model allowed the choice of four separate options for first- and second-line metastatic treatment. Opinions from the UK clinical oncologists[22] suggested that it might be applicable to separate first-line metastatic treatments into four categories – pembrolizumab + pemetrexed, pemetrexed + cisplatin, pembrolizumab, pembrolizumab and carboplatin. The model used the four treatment options presented in Table 52 to define first-line metastatic treatment.

Table 53 presents the market shares as estimated by UK clinical oncologists. It is unknown whether patients initially on immunotherapy can re-challenge after recurrence, so in the model, patients in the atezolizumab arm can only receive subsequent chemotherapy. Patients in the BSC arm can receive immunotherapy as they have not had prior immunotherapy. For pembrolizumab, patients in the model remained on treatment for a maximum of 2 years to account for the treatment duration caps imposed on the use of pembrolizumab (85, 162). The model allows this treatment duration cap to be adjusted. Table 54 presents the weighted average monthly treatment costs for the atezolizumab and BSC arms.

Table 52: Treatment options (1L metastatic treatment)

Inputs	Option 1	Option 2	Option 3	Option 4
Drug 1	Pembrolizumab	Pemetrexed	Pembrolizumab	Pembrolizumab
Dose size	200mg/ fixed	500mg/m^2	200mg/ fixed	200mg/ fixed
Doses per cycle	1	1	1	1
Weeks btw. cycles	3	3	3	3
Drug 2	Pemetrexed	Cisplatin	n/a	Carboplatin
Dose size	500mg/m^2	75mg/m^2	n/a	150mg AUC
Doses per cycle	1	1	n/a	1
Weeks btw. cycles	3	3	n/a	3
Estimated monthly cost	£9,696.26	£ 2090.39	£8,058.13	£8,536.47

AUC: area under the curve

[22] Three UK clinical oncologists were consulted in 1:1 video calls in August 2021. They suggested more than four treatment options, however, to avoid overcomplicating the model, the four treatment options with the highest estimated proportion of use was included in the model. There is flexibility in the model to change these treatment options.

NB: These figures can be found in '1L Met. Recurrence Tx Schedule' tab of the model. The reported monthly cost accounts for administration costs.

Table 53: Market shares of 1L treatment options

Atezolizumab arm		BSC arm	
Treatment options	**Proportion (%)**	**Treatment options**	**Proportion (%)**
Pemetrexed + cisplatin	100	Pembrolizumab + pemetrexed	28
-	-	Pemetrexed + cisplatin	23
-	-	Pembrolizumab	33
-	-	Pembrolizumab + carboplatin	16

NB: UK clinical oncologists gave their estimation of market shares by squamous and non-squamous NSCLC; therefore, these average proportions are weighted by 70% non-squamous and 30% squamous

Table 54: Weighted average monthly treatment costs (1L Metastatic Treatment)

Arm	Overall weighted average monthly treatment cost (£)
Atezolizumab	£2,090.39
BSC	£7,220.76

For 2L metastatic recurrence, the model used the four treatment options presented in Table 55 to define second-line metastatic treatment. The market shares estimated by UK clinical oncologists are presented in Table 56. Due to the question of whether patients initially on immunotherapy could re-challenge after recurrence, these shares determine the mix of treatment options that patients receive in the atezolizumab arm (only subsequent chemotherapy) and BSC arm of the model (may receive subsequent immunotherapy). Patients remained on treatment until they died to account for the potential use of later lines of treatments.

Table 57 presents the weighted average monthly treatment costs for the atezolizumab and BSC arms.

Table 55: Treatment options (2L metastatic treatment)

Inputs	Option 1	Option 2	Option 3	Option 4
Drug 1	Nintedanib	Pemetrexed	Docetaxel	Atezolizumab
Dose size	150mg/ fixed	500mg/ m^2	160mg/ fixed	1,200mg/ fixed
Doses per cycle	2	1	1	1
Weeks btw. cycles	3	3	3	3
Drug 2	Docetaxel	Cisplatin	n/a	n/a
Dose size	160mg/ fixed	75mg/m^2	n/a	n/a
Doses per cycle	1	1	n/a	n/a
Weeks btw. cycles	3	3	n/a	n/a
Estimated monthly cost	£6,716.38	£2,090.39	£480.75	£1,951.95

NB: These figures can be found in '2L Met. Recurrence Tx Schedule' tab of the model. The reported monthly cost accounts for administration costs.

Table 56: Market shares of 2L treatment options

Atezolizumab arm		BSC arm	
Treatment options	**Proportion (%)**	**Treatment options**	**Proportion (%)**
Pemetrexed + cisplatin	55	Nintedanib + docetaxel	29
Docetaxel	45	Pemetrexed + cisplatin	22
-	-	Docetaxel	18
-	-	Atezolizumab	31

Table 57: Weighted average monthly treatment costs (2L metastatic treatment)

Arm	Overall weighted average monthly treatment cost (£)
Atezolizumab	1355.00
BSC	3087.81

Follow-up costs

Patients who had metastatic recurrence received follow-up healthcare regardless of treatment status. However, the model assumed that patients who were not treated or were on second-line treatment did not utilise CT chest scans intended to detect disease progression.

Table 58 summarises follow-up healthcare resource use. The model did not allow the use of these resources to be finite in time to account for the fact that the majority of patients who

have metastatic recurrence do not recover. Therefore, it was plausible to assume that they would continue to use these resources until death.

The model sourced information on the use of these resources from UK clinical oncologists. This lead to a monthly CT chest scan cost of £39.67 for patients on first line metastatic treatment, and monthly other healthcare resource costs of £391.78 (or £352.11 with no CT scans) and £608.34 for patients in the first-line and second-line metastatic recurrence health states.

Table 58: 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	119.01	NHS Reference Costs 2019-2020, Diagnostic Imaging, Outpatient, HRG code RD24Z (two areas with contrast) – aligned with TA705 (IMpower110)
Chest radiography	6.79 scans	6.50 scans	UK clinical expert opinion	32.73	Per visit. NHS Reference Costs 2019-20: Code 370 outpatient medical oncology
Electrocardiogram	1.04 scans	0.88 scans	UK clinical expert opinion	147.15	NHS Reference Costs 2019-2020, Complex ECG, HRG code EY51Z, service code 370. Per scan.
Outpatient visit	9.61 visits*	7.91 visits*	UK clinical expert opinion	192.85	Band 8a, Cost per hour. Personal Social Service Research Unit in UK, 2020
Community nurse	8.70 visits*	8.70 visits*	UK clinical expert opinion	64.00	Band 8b, Cost per hour. Personal Social Service Research Unit in UK, 2020
Clinical nurse specialist	12 visits*	12 visit*	UK clinical expert opinion	81.00	Cost per hour. Personal Social Service Research Unit in UK, 2020.
GP surgery	12 visits	0 visits	UK clinical expert opinion	39.00	Per visit. NHS Reference Costs 2019-20: Code 370 outpatient medical oncology
GP home visit	0 visits	26.09 visits	UK clinical expert opinion	100.62	PSSRU 2016, p.145: Cost per home visit including 11.4 minutes for consultations and 12 minutes for travel (from TA531, inflated using the PSSRU HCHS index 2020)
Therapist visit	0 visits	26.09 visits	UK clinical expert opinion	49.00	PSSRU 2020; cost per hour for community occupational therapist (including training)
Total monthly cost (per cycle)	£391.78 (or 352.11 with no treatment)	£608.34 (with treatment or with no treatment)	-	-	-

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

B.3.5.3 Subsequent therapies

The economic model included costs and resource use of subsequent treatment for patients who have progressed beyond DFS health state. The distribution of subsequent treatments was multiplied by the acquisition and administration costs of each subsequent treatment and applied based on individual treatment regimen. Those patients who were not modelled to receive a subsequent treatment were modelled to receive best supportive care, which was associated with other healthcare resource use costs. See Section B.3.5.2 for more details on the treatments included within each health state.

B.3.5.4 Adverse reaction unit costs and resource use

Given the low number of occurrences per AE reported in IMpower010 (

Table 12); the base case does not consider AE management costs related to treating with atezolizumab. AEs for subsequent therapies in progressive health states have been outlined in Section B.3.5.2. Adverse event management costs and resource use are presented below in Sections B.3.5.4.1 to B.3.5.4.2.

B.3.5.4.1 Locoregional recurrence

AEs in the locoregional recurrence health state were informed by the TA578 durvalumab cost effectiveness analysis (40). Patients who were treated after locoregional recurrence incurred the AE management cost from the standard of care arm of TA578 (based on data from the PACIFIC trial). Table 59 presents the AEs (occurrences - bi-weekly) and unit costs that the analysis in TA578 considered. This lead to an AE management monthly cost of £14.05 for patients on curative treatment and £0 for palliative treatment.

Table 59: AE occurrence and unit cost of management (NICE TA578 (40), Table 49, costs updated to NHS reference costs 2019-2020)

AE	Bi-weekly probability of event	Unit cost	Source
Anaemia	0.002	£642	NHS reference costs 2019/2020 - SA05J
Haemoptysis	0.001	£477	NHS reference costs 2019/2020 - DZ19N
Hypokalaemia	0.003	£178	NHS reference costs 2019/2020 - SC-300
Pneumonia	0.003	£921	NHS reference costs 2019/2020 - DZ11V
Pneumonitis	0.001	£477	NHS reference costs 2019/2020 - DZ19N
Radiation pneumonitis	0.002	£477	NHS reference costs 2019/2020 - DZ19N
Endocrinopathy	0.001	£535	NHS reference costs 2019/2020 - KA08C
Total monthly cost (per cycle)	£14.05		

B.3.5.4.2 First-line/Second-line metastatic recurrence

The model attained information on AE management costs of first- and second-line metastatic treatment from two atezolizumab models submitted to NICE, TA584 (IMpower150 trial) (110) and TA520 (OAK trial)(78). This allowed separate costs for patients being treated with first- and second-line treatment, and for immunotherapy and chemotherapy treatment to be considered. Table 60 presents the AE occurrences and unit costs used. This led to the following monthly AE management cost: £87.07 for patients on first-line immunotherapy, £106.41 for patients on first-line chemotherapy, £12.18 for patients on second-line immunotherapy, and £308.41 for patients on second-line chemotherapy.

The model assumed that patients on immunotherapy and chemotherapy incurred these AE management costs irrespective of the specific drug that they received for treatment. Using a weighted average informed by the proportion of patients on each treatment, resulted in the following AE management monthly cost estimations: £87.07 in the atezolizumab arm and £93.45 in the BSC arm for first-line metastatic treatment, and £308.41 in the atezolizumab arm and £216.58 in the BSC arm for second-line metastatic treatment.

Table 60: AE occurrences and unit cost of management (IMpower150/OAK Global Models)

AE	Weekly probability of event - intervention arm (atezolizumab combo)	Weekly probability of event - control arm	Unit cost (£)	Source
1L metastatic recurrence - IMpower150 Global Model				
Anaemia	0.00140	0.00566	£ 2904.99	NICE TA531 - inflated to 2019/2020 using the PSSRU HCHS index
Fatigue	0.00068	0.00000	£ 3083.17	Brown 2013 (inflated to 2019-20 using PSSRU inflation indices)
Febrile neutropenia	0.00213	0.00000	£ 7507.93	NICE TA531- inflated to 2019-20 using the PSSRU HCHS index
Leukopenia	0.00042	0.00000	£ 398.59	NICE TA531 - inflated to 2019-20 using the PSSRU HCHS index
Neutropenia	0.00342	0.00698	£ 636.01	Brown 2013 (inflated to 2019-20 using PSSRU inflation indices)
White Blood Cell Count Decreased	0.00088	0.00000	£ 475.33	NICE TA484, NICE TA520, NICE TA525, TA584 - inflated to 2019-20 using the PSSRU HCHS index
Total monthly cost	£87.07	£93.45	-	-
2L metastatic recurrence - OAK Global Model				
Anaemia	0.00049	0.00316	£1,232.30	HRG 2018/19 (SA04H [Iron Deficiency Anaemia with CC Score 10-13])
Fatigue	0.00057	0.00316	£3,260.89	TA520 (used Nivolumab [ID900/TA713, ID811/TA655]) - inflated from 2016/17 to 2019/2020 using the PSSRU HCHS index
Febrile neutropenia	0.00000	0.00816	£5,937.43	TA520 (used Nivolumab [ID900/TA713, ID811/TA655]) - inflated from 2016/17 to 2019/2020 using the PSSRU HCHS index

Leukopenia	0.00000	0.00297	£383.64	TA520 (used Nivolumab [ID900/TA713, ID811/TA655]) - inflated from 2016/17 to 2019/2020 using the PSSRU HCHS index
Neutropenia	0.00016	0.01295	£383.64	TA520 (used Nivolumab [ID900/TA713, ID811/TA655]) - inflated from 2016/17 to 2019/2020 using the PSSRU HCHS index
Total monthly cost	£308.41	£216.58	-	-

NB: See 'KM IMpower150' and 'KM OAK' for these data

B.3.5.5 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 non-small-cell lung cancer (163).

The model differentiated end-of-life cost based on whether the death was all-cause or disease related; In the atezolizumab arm, 49% and 51% had all-cause and disease-related mortality, respectively and in the BSC arm, 35% and 65% had all-cause and disease-related mortality, respectively. 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 has been explored in Section B.3.8.3 removing end of life costs.

Table 61: End of life cost

Death	AE management cost
All-cause	£0
Disease related	£4,598.01 per episode

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

B.3.6.1 Summary of base-case analysis inputs

Table 62 summarises all key variable applied in the base case of the economic model.

Table 62: 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	74.07 kg	Fixed	
Height	169.00 cm	Fixed	
Body surface area	1.85 m^2	Fixed	
Proportion of males (%)	66.80%	Fixed	
Population in Analysis	PD-L1+ Stage II–IIIA	Fixed	
Efficacy inputs			
Disease-free survival			
Parametric distribution – atezolizumab arm	Log-logistic	Fixed	Section B.3.3.3
Parametric distribution – BSC arm	Log-logistic	Fixed	
First event occurrence by type – trial data to use to inform recurrence type split	Separate by arm	Fixed	
First event occurrence by type – Atezo arm: proportion of patients with locoregional recurrence	[redacted]	Fixed	
First event occurrence by type – Atezo arm: proportion of patients with first line metastatic recurrence	[redacted]	Fixed	
First event occurrence by type – Atezo arm: Transition probability to death (monthly)	[redacted]	Fixed	
First event occurrence by type – BSC arm: proportion of patients with locoregional recurrence	[redacted]	Fixed	
First event occurrence by type – Atezo arm: proportion of patients with first line metastatic recurrence	[redacted]	Fixed	
First event occurrence by type – Atezo arm: Transition probability to death (monthly)	[redacted]	Fixed	

Treatment effect – Duration of atezo treatment effect	Limited to 60 months	Fixed	
Cured patients – maximum proportion of cured patients	91.5 %	Fixed	Section B.3.3.4
Cured patients – cure proportion starts to increase	36 months	Fixed	
Cured patients – cure proportion maximum reached	72 months	Fixed	
Excess mortality of long-term survivors – standardised mortality ratio	1.25	Fixed	
Locoregional recurrence			
Treatment setting - % of patients by treatment intent: curative treatment	80%	Dirichlet	Section B.3.3.7
Treatment setting - % of patients by treatment intent: palliative treatment	20%	Dirichlet	
Treatment setting - Curative treatment regimen: include radiotherapy	Yes	Fixed	
Treatment setting - Curative treatment regimen: include chemotherapy	Yes	Fixed	
Treatment setting - Curative treatment regimen: treatment regimen drug 1	Cisplatin	Fixed	
Treatment setting - Curative treatment regimen: treatment regimen drug 2	Vinorelbine	Fixed	
Treatment setting - Palliative treatment regimen: include radiotherapy	No	Fixed	
Treatment setting - Palliative treatment regimen: include chemotherapy	No	Fixed	
Efficacy by treatment intent - use result from survival analysis or calculation (based on median)	Simple calculation	Fixed	
Efficacy by treatment intent - Transition probability to first line metastatic recurrence: curative treatment	0.036	Beta	
Efficacy by treatment intent - % progression to first line metastatic recurrence as first event: curative treatment	81%	Beta	
Efficacy by treatment intent – Transition probability to Death: palliative treatment and no treatment	0.136	Beta	
First-line metastatic recurrence			
Treatment setting - % of patients by treatment intent	[redacted]	Beta	Section B.3.3.8
Treatment setting – limit treatment duration	Yes	Fixed	
Treatment setting – Treatment duration	24 months	Fixed	

Treatment setting – Treatment option 1	Pembrolizumab and pemetrexed	Fixed	
Treatment setting – Treatment option 2	Pemetrexed and cisplatin	Fixed	
Treatment setting – Treatment option 3	Pembrolizumab	Fixed	
Treatment setting – Treatment option 4	Pembrolizumab and carboplatin	Fixed	
Treatment setting – Re-challenging with immunotherapy allowed after treatment initiation	12 months	Fixed	
Treatment setting – Re-challenging with immunotherapy: Atezo arm, option 2 with pemetrexed and cisplatin	[redacted]	Dirichlet	
Treatment setting – Re-challenging with immunotherapy: BSC arm, option 1 with pembrolizumab and pemetrexed	[redacted]	Dirichlet	
Treatment setting – Re-challenging with immunotherapy: BSC arm, option 2 with pemetrexed and cisplatin	[redacted]	Dirichlet	
Treatment setting – Re-challenging with immunotherapy: BSC arm, option 3 with pembrolizumab	[redacted]	Dirichlet	
Treatment setting – Re-challenging with immunotherapy: BSC arm, option 4 with pembrolizumab and carboplatin	[redacted]	Dirichlet	
Efficacy by treatment intent – Allow second line metastatic recurrence	Yes	Fixed	
Efficacy by treatment intent – Survival analysis results	Impower150 trial	Fixed	
Efficacy by treatment intent – Transition probability to second line metastatic recurrence - Treatment option 1	0.05	Fixed	
Efficacy by treatment intent – Transition probability to second line metastatic recurrence - Treatment option 2	0.11	Fixed	
Efficacy by treatment intent – Transition probability to second line metastatic recurrence - Treatment option 3	0.05	Fixed	
Efficacy by treatment intent – Transition probability to second line metastatic recurrence - Treatment option 4	0.05	Fixed	
Efficacy by treatment intent – Transition probability to second line metastatic recurrence – Weighted average for atezo arm	0.11	Fixed	

Efficacy by treatment intent – Transition probability to second line metastatic recurrence – Weighted average for BSC arm	0.07	Fixed	
Efficacy by treatment intent – Transition probability to second line metastatic recurrence - % progression as first event	82.20%	Beta	
Efficacy by treatment intent –Use result from survival analysis or calculation (based on median)	Simple calculation	Fixed	
Efficacy by treatment intent –Transition probability to death: no treatment	0.23	Beta	
Second-line metastatic setting			
Treatment setting - % of patients by treatment intent	[redacted]	Beta	Section B.3.3.9
Treatment setting – Treatment option 1	Nintedanib and docetaxel	Fixed	
Treatment setting – Treatment option 2	Pemetrexed and cisplatin	Fixed	
Treatment setting – Treatment option 3	Docetaxel	Fixed	
Treatment setting – Treatment option 4	Atezolizumab	Fixed	
Treatment setting –Atezolizumab arm, option 2 with pemetrexed and cisplatin	[redacted]	Dirichlet	
Treatment setting –Atezolizumab arm, option 3 with docetaxel	[redacted]	Dirichlet	
Treatment setting –BSC arm, option 1 nintedanib and docetaxel	[redacted]	Dirichlet	
Treatment setting –BSC arm, option 2 with pemetrexed and cisplatin	[redacted]	Dirichlet	
Treatment setting –BSC arm, option 3 with docetaxel	[redacted]	Dirichlet	
Treatment setting –BSC arm, option 4 with atezolizumab	[redacted]	Dirichlet	
Efficacy by treatment intent – Transition probability to death, treatment option 1	0.07	Fixed	
Efficacy by treatment intent – Transition probability to death, treatment option 2	0.07	Fixed	
Efficacy by treatment intent – Transition probability to death, treatment option 3	0.07	Fixed	
Efficacy by treatment intent – Transition probability to death, treatment option 4	0.05	Fixed	

Efficacy by treatment intent – Transition probability to death, weighted average for atezo arm	0.07	Fixed	
Efficacy by treatment intent – Transition probability to death, weighted average for BSC arm	0.06	Fixed	
Efficacy by treatment intent –Use result from survival analysis or calculation (based on median)	Simple calculation	Fixed	
Efficacy by treatment intent –Transition probability to death: no treatment	0.23	Beta	
Cost inputs			
Drug costs			
Drug costs - Proportion of vials that are shared across different patients	100%	Fixed	Section B.3.5.1
Drug costs - Proportion of new vial that should be used to justify opening	2%	Fixed	
Drug costs – Atezolizumab: Composition (mg) = 840 – List Price (PAS price)	£2665.38 [redacted])	Fixed	
Drug costs – Atezolizumab: Composition (mg) = 1200 - List Price (PAS price)	£3807 [redacted])	Fixed	
Radiotherapy – Cost per fraction	£144.54	Fixed	
CT scan	£119.01	Fixed	
Administration costs			
IV administration cost	£299.61	Gamma	Section B.3.5.2
Disease-free survival cost and resource use			
Follow-up costs – CT scans: change in scanning schedule	24 months	Fixed	Section B.3.5.2
Follow-up costs – CT scans: Interval between scans in months (first 24 months)	6 months	Fixed	
Follow-up costs – CT scans: Interval between scans in months (after 24 months)	12 months	Fixed	
Follow-up costs – CT scans: Month at which CT scans cease	60 months	Fixed	
Follow-up costs – Include other healthcare resource costs	Yes	Fixed	
Follow-up costs – Duration of healthcare resource use	60 months	Fixed	
Follow-up costs – Healthcare resource use cost (monthly)	£53.19	Fixed	
One-off AE management cost	£0	Fixed	Section B.3.5.5

Locoregional recurrence cost and resource use			
Curative treatment –Chemotherapy drug 1	Cisplatin, 80 mg/m^2, once every 3 weeks for 4 cycles	Fixed	Section B.3.5.2
Curative treatment –Chemotherapy drug 2	Vinorelbine, 60 mg/m^2, once every 3 weeks for 4 cycles	Fixed	
Curative treatment –Radiotherapy	Total treatment dose 66 Gy, 5 fractions per week	Fixed	
Curative treatment – AE cost (monthly)	£14.05	Gamma	
Curative treatment – Follow-up costs – Include other healthcare resource costs	Yes	Fixed	
Palliative treatment – AE cost	£0	Gamma	Section B.3.5.5
First-line metastatic recurrence cost and resource use			
Drug option 1	Pembrolizumab, 200mg every 3 weeks and pemetrexed 500 mg/m^2 every 3 weeks	Fixed	Section B.3.5.3
Drug option 2	Pemetrexed 500 mg/m^2 every 3 weeks and cisplatin 75 mg/m^2 every 3 weeks	Fixed	
Drug option 3	Pembrolizumab, 200mg every 3 weeks	Fixed	
Drug option 4	Pembrolizumab, 200mg every 3 weeks and carboplatin 150 AUC every 3 weeks	Fixed	
Overall weighted average costs – Atezo arm: Treatment cost (monthly)	£2089.91	Gamma	
Overall weighted average costs – Atezo arm: AE cost (monthly)	£87.07	Gamma	
Overall weighted average costs – BSC arm: Treatment cost (monthly)	£7221.98	Gamma	
Overall weighted average costs – BSC arm: AE cost (monthly)	£93.45	Gamma	
Follow-up care costs – Include other healthcare resource costs	Yes	Fixed	

No treatment costs – Include other healthcare resource costs	Yes	Fixed	
Second-line metastatic recurrence cost and resource use			
Drug option 1	Nintedanib 300 mg every 3 weeks and docetaxel 75 mg/m^2 every 3 weeks	Fixed	Section B.3.5.3
Drug option 2	Pemetrexed 500 mg/m^2 every 3 weeks and cisplatin 75 mg/m^2 every 3 weeks	Fixed	
Drug option 3	Docetaxel 75 mg/m^2 every 3 weeks	Fixed	
Drug option 4	Atezolizumab 1200 mg every 3 weeks	Fixed	
Overall weighted average costs – Atezo arm: Treatment cost (monthly)	£1355	Gamma	
Overall weighted average costs – Atezo arm: AE cost (monthly)	£308.41	Gamma	
Overall weighted average costs – BSC arm: Treatment cost (monthly)	£3087.81	Gamma	
Overall weighted average costs – BSC arm: Treatment cost (monthly)	£216.58	Gamma	
Follow-up care costs – Include other healthcare resource costs	Yes	Fixed	
No treatment costs – Include other healthcare resource costs	Yes	Fixed	
End of life costs			
Disease-related death	£4598.01	Gamma	Section B.3.5.7
Utilities – base case			
Disease-free survival			
Literature source	Jang et al. 2010	Fixed	Section B.3.4.4
On treatment disutility	0.25	Beta	
Off treatment disutility	0.25	Beta	
AE total disutility	0	Beta	
Locoregional recurrence			
Literature source	Chouaid et al. 2013	Fixed	Section B.3.4.4
Curative treatment disutility	0.08	Beta	

Palliative treatment – no treatment disutility	0.17	Beta	
First-line metastatic recurrence			
Literature source	IMpower150	Fixed	Section B.3.4.4
Treatment disutility	0.11	Beta	
No treatment disutility	0.17	Beta	
Second-line metastatic recurrence			
Literature source	IMpower150	Fixed	Section B.3.4.4
Treatment disutility	0.13	Beta	
No treatment disutility	0.17	Beta	
General population			
Adjust values for patients in DFS	0.95	Fixed	Section B.3.4.4

Abbreviations: CI, confidence interval

B.3.6.2 Assumptions

The key assumptions applied in the base case of the economic model are specified in Table 63.

Table 63: Key assumptions used in the economic model (base case)

Area	Assumption	Justification
Time horizon	40 years	Aligned with NICE reference case. Time horizon sufficiently long to reflect any differences in costs or outcomes between the technologies being compared
Clinical inputs	Treatment effect duration	A five-year treatment effect was chosen as this aligns with previous NSCLC appraisals (TA531 (85), TA428 (86), TA557 (87), TA600 (100). At this point in the model, the probability of a patient in the atezolizumab arm experiencing an event equals the probability of a patient in the best supportive care arm experiencing an event.
	"Cure" proportion assumptions	Validated with UK clinical oncologists that a small proportion of patients can be considered "cured" if disease-free for five years. This is supported by Sonoda et al. 2019 which shows that 6% and 2.5% of recurrences occur at 5–10 years and 10+ years in a sample of patients who underwent curative resection and systematic lymph node dissection.
	Transition probabilities	External sources were used to inform the transition probabilities to locoregional and metastatic recurrence health states. In the absence of specific clinical trial data, we used data from other clinical trials. These were validated with UK clinical oncologists and these

		data have been appraised in previous NICE appraisals.
	DFS extrapolations	Extrapolation of DFS curves was based on NICE DSU recommendation (164). Best fit according to statistical and visual fit to observed data and long-term clinical plausibility. In order to validate long-term DFS, all available clinical data, as well as clinical expert opinion were considered.
HRQoL	Source utilities	As there were no patient reported outcomes measured in the IMpower010, utility sources were identified using a HRQoL SLR and through identifying past NICE appraisals in NSCLC.
	AEs not applied for DFS	The rate of Grade ≥ 3 treatment-related AEs were all less than 2%, therefore were not included in the model. These criteria for selecting AEs to include are aligned with previous appraisals (TA531 (85), TA428 (86), TA520 (165)
	AE disutilities not included	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
Costs and resource use	NHS reference costs, PSSRU	Aligned with NICE reference case and validated with UK clinical oncologists.

B.3.7 Base-case results

Summary of base-case cost effectiveness results

- **Cost effectiveness results are presented with and without confidential PAS for atezolizumab (list price for all other drugs) for the following population:**
  - **Stage II–IIIA patients following resection and platinum-based chemotherapy with NSCLC whose tumours have PD-L1 expression on ≥ 1% TC, with EGFR mutant or ALK-positive**
- **In this population, the resulting base case incremental cost effectiveness ratio (ICER) when comparing atezolizumab to BSC was:**
  - [redacted] **per quality-adjusted life year (QALY) gained at PAS price**
  - **£53,549 per QALY gained at list price**
- **A limitation of the with-PAS analysis is that confidential discounts are in place for other therapies in the pathway which Roche are unable to account for.**

This analysis is also limited by the availability of relevant data which introduces a degree of uncertainty into the analysis

B.3.7.1 Base-case incremental cost effectiveness analysis results

Base case results of the economic model are presented in Table 64 (list price) and Table 65 (PAS price; [redacted] discount) for the Stage II–IIIA patients following resection and platinum-based chemotherapy with NSCLC whose tumours have PD-L1 expression on ≥ 1% TC. In these comparisons, all comparators (and therapies included in the treatment pathway) are at list price.

Since the osimertinib NICE appraisal for adjuvant treatment of EGFR mutation-positive non-small-cell lung cancer after complete tumour resection is ongoing (52), results for the Stage II-IIIA patients following resection and platinum-based chemotherapy with NSCLC whose tumours have PD-L1 expression on ≥ 1% TC, *excluding* EGFR mutant or ALK-positive population have also been included (see Section B.3.9).

Table 64: Base case cost effectiveness results – Stage II–IIIA population – list price

Technologies	Total costs	Total LYG	Total QALYs	Incremental costs	Incremental LYG	Incremental QALYs	ICER incremental (£/QALY)
Atezolizumab	[redacted]	8.65	[redacted]	[redacted]	1.36	[redacted]	£53,549
BSC	[redacted]	7.29	[redacted]				

Table 65: Base case cost effectiveness results – Stage II–IIIA population – PAS price

Technologies	Total costs	Total LYG	Total QALYs	Incremental costs	Incremental LYG	Incremental QALYs	ICER incremental (£/QALY)
Atezolizumab	[redacted]	8.65	[redacted]	[redacted]	1.36	[redacted]	[redacted]
BSC	[redacted]	7.29	[redacted]				

In the Stage II–IIIA population at list price, atezolizumab provided [redacted] QALYs and 8.65 life years at a total overall cost of [redacted]. In contrast, BSC provided [redacted] QALYs and 7.29 life years, at a total cost of [redacted]. The resulting base ICER when comparing atezolizumab to BSC was £53,549 per QALY gained.

Results of the with-PAS analysis showed that adjuvant atezolizumab treatment resulted in reduced total costs in the atezolizumab arm of [redacted] and reduced total costs in the BSC arm, due to atezolizumab being used in metastatic states, of [redacted]. This resulted in an ICER of £[redacted], significantly below the cost effectiveness threshold, for the Stage II-IIIA population.

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 for adjuvant atezolizumab and list price for all other therapies in the pathway, atezolizumab is cost-effective vs BSC in the adjuvant setting and good value for money to the NHS, in the Stage II-IIIA population.

However, it should be noted that the with-PAS analysis does not account for confidential discounts of therapies used in the treatment pathway, pembrolizumab for first-line metastatic NSCLC and nintedanib for second-line metastatic NSCLC.

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 sensitivity analyses results

- **Extensive sensitivity and scenario analyses were conducted in the economic model to demonstrate the uncertainty around the parameters used, assess the plausibility of different scenarios and approaches, and help understand what key variables and assumptions potentially have a major impact on cost effectiveness results**
- **The PSA ICER results when comparing atezolizumab with PAS to BSC was £[redacted] per QALY gained, consistent with the deterministic base case**
- **The one-way sensitivity analyses showed that the transition probability to first-line metastatic health state in the BSC arm, discount costs and effects, utility treatment, and administration costs are the most influential parameters on the ICER**

- **These results help to quantify and understand the impact of the uncertainty in the analysis on cost effectiveness and decision-making. Overall. The results show that the model results are robust and are cost-effective in all scenarios presented**

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 66. The with-PAS equivalent comparison is presented in Table 67. Deterministic and probabilistic results are similar, therefore not indicating any signs of non-linearity in the model.

Table 66: PSA results compared to base-case (list price)

	Costs		QALYs		ICERs	
	Deterministic base case	**PSA**	**Deterministic base case**	**PSA**	**Deterministic base case**	**PSA**
Stage II-IIIA population						
Atezolizumab	[redacted]	[redacted]	[redacted]	[redacted]	**£53,549**	**£54,566**
BSC	[redacted]	[redacted]	[redacted]	[redacted]	-	-

Table 67: PSA results compared to base-case (with PAS)

	Costs		QALYs		ICERs	
	Deterministic base case	**PSA**	**Deterministic base case**	**PSA**	**Deterministic base case**	**PSA**
Stage II-IIIA population						
Atezolizumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
BSC	[redacted]	[redacted]	[redacted]	[redacted]	-	-

The incremental cost effectiveness planes in Figure 27 and Figure 28 show the individual PSA iterations for the comparisons of atezolizumab to BSC in the Stage II–IIIA populations at list and PAS price, respectively. At PAS price, atezolizumab was dominant in 30.3% of the simulations; supporting the view that atezolizumab is a cost-effective option for the NHS in patients with Stage II–IIIA NSCLC. Cost effectiveness acceptability curves for the comparisons of atezolizumab to BSC in the Stage II–IIIA populations at list and PAS price are presented in Figure 29 and Figure 30. At PAS price, atezolizumab is deemed the most likely cost-effective treatment option beyond a willingness-to-pay (WTP) of approximately £2,500 per QALY. At a £20,000 and £30,000 WTP, the likelihood of atezolizumab being the most cost-effective treatment option rises to 90% and 94%, respectively.

Figure 27: Incremental cost effectiveness plane – atezolizumab vs BSC in Stage II–IIIA NSCLC, list price

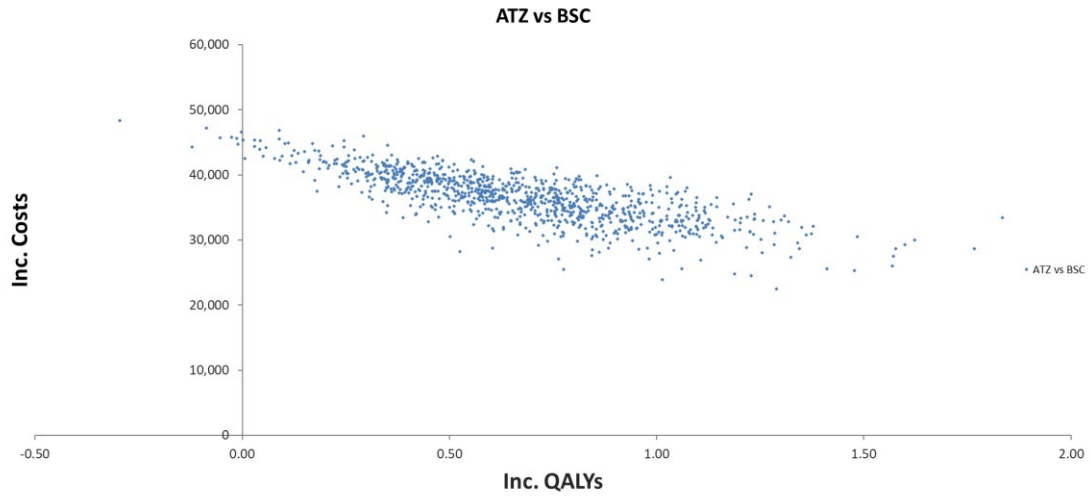


Figure 28: Incremental cost effectiveness plane – atezolizumab vs BSC in Stage II–IIIA NSCLC, PAS price

[redacted]

Figure 29: Cost effectiveness acceptability curve – atezolizumab vs BSC in Stage II–IIIA NSCLC, list price

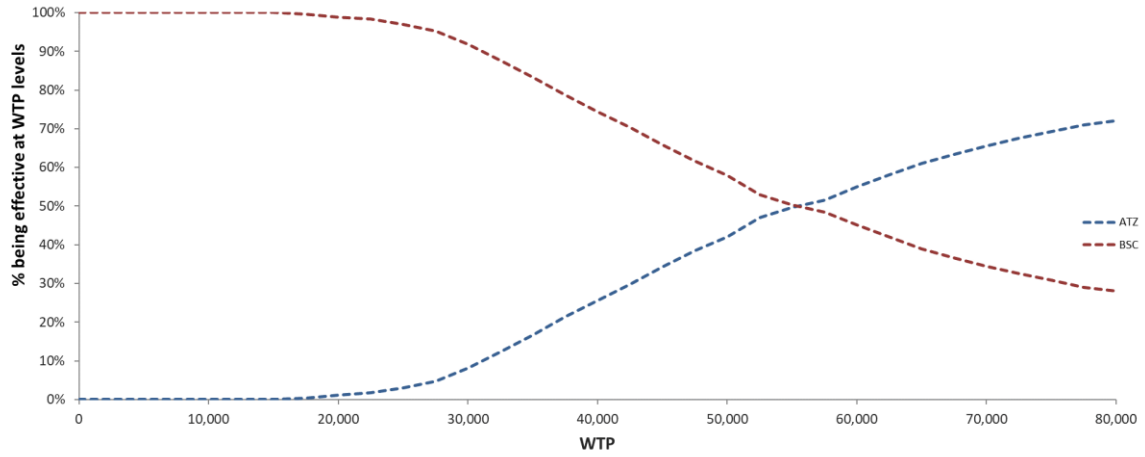


Figure 30: Cost effectiveness acceptability curve – atezolizumab vs BSC in Stage II–IIIA NSCLC, PAS price

[redacted]

B.3.8.2 Deterministic sensitivity analysis

The choice of parameters to include in the deterministic sensitivity analysis (DSA) was considered *a priori* with focus on the parameters which have the greatest impact on the resulting ICERs. The parameter values used which had the greatest impact on the ICER are presented in Table 68 below. The base case values of most parameters were varied using 20% and 80% confidence intervals for the variables, with the exception of discount rates, which were varied from 1.5% to 5.0%. Key remaining model parameters were tested in scenario analyses (see Section B.3.8.3).

Table 68: Parameter values for univariate sensitivity analysis

Parameter	Base case value	Lower value	Higher value
Transition probability (PFS - LR CT)	[redacted]	0.03	0.04
Transition probability (1LMTx - ATZ)	[redacted]	0.10	0.11
Transition probability (1LMTx - BSC)	[redacted]	0.06	0.07
Disutility treatment (DFS)	0.25	0.18	0.31
Disutility no treatment (DFS)	0.25	0.18	0.31
Disutility treatment (LR - CT)	0.08	0.015	0.050
Disutility treatment (LR - PT)	0.17	0.015	0.050
Disutility treatment (1LM)	0.11	0.10	0.11

Disutility no treatment (1LM)	0.17	0.15	0.19
Disutility treatment (2LM)	0.13	0.12	0.14
Disutility no treatment (2LM)	0.17	0.15	0.19
% have progression as first event - 1L metastatic recurrence	[redacted]	0.76	0.89
Discount costs	0.04	0.015	0.050
Discount effects	0.04	0.015	0.050
Administration cost	£299.61	£273.03	£323.41
Total AE management cost - LRR	£14.05	£13.00	£15.21
Total AE management cost - 1L Met Atezo	£87.07	£79.89	£94.32
Total AE management cost - 1L Met BSC	£93.45	£89.05	£97.74
Total AE management cost - 2L Met Atezo	£308.41	£287.03	£323.31
Total AE management cost - 2L Met BSC	£216.58	£200.12	£230.58
End of life cost - disease death	£4,598.01	£4,221.28	£4,964.31

Deterministic sensitivity analyses with-PAS results for the Stage II–IIIA population are presented in Figure 31 (see Appendix N for list price results).

Based on the deterministic sensitivity analyses at PAS price, the most influential parameters appear to be the transition probability to first-line metastatic health state in the BSC arm, discount costs and effects, utility treatment, and administration costs. All results remained significantly below the cost effectiveness 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. This is further evidenced by discount rates being included in the top 10 most sensitive inputs, as discount rates impact results more broadly throughout the model than any other input.

Figure 31: Tornado diagram – Stage II–IIIA, PAS price

B.3.8.3 Scenario analysis

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

Model settings

- Time horizon

Clinical inputs

- Alternative plausible DFS extrapolations (Section B.3.3.3)
- Trial data to inform recurrence types and death (Section B.3.3.6)
- Treatment effect duration (B.3.3.4)
- Cure proportion (B.3.3.3.5)
- Standardised mortality rate (B.3.3.4)
- Transition probability calculation method (B.3.3.6)
- Allow second-line metastatic recurrence (B.3.3.6)
- Month at which there is a change to CT scanning schedule (B.3.5.2)
- Time to off treatment (B.3.5.2.1)

Health state utilities

- Health state utility calculation method (B.3.4.3.1)
- Source of utility inputs for disease-free survival (B.3.4.2.1)

Costs and resource use

- Atezolizumab treatment schedule (B.3.5.1.1)

Results of the scenario analyses are presented in Table 69 for the Stage II–IIIA population at PAS price for atezolizumab (results at list price are presented in Appendix N).

All scenario results remain cost-effective, with the most sensitive scenarios based on the DFS distribution selection. Sensitivity to these scenarios are expected as they determine early movements from the DFS health state, impacting downstream costs and outcomes in progressive states. It should be noted that, whilst sensitive to distribution choice, all distributions explored were judged to be conservative during validation with UK clinical experts.

Table 69: Results from scenario analyses – Stage II–IIIA NSCLC population (PAS price for atezolizumab)

Parameter	Value	Atezolizumab			Best Supportive Care			ATZ vs. BSC	
		Life Years	QALYS	Costs	Life Years	QALYS	Costs	Inc. costs per LY gained	Inc. costs per QALY gained
Base case		8.65	[redacted]	[redacted]	7.29	[redacted]	[redacted]	[redacted]	[redacted]
DFS distributions	Exponential	8.33	[redacted]	[redacted]	6.78	[redacted]	[redacted]	[redacted]	[redacted]
	Weibull	8.06	[redacted]	[redacted]	6.84	[redacted]	[redacted]	[redacted]	[redacted]
	Log-normal	8.88	[redacted]	[redacted]	7.38	[redacted]	[redacted]	[redacted]	[redacted]
	Generalized Gamma	8.63	[redacted]	[redacted]	7.87	[redacted]	[redacted]	[redacted]	[redacted]
	Gompertz	8.30	[redacted]	[redacted]	7.55	[redacted]	[redacted]	[redacted]	[redacted]
	Gamma	8.07	[redacted]	[redacted]	6.76	[redacted]	[redacted]	[redacted]	[redacted]
Trial data used to inform recurrence type split	Pool across Arms	8.70	[redacted]	[redacted]	7.41	[redacted]	[redacted]	[redacted]	[redacted]
Treatment effect	Maintained over Time	8.63	[redacted]	[redacted]	7.29	[redacted]	[redacted]	[redacted]	[redacted]
Standardised mortality rate	1.50	8.41	[redacted]	[redacted]	7.05	[redacted]	[redacted]	[redacted]	[redacted]
	2.00	8.00	[redacted]	[redacted]	6.65	[redacted]	[redacted]	[redacted]	[redacted]
Atezolizumab treatment schedule	1, 680mg/ every 4 weeks	8.65	[redacted]	[redacted]	7.29	[redacted]	[redacted]	[redacted]	[redacted]
LRR: Efficacy by treatment intent	Digitised Data	8.99	[redacted]	[redacted]	7.68	[redacted]	[redacted]	[redacted]	[redacted]
Metastatic recurrence 1L: Efficacy by treatment intent	Digitised Data	8.71	[redacted]	[redacted]	7.36	[redacted]	[redacted]	[redacted]	[redacted]
Metastatic recurrence 1L: allow metastatic recurrence 2L	No	8.98	[redacted]	[redacted]	7.73	[redacted]	[redacted]	[redacted]	[redacted]

Metastatic recurrence 1L - Efficacy source	IMpower110	8.63	[redacted]	[redacted]	7.26	[redacted]	[redacted]	[redacted]	[redacted]
Metastatic recurrence 2L - Efficacy by treatment intent	Digitised Data	8.70	[redacted]	[redacted]	7.35	[redacted]	[redacted]	[redacted]	[redacted]
DFS cost inputs: scanning schedule	36.00	8.65	[redacted]	[redacted]	7.29	[redacted]	[redacted]	[redacted]	[redacted]
Time-to-off treatment	Until Progression or Death	8.65	[redacted]	[redacted]	7.29	[redacted]	[redacted]	[redacted]	[redacted]
Utility method	Source utilities	8.65	[redacted]	[redacted]	7.29	[redacted]	[redacted]	[redacted]	[redacted]
DFS utility source input	Grutters et al. (2010)	8.65	[redacted]	[redacted]	7.29	[redacted]	[redacted]	[redacted]	[redacted]
	Manser et al. (2006)	8.65	[redacted]	[redacted]	7.29	[redacted]	[redacted]	[redacted]	[redacted]
	Black, Keeler and Soneji (2014)	8.65	[redacted]	[redacted]	7.29	[redacted]	[redacted]	[redacted]	[redacted]
	Yang et al. (2014)	8.65	[redacted]	[redacted]	7.29	[redacted]	[redacted]	[redacted]	[redacted]
Metastatic recurrence 1L utility source input	IMpower110	8.65	[redacted]	[redacted]	7.29	[redacted]	[redacted]	[redacted]	[redacted]
	Chouaid et al. (2013)	8.65	[redacted]	[redacted]	7.29	[redacted]	[redacted]	[redacted]	[redacted]
Metastatic recurrence 2L utility source input	IMpower110	8.65	[redacted]	[redacted]	7.29	[redacted]	[redacted]	[redacted]	[redacted]
	Chouaid et al. (2013)	8.65	[redacted]	[redacted]	7.29	[redacted]	[redacted]	[redacted]	[redacted]
	Nafees et al. (2008)	8.65	[redacted]	[redacted]	7.29	[redacted]	[redacted]	[redacted]	[redacted]
Allow vial sharing	No	8.65	[redacted]	[redacted]	7.29	[redacted]	[redacted]	[redacted]	[redacted]
End of Life costs	Exclude	8.65	[redacted]	[redacted]	7.29	[redacted]	[redacted]	[redacted]	[redacted]
Time horizon	10.00	5.83	[redacted]	[redacted]	5.15	[redacted]	[redacted]	[redacted]	[redacted]
	20.00	7.92	[redacted]	[redacted]	6.74	[redacted]	[redacted]	[redacted]	[redacted]
	30.00	8.59	[redacted]	[redacted]	7.25	[redacted]	[redacted]	[redacted]	[redacted]
“Cure” proportion implementation	5 years	8.42	[redacted]	[redacted]	7.07	[redacted]	[redacted]	[redacted]	[redacted]
	6 years	8.04	[redacted]	[redacted]	6.76	[redacted]	[redacted]	[redacted]	[redacted]

	Ramp up 2–8 years	8.49	[redacted]	[redacted]	7.18	[redacted]	[redacted]	[redacted]	[redacted]
	Ramp up 3–8 years	8.24	[redacted]	[redacted]	6.96	[redacted]	[redacted]	[redacted]	[redacted]
Maximum “cure” proportion	20%	7.25	[redacted]	[redacted]	6.10	[redacted]	[redacted]	[redacted]	[redacted]
	40%	7.53	[redacted]	[redacted]	6.35	[redacted]	[redacted]	[redacted]	[redacted]
	60%	7.88	[redacted]	[redacted]	6.66	[redacted]	[redacted]	[redacted]	[redacted]
	80%	8.33	[redacted]	[redacted]	7.03	[redacted]	[redacted]	[redacted]	[redacted]

B.3.8.4 Summary of sensitivity analyses results

PSA, DSA and scenario analysis have been conducted to investigate the uncertainty around the economic model.

PSA results at PAS price were compared to the base case in Table 67. The PSA simulations produced a mean ICER of [redacted] per QALY gained. This value is close to the base case value of [redacted] per QALY gained. Atezolizumab was dominant in 30.3% of the simulations. Furthermore, the cost effectiveness acceptability curve showed that the atezolizumab arm had a > 90% probability of being the most cost-effective treatment at the £30,000 willingness-to pay-threshold at PAS price.

The results of the DSA showed that the model drivers were the transition probability to first-line metastatic health state after curative treatment in the BSC arm, discount costs and effects, utility treatment, and administration costs. The lowest ICER at £[redacted] per QALY gained was produced using the lower value of transition probability to first-line metastatic recurrence in the atezolizumab arm (0.10), and the highest ICER at £[redacted] per QALY gained using the highest value of transition probability to first-line metastatic health state in the BSC arm (0.07). The impact of discounting costs and effects was expected, given the discounting is applied across all the health states and in total, have a noticeable effect on the ICER.

A number of scenario analyses were conducted as part of this submission. The parameters varied included those pertaining to the model settings, clinical parameters, health state utilities, and cost and resource use. ICERs produced by the scenario analysis ranged from £[redacted] per QALY gained (Generalised Gamma for DFS distribution) to atezolizumab dominating BSC (allowing second-line metastatic recurrence).

This analysis was limited by the availability of relevant data. To compensate for the shortfall in data, assumptions and expert opinion were utilised. These factors introduced a degree of uncertainty into the analysis. The extensive sensitivity analysis aimed to quantify and understand the impact of this uncertainty on cost effectiveness and decision making.

B.3.9 Subgroup analysis

Summary of cost effectiveness results for the Stage II–IIIA population, excluding EGFR/ALK+:

- **In the Stage II–IIIA population, excluding EGFR/ALK+ mutations, the resulting with-PAS ICER when comparing atezolizumab to BSC was [redacted] per QALY gained**
- **The PSA (with PAS) ICER results when comparing atezolizumab to BSC was [redacted] per QALY gained, consistent with the deterministic results**
- **The one-way sensitivity analyses showed that the transition probability to first-line metastatic health state in the BSC arm, discount costs, administration costs, and proportion who have progression as first event to first-line metastatic health state were the most influential parameters on the ICER**

Here, the deterministic and probabilistic cost effectiveness analysis results (with-PAS price) are presented for the Stage II-IIIA patients following resection and platinum-based chemotherapy with NSCLC whose tumours have PD-L1 expression on ≥ 1% TC, *excluding EGFR mutant or ALK-positive population*. As previously outlined, osimertinib is currently in an ongoing NICE appraisal for adjuvant treatment in EGFR mutation-positive NSCLC after complete tumour resection.

B.3.9.1 Deterministic analysis (subgroup)

Results at list price are presented in Appendix N. Table 70 presents the deterministic cost effectiveness results of the economic model at PAS price.

Table 70: Deterministic cost effectiveness results – Stage II–IIIA, PD-L1 ≥ 1% NSCLC, excluding EGFR mutant or ALK-positive – PAS price

Technologies	Total costs	Total LYG	Total QALYs	Incremental costs	Incremental LYG	Incremental QALYs	ICER incremental (£/QALY)
Atezolizumab	[redacted]	9.16	[redacted]	[redacted]	1.62	[redacted]	[redacted]
BSC	[redacted]	7.54	[redacted]				

In the Stage II–IIIA population, excluding EGFR/ALK+ and at PAS price for atezolizumab and all comparators:

- Atezolizumab provided [redacted] QALYs and 9.16 life years at a total overall cost of [redacted]. In contrast, BSC provided [redacted] QALYs and 7.54 life years, at a total cost of [redacted]. The resulting ICER when comparing atezolizumab at PAS price to BSC was [redacted] per QALY gained for the Stage II–IIIA, excluding EGFR/ALK+ population.

However, as before, it should be noted that the with-PAS analysis does not account for confidential discounts of therapies used in the treatment pathway, pembrolizumab for first-line metastatic NSCLC and nintedanib for second-line metastatic NSCLC.

The clinical outcomes from the model and the disaggregated results of the cost effectiveness analysis for the Stage II–IIIA, excluding EGFR/ALK+ population are presented in Appendix N.

B.3.9.2 Sensitivity analysis (subgroup)

B.3.9.2.1 Probabilistic sensitivity analysis (subgroup)

To assess the uncertainty surrounding the variables included in the cost effectiveness model, a probability sensitivity analysis PSA was undertaken using 1,000 iterations. Results of the PSA compared to deterministic results at PAS price are presented in Table 71 (results at list price can be found in Appendix N). Deterministic and probabilistic results are similar, therefore not indicating any signs of non-linearity in the model.

Table 71: PSA results compared to deterministic results, Stage II–IIIA, PD-L1 ≥ 1% NSCLC, excluding EGFR mutant or ALK-positive (PAS price)

	Costs		QALYs		ICERs	
	Deterministic	**PSA**	**Deterministic**	**PSA**	**Deterministic**	**PSA**
Stage II–IIIA population, excluding EGFR/ALK+						
Atezolizumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
BSC	[redacted]	[redacted]	[redacted]	[redacted]	-	-

The incremental cost effectiveness plane in Figure 32 show the PSA iterations for the comparison of atezolizumab to BSC in the Stage II–IIIA populations without EGFR/ALK+, at PAS price. In addition, the cost effectiveness acceptability curves for the comparisons of atezolizumab to BSC in the Stage II-IIIA populations without EGFR/ALK+, at PAS price are shown in Figure 33. At PAS price, atezolizumab is deemed the most likely cost-effective treatment option beyond a willingness-to-pay (WTP) of approximately £[redacted] per QALY. At a £20,000 and £30,000 WTP, the likelihood of atezolizumab being the most cost-effective treatment option rises to [redacted] and [redacted], respectively.

Incremental cost effectiveness planes and cost effectiveness acceptability curves at list price for atezolizumab vs BSC in the Stage II–IIIA population excluding EGFR/ALK+ can be found in Appendix N.

Figure 32: Incremental cost effectiveness plane – atezolizumab vs BSC in Stage II–IIIA, PD-L1 ≥ 1% NSCLC, excluding EGFR mutant or ALK-positive (PAS price)

[redacted]

Figure 33: Cost effectiveness acceptability curve – atezolizumab vs BSC in Stage II–IIIA, PD-L1 ≥ 1% NSCLC, excluding EGFR mutant or ALK-positive (PAS price)[redacted]

B.3.9.2.2 Deterministic sensitivity analysis (subgroup)

Deterministic sensitivity analyses with-PAS results for the Stage II–IIIA population, excluding EGFR/ALK+ population are presented in Figure 34 (results at list price shown in Appendix N).

Based on the deterministic sensitivity analyses at PAS price, the most influential parameters appear to be the transition probability to first-line metastatic health state in the BSC arm, discount costs, administration costs, and proportion who have progression as first event to first-line metastatic health state.

Results of the DSA are similar to the Stage II-IIIA population results and should be interpreted similarly. Therefore, as discussed in Section B.3.8.2, the DSA 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. This is further evidenced by discount rates being included in the top 10 most sensitive inputs, as discount rates impact results more broadly throughout the model than any other input.

Figure 34: Tornado diagram – atezolizumab vs BSC in Stage II–IIIA, PD-L1 ≥ 1% NSCLC, excluding EGFR mutant or ALK-positive (PAS price)

B.3.9.2.3 Scenario analysis (subgroup)

Scenario analyses (with PAS) were conducted to assess uncertainty around remaining parameter inputs and structural assumptions in the model for the Stage II-IIIA population, excluding EGFR/ALK+ (Table 72). This was carried out as described in Section B.3.8.3 for the Stage II-IIIA population. Similar to the PSA and DSA, sensitivity of results were consistent with the Stage II-IIIA population and should be interpreted similarly. Results at list price are presented in Appendix N.

Table 72: Results from scenario analyses – Stage II-IIIA, PD-L1 >1% NSCLC, excluding EGFR mutant or ALK-positive (PAS price for atezolizumab)

Parameter	Value	Atezolizumab			Best Supportive Care			ATZ vs. BSC	
		Life Years	QALYS	Costs	Life Years	QALYS	Costs	Inc. costs per LY gained	Inc. costs per QALY gained
Base case		9.16	[redacted]	[redacted]	7.54	[redacted]	[redacted]	[redacted]	[redacted]
DFS distributions	Exponential	8.76	[redacted]	[redacted]	7.00	[redacted]	[redacted]	[redacted]	[redacted]
	Weibull	8.65	[redacted]	[redacted]	7.16	[redacted]	[redacted]	[redacted]	[redacted]
	Log-normal	9.38	[redacted]	[redacted]	7.64	[redacted]	[redacted]	[redacted]	[redacted]
	Generalized Gamma	9.22	[redacted]	[redacted]	8.16	[redacted]	[redacted]	[redacted]	[redacted]
	Gompertz	9.00	[redacted]	[redacted]	7.97	[redacted]	[redacted]	[redacted]	[redacted]
	Gamma	8.62	[redacted]	[redacted]	7.07	[redacted]	[redacted]	[redacted]	[redacted]
Trial data used to inform recurrence type split	Pool across Arms	9.17	[redacted]	[redacted]	7.68	[redacted]	[redacted]	[redacted]	[redacted]
Treatment effect	Maintained over Time	9.16	[redacted]	[redacted]	7.54	[redacted]	[redacted]	[redacted]	[redacted]
Standardised mortality rate	1.50	8.88	[redacted]	[redacted]	7.28	[redacted]	[redacted]	[redacted]	[redacted]
	2.00	8.42	[redacted]	[redacted]	6.86	[redacted]	[redacted]	[redacted]	[redacted]
Atezolizumab treatment schedule	1, 680mg/ every 4 weeks	9.16	[redacted]	[redacted]	7.54	[redacted]	[redacted]	[redacted]	[redacted]
LRR: Efficacy by treatment intent	Digitised Data	9.50	[redacted]	[redacted]	7.91	[redacted]	[redacted]	[redacted]	[redacted]
Metastatic recurrence 1L:	No	9.45	[redacted]	[redacted]	7.96	[redacted]	[redacted]	[redacted]	[redacted]

Efficacy by treatment intent									
Metastatic recurrence 1L - Efficacy source	IMpower110	9.14	[redacted]	[redacted]	7.51	[redacted]	[redacted]	[redacted]	[redacted]
Metastatic recurrence 2L - Efficacy by treatment intent	Digitised Data	9.20	[redacted]	[redacted]	7.60	[redacted]	[redacted]	[redacted]	[redacted]
DFS cost inputs: scanning schedule	36.00	9.16	[redacted]	[redacted]	7.54	[redacted]	[redacted]	[redacted]	[redacted]
Time-to-off treatment	Until Progression or Death	9.16	[redacted]	[redacted]	7.54	[redacted]	[redacted]	[redacted]	[redacted]
Utility method	Source utilities	9.16	[redacted]	[redacted]	7.54	[redacted]	[redacted]	[redacted]	[redacted]
DFS utility source input	Grutters et al. (2010)	9.16	[redacted]	[redacted]	7.54	[redacted]	[redacted]	[redacted]	[redacted]
	Manser et al. (2006)	9.16	[redacted]	[redacted]	7.54	[redacted]	[redacted]	[redacted]	[redacted]
	Black, Keeler and Soneji (2014)	9.16	[redacted]	[redacted]	7.54	[redacted]	[redacted]	[redacted]	[redacted]
	Yang et al. (2014)	9.16	[redacted]	[redacted]	7.54	[redacted]	[redacted]	[redacted]	[redacted]
Metastatic recurrence 1L utility source input	IMpower110	9.16	[redacted]	[redacted]	7.54	[redacted]	[redacted]	[redacted]	[redacted]
	Chouaid et al. (2013)	9.16	[redacted]	[redacted]	7.54	[redacted]	[redacted]	[redacted]	[redacted]
Metastatic recurrence 2L utility source input	IMpower110	9.16	[redacted]	[redacted]	7.54	[redacted]	[redacted]	[redacted]	[redacted]
	Chouaid et al. (2013)	9.16	[redacted]	[redacted]	7.54	[redacted]	[redacted]	[redacted]	[redacted]

	Nafees et al. (2008)	9.16	[redacted]	[redacted]	7.54	[redacted]	[redacted]	[redacted]	[redacted]
Allow vial sharing	0.00	9.16	[redacted]	[redacted]	7.54	[redacted]	[redacted]	[redacted]	[redacted]
End of Life costs	Exclude	9.16	[redacted]	[redacted]	7.54	[redacted]	[redacted]	[redacted]	[redacted]
Time horizon	10.00	6.07	[redacted]	[redacted]	5.26	[redacted]	[redacted]	[redacted]	[redacted]
	20.00	8.37	[redacted]	[redacted]	6.96	[redacted]	[redacted]	[redacted]	[redacted]
	30.00	9.10	[redacted]	[redacted]	7.50	[redacted]	[redacted]	[redacted]	[redacted]
"Cure" proportion implementation	5 years	8.96	[redacted]	[redacted]	7.33	[redacted]	[redacted]	[redacted]	[redacted]
	6 years	8.58	[redacted]	[redacted]	7.03	[redacted]	[redacted]	[redacted]	[redacted]
	Ramp up 2–8 years	8.99	[redacted]	[redacted]	7.44	[redacted]	[redacted]	[redacted]	[redacted]
	Ramp up 3–8 years	8.76	[redacted]	[redacted]	7.22	[redacted]	[redacted]	[redacted]	[redacted]
Maximum "cure" proportion	20%	7.76	[redacted]	[redacted]	6.35	[redacted]	[redacted]	[redacted]	[redacted]
	40%	8.04	[redacted]	[redacted]	6.61	[redacted]	[redacted]	[redacted]	[redacted]
	60%	8.39	[redacted]	[redacted]	6.91	[redacted]	[redacted]	[redacted]	[redacted]
	80%	8.84	[redacted]	[redacted]	7.29	[redacted]	[redacted]	[redacted]	[redacted]

B.3.10 Validation

The modelling approach and structure is consistent with the only other NICE appraisal looking at a similar population: Osimertinib for adjuvant treatment of EGFR mutation-positive non-small-cell lung cancer after complete tumour resection (ID3835) (83). 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]. The feedback provided confirmed that the structure of the model accurately represents the disease and treatment pathways of early NSCLC. In addition, 1:1 discussions were held with UK oncologists in August 2021 regarding the model assumptions approach to "cure", and model extrapolations and they agreed with the company's approach to the curve adjustments (see Section B.3.3.4 for further details). 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 B.3.3.3 and B.3.3.4. The clinical outcomes in both 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 the osimertinib NICE submission (ID3835) and similar to this submission, Roche uses the NHS reference costs, the PSSRU, clinical expert opinion and in addition, previous atezolizumab appraisals to inform the cost and resource use inputs (TA520 (78), TA584 (110), TA705 (163).

A formal quality assessment and validation of model outcomes was carried out by an independent assessor prior to submission. A technical cell by cell verification of formulas, functions, and coding was performed as part of this process. A number of 'pressure tests'

[23] April 2021: Four UK oncologists were consulted in 1:1 interviews and two UK health economists from a UK consultancy were consulted in an interview
July 2021: An advisory board was held with 11 UK clinical oncologists and surgeons
August 2021: Three oncologists were consulted in 1:1 interviews

were also conducted using extreme values and these were compared to expected outputs to assess the functional accuracy.

B.3.11 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 in the transition probability 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**
- **In a potentially curative setting, preventing early lung cancer recurrence or progression to metastatic disease has significant benefits for both patients and society**

B.3.11.1 Comparison with published economic literature

This is the first economic evaluation focused on assessing the cost effectiveness of atezolizumab for the adjuvant treatment of patients with Stage II–IIIA, PD-L1 TC ≥ 1% NSCLC versus best supportive care from a UK health system perspective. Roche have included the Stage II–IIIA, PD-L1 ≥ 1% NSCLC, excluding EGFR mutant or ALK-positive population as we are aware of the ongoing appraisal for osimertinib (ID3835 (83).

Since no study assessing the cost effectiveness for the target population was identified from the SLR, it is not possible to compare the results of the economic model developed in this submission with any publications. However, as discussed in B.3.3.3, the results for the BSC arm are comparable to published literature.

B.3.11.2 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 [redacted].

The analysis is applicable to clinical practice in England since:

- The patient population in IMpower010 trial and the de novo economic evaluation are reflective of patients following resection and platinum-based chemotherapy with NSCLC whose tumours have PD-L1 expression on ≥ 1% of tumour cells. 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 for osimertinib 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 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.3.11.3 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.3.11.2. A conservative assumption has also been used in limiting the treatment effect at 5 years. Although there is a lack of evidence to support this, 5 years was adopted in alignment with previous NICE appraisals for atezolizumab (TA531 (85), TA428 (99), TA557 (87), TA600 (88).

The economic evaluation is also associated with 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.

- Published literature and previous NICE appraisals for transition probabilities – The model used published literature and previous NICE appraisals for data on the progressive health states and the heterogeneity of these studies contributes to the uncertainty on the ICER. This was accounted for with the extensive scenario analyses carried out which showed that varying the transition probabilities did not have much impact on the ICER (remained below £3,100 per QALY gained).
- PRO data – No PRO data was collected as part of IMpower010. The systematic literature review (Appendix K) 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.
- Adjusting the DFS curves – Given the short follow-up data available for IMpower010 and the higher frequency of recurrences during this time, it was necessary to adjust the curves to avoid overestimating the proportions of patients who have recurrences in the longer term (this introduced an unrealistic 'kink' in the DFS curves). Assumptions were made on the cure rate, mortality, and treatment effect, based on published literature, previous NICE appraisals, and clinical validation.
- Subsequent therapies – Based on UK clinical oncologists' opinion, the model assumes that patients on the atezolizumab arm would not receive subsequent immunotherapy, however, the model currently assumes efficacy would not be affected (although treatment effect would cease at five years). There are no currently available data to address the level of impact on efficacy.

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.3.11.4 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. It is the first and only immunotherapy and PD-L1 inhibitor to have met its primary endpoint of DFS in the adjuvant setting (IMpower010). Atezolizumab reduced the risk of recurrence, new primary NSCLC formation, or death by 34% (DFS HR 0.66) compared to BSC, in the PD-L1 ≥ 1% Stage II–IIIA population

Atezolizumab has the potential to become the new standard of care in this setting. In IMpower010, a DFS benefit was observed (DFS HR: 0.66; 95% CI: 0.50, 0.88; $p = 0.0039$), with a significant 34% reduction in risk of disease relapse in patients with resected, PD-L1 TC ≥ 1% Stage II–IIIA NSCLC when treated with atezolizumab versus BSC. In addition, there were no new safety signals demonstrated in IMpower010 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 resected PD-L1 ≥ 1% Stage II–IIIA NSCLC, 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. 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 for patients with Stage II–IIIA, PD-L1 TC ≥ 1% NSCLC [redacted] per QALY gained). 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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NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single technology appraisal

Atezolizumab for adjuvant treatment of resected non-small-cell lung cancer [ID3852]

Clarification questions

November 2021

File name	Version	Contains confidential information	Date
ID3852 Atezolizumab Clarification letter_company response_v2_Mar2022	3	Yes	8Mar2022

Section A: Clarification on effectiveness data

Literature searches

A1. PRIORITY QUESTION. Please could the company indicate whether any clinical trial register searches were carried out (e.g. a search of Clinicaltrials.gov or similar)? [Appendix D Section 1.3]

A search of the Cochrane central register of controlled trials (CENTRAL) database was carried out. Other clinical trial registries such as clinicaltrials.gov, and the WHO International Clinical Trials Registry Platform (ICTRP) are indexed in the CENTRAL database and therefore were also searched via this database.

A2. Please could the company confirm that no subject heading/controlled vocabulary searches were carried out, for example for the drug names in Embase.com in Table 2- line #6? [Appendix D]

The subject heading/controlled vocabulary was used in the searches, specifically for the patient population and study design strings, as well as to remove irrelevant studies (e.g. pre-clinical animal studies). The title/abstract restriction for the drug names were used in Embase, and did not include subject heading/ controlled vocabulary for those terms.

Clinical effectiveness data

A3. The ERG noted that no health-related quality of life data were available from the pivotal trial. The company stated that this was because patient-related outcomes were not commonly used when the trial was designed. However, the ERG noted that EQ-5D-3L has been the standard for NICE for a considerable time. Could the company expand on why it did not include a measure of quality of life when designing its trial?

Whilst EQ-5D-3L has been the standard for some time, the assessment of HRQOL was not routine in the early lung cancer setting at the time of study design for IMpower010. Along with IMpower010, other cancer immunotherapy trials in the adjuvant setting for early stage NSCLC are not collecting health-related quality of life

data - ANVIL (1), ALCHEMIST (2), Checkmate-816 (3), Checkmate-77T (4), and KEYNOTE-091/PEARLS (5), suggesting that it was not routine for either the early lung cancer setting or for adjuvant/ neoadjuvant studies.

This may be because patients with early NSCLC are generally an asymptomatic patient population and are diagnosed incidentally. Additionally, following surgery these patients are tumour-free and considered disease-free. Therefore, at the time of study initiation, it was thought to be difficult to demonstrate an impact of atezolizumab on disease-related quality of life in a patient population that is relatively asymptomatic.

A4. In the Kaplan-Meier (KM) curves for disease-free survival (DFS) shown in Doc B (e.g. figure 4, figure 11) there are many censoring marks within the later assessments. The ERG understands this is because these later assessments are the last follow-up times for some disease-free patients (*"Data for patients who did not have any disease-free survival events were censored at the date of the last tumour assessment"*, Felip et al 2021 p4). Please could the company confirm or correct the ERG's interpretation.

The ERG's interpretation can be confirmed. According to section 4.4.1 of the statistical analysis plan (SAP), "Data for patients who are not reported as experiencing disease recurrence, a new primary NSCLC, or death will be censored at the date of the last tumour assessment."

A5. For patients who have locoregional recurrence, the submission states (section 3.3.6.1, p88) the following proportions for treatment intent: Curative treatment: 80%, Palliative treatment: 20%, No treatment: 0%. It is stated that 'estimate[s] [are] from Sonoda et al. 2019'. However, the ERG have been unable to locate these values in Sonoda et al 2019. Please can the company point to where these values can be found in the aforementioned publication?

This was an error and the reference here should be Sonoda et al. 2020 (6).

The evidence used in the submission can be found in Table 4 of Sonoda et al. 2020 (6), which is titled 'Sites of recurrence and treatment of recurrence patients and post-recurrence patients'. Row 12 of Table 4 shows that out of the 128 patients in the

sample who experienced locoregional recurrence, 23 received best supportive care and 105 received radical local treatment. This corresponds to a proportion of patients (18%) not receiving radical local treatment.

A6. In B.2.6.5, the median times to relapse are given as 17.6 (atezolizumab arm) and 10.9 months (BSC arm). But in figure 7 the median times for locoregional and distant combined are given as 24.0 and 5.3 months, which does not correspond.

Also, the sample sizes in figure 7 (written at base of bars) do not add up.
Blue bars: LR (n=35), distant (n=28), LR and distant (n=9)
Red bars: LR (n=42), distant (n=40), LR and distant (n=17)
Please clarify (or correct).

To clarify, the patients who experienced both locoregional (LR) and distant relapse are not a combination of LR-only relapse and distant-only relapse. They are a distinct and separate group of patients, who on relapse had both LR and distant recurrence.

Therefore in Figure 7, for those patients who experienced locoregional and distant recurrence (24.0 months and 5.3 months for the atezolizumab arm and BSC arm respectively), this should not correspond with the median time to any relapse (17.6 months and 10.9 months for the atezolizumab arm and BSC arm, respectively). As the median time to any relapse includes four different groups of patients, which includes LR-only relapse, distant-only relapse, both locoregional- and distant-relapse or central nervous system (CNS)-only relapse.

This is also the case for the sample size of each group, written at the base of the bars. The LR and distant group is not a combination of LR-only and distant-only relapse. Therefore, the sample size for LR-only relapse and for distant-only relapse should not add up to the sample size for LR and distant relapse.

Section B: Clarification on cost-effectiveness data

Company note: Since submission of the dossier on 28th October 2021, an error was identified and corrected in the model. Under the Utility Inputs sheet, the disutility input (F13) was using the Manser et al. 2006 source rather than the Jang et al. 2010 source. This changed the ICER from £2,224 to £1,464 per QALY.

Model type and structural assumptions

B1. Please justify the use of the cohort-level, discrete-time nature of the company's cost-effectiveness model, versus other available model types, given the strong assumptions of time-invariant transition probabilities in post-DFS states in the company's analysis. Refer to precedent in the model-based economic evaluations identified in the systematic review reported in Appendix J, categorising the identified studies by model type.

A Markov model was developed to determine the cost-effectiveness of atezolizumab as adjuvant treatment versus best supportive care in patients with early NSCLC. This is similar to the model that was developed to determine the cost-effectiveness of osimertinib as adjuvant treatment in EGFR mutation-positive NSCLC patients after complete tumour resection [NICE TA10756] (7). The SLR identified 14 economic evaluations that reported the use of a model, and showed that cohort-level and individual-level models were evenly used (7 cohort-level models, 7 individual-level models; moreover, no discrete event simulations or partitioned survival analyses). The benefit of using a Markov model is that it significantly reduces the complexity of the model, and reduces the time required to run macros (e.g. PSA). While the use of an individual-level approach may have improved the accuracy of the model results by allowing the post-DFS health state transitions to be time-dependent and depend from which health state the transition occurs, sensitivity analysis shows that results of the model are not sensitive to changes in these transition probabilities (see Figure 49 in the Appendices).

In addition to the literature supporting the use of a Markov structure, the model was validated with UK clinical oncologists and UK Health Economists during model

conceptualisation, and post-model build (see confidential folder “ERG Request for Expert Opinion Documents” for further information).

B2. Please justify the choice of a 1-month cycle length versus a 1-week cycle length, when the assumed atezolizumab treatment cycles are three weeks in length.

The model uses a one-month cycle to improve the speed of the model when running macros given it considers a lifetime time-horizon. Moreover, given the slower speed of progression in early NSCLC versus metastatic NSCLC, the use of a monthly cycle length appears more appropriate. This is similar to the osimertinib cost-effectiveness model for the adjuvant treatment of EGFR mutation-positive NSCLC after complete tumour resection [NICE TA10756] (7). However, the model uses a treatment schedule with weekly cycles to accurately account for the proportion of patients who discontinue each cycle of treatment, and to calculate the cost of atezolizumab treatment each week (summarised monthly). It is important to note that, due to the treatment schedule, atezolizumab treatment costs are applied within the first year of the model only and therefore would not be impacted by discounting. Thus, the use of a monthly cycle will not have an impact on these costs.

B3. Please justify the modelling assumption that people with locoregional recurrence receiving either palliative treatment or no treatment cannot experience metastasis.

Patients who have locoregional recurrence and treat with palliative intent or receive no treatment remain in the locoregional recurrence health state until death. This restriction does not imply that patients cannot experience metastasis in the model. It is assumed that the effect that metastasis has on the overall survival of these patients is captured in the transition probability from the locoregional recurrence health state to the death health state for these patients, as it is plausible to assume that some patients in the sample of Kruser et al. 2014 (8) may have experienced metastasis before death. The only restriction that this has on the model is that these patients cannot receive 1L or 2L treatment after metastasis. This restriction was deemed appropriate when the model structure was presented to UK clinical oncologists.

B4. Please justify the assumption that patients who discontinued atezolizumab treatment early in IMpower010 are no different to patients who complete the full 16 cycles (in terms of their immediate HRQL and resource use implications, and long-term prognosis), until and unless a DFS event is experienced.

In the model, the health related quality of life and healthcare resource use of patients who discontinue atezolizumab before the full 16 cycles is similar to those who complete the full 16 cycles, until they experience a DFS event. As the IMpower010 trial does not collect PROs, it is unclear if the health related quality of life of these groups of patients differ, and whether this difference is statistically significant. Evidence from the literature is unavailable to determine if this is the case. Moreover, there is a lack of evidence in the literature to determine if the healthcare resource use of these patients differ. With respect to long-term prognosis, we can expect that the transition probabilities from the DFS to the post-DFS health states should already capture any effect that patients who discontinued treatment before 16 cycles have on their values. This is because DFS was analysed with the use of patients who did and did not complete the full 16 cycles. It was therefore assumed that, beyond choice of therapy, downstream outcomes and resource use would not be impacted by prior treatment.

IMpower010 data / analysis

B5. In the company submission, Figures 20 and 21 of Document B are described as "OS curve extrapolations". Please confirm that these are projections of overall survival (OS) from the company's cost-effectiveness model, and as such not based on the observed OS data from IMpower010.

This is correct. Figures 20 and 21 were mislabelled and are in fact projections of OS rather than observed OS data from IMpower010.

B6. PRIORITY QUESTION. Appendix N shows median DFS, model vs IMpower010, for the target group and subgroup.

a. Please also provide DFS% comparisons, every 3 months (cycles), model vs IMpower10 (KM), up to the end of the available KM data.

In IMpower010, the tumour assessment schedule was every 4 months during the first year, every six months from the second year until year 5 and annually afterwards until disease recurrence, death, loss to follow-up, consent withdrawal, or study termination by the Sponsor, whichever occurs first. Therefore, we have provided DFS% every 4 months in the first year and every 6 months thereafter.

Please see Table 1 and Table 2 for the DFS comparisons between model vs. IMpower010 (KM) data.

Table 1: DFS from the model versus clinical trial - atezolizumab, PD-L1 ≥ 1% Stage II–IIIA NSCLC

Months	Model results	IMpower010, PD-L1 ≥ 1% Stage II–IIIA NSCLC, EGFR mutant or ALK-positive KM estimates
0	[redacted]	1.00
4	[redacted]	0.96
8	[redacted]	0.92
12	[redacted]	0.87
18	[redacted]	0.81
24	[redacted]	0.75
30	[redacted]	0.68
36	[redacted]	0.60
42	[redacted]	0.55
48	[redacted]	0.51
54	[redacted]	0.51

Table 2: DFS from the model versus clinical trial - BSC, PD-L1 ≥ 1% Stage II–IIIA NSCLC

Months	Model results	IMpower010, PD-L1 ≥ 1% Stage II–IIIA NSCLC , EGFR mutant or ALK-positive KM estimates
0	[redacted]	1.00
4	[redacted]	0.91
8	[redacted]	0.79
12	[redacted]	0.75

18	[redacted]	0.67
24	[redacted]	0.61
30	[redacted]	0.56
36	[redacted]	0.48
42	[redacted]	0.43
48	[redacted]	0.43
54	[redacted]	0.43

b. Please also provide OS% comparisons, every 3 months (cycles), model vs IMpower10 (KM), up to the end of the available KM data.

Similarly, for DFS, we have provided OS% every 4 months in the first year and every 6 months thereafter. Please see Table 3 and Table 4 for the OS comparisons between model vs. IMpower010 (KM) data. Note that after month 36, there is high uncertainty given the small number of patients at risk and the small number of events occurring after then.

Table 3: OS from the model versus clinical trial - atezolizumab, PD-L1 ≥ 1% Stage II–IIIA NSCLC

Months	Model results	IMpower010, PD-L1 ≥ 1% Stage II–IIIA NSCLC, EGFR mutant or ALK-positive KM estimates
0	[redacted]	1.00
4	[redacted]	0.99
8	[redacted]	0.98
12	[redacted]	0.97
18	[redacted]	0.93
24	[redacted]	0.91
30	[redacted]	0.87
36	[redacted]	0.82
42	[redacted]	0.79
48	[redacted]	0.79
54	[redacted]	0.79

Table 4: OS from the model versus clinical trial - BSC, PD-L1 ≥ 1% Stage II–IIIA NSCLC

Months	Model results	IMpower010, PD-L1 ≥ 1% Stage II–IIIA NSCLC, EGFR mutant or ALK-positive KM estimates
0	[redacted]	1.00
4	[redacted]	1.00
8	[redacted]	0.97
12	[redacted]	0.95
18	[redacted]	0.93
24	[redacted]	0.87
30	[redacted]	0.82
36	[redacted]	0.79
42	[redacted]	0.73
48	[redacted]	0.73
54	[redacted]	0.73

B7. PRIORITY QUESTION. Please provide a smoothed hazard plot (or equivalent reflection of the estimated hazards over time) and a Q-Q plot for the IMpower010 DFS Stage II–IIIA PD-L1+ KM data informing the cost-effectiveness analysis. Separately, please provide a smoothed hazard plot (or equivalent) for each parametric model fitted to the DFS data, overlaying the corresponding DFS KM hazard-time plot in each case.

Given that the estimation of the smoothed hazard function can be very unstable since it may depend heavily on the features of the algorithm used, the company has provided the plot of KM cumulative hazard vs time (see Figure 1 and Figure 2). The cumulative hazard estimated with each parametric function is overlayed with the KM cumulative hazard in one plot (see Figure 3 and Figure 4). The cumulative hazard plots for each parametric model fitted to the DFS data is also provided in separate plots in Figure 5–Figure 18. These cumulative hazard plots show the probability of experiencing DFS events until time t and its 95% confidence interval (shaded area/dotted lines).

In addition, the Q-Q plots for each parametric function are provided (see Figure 19–Figure 30), showing the observed quantiles (observed times at which DFS events occurred) and the predicted ones for each parametric function corresponding to the probability estimated via the KM method after an adjustment. These plots can be

useful to assess the fitting of the parametric function to the observed survival data, although after month 36 there is high uncertainty, given the small number of patients at risk and the small number of events occurring after then.

Figure 1: Cumulative Hazard Plot (IMpower010, DFS, Stage II-IIIA, PD-L1+, 21 Jan 2021 Data-Cut, Atezolizumab Arm)

Figure 2: Cumulative Hazard Plot (IMpower010, DFS, Stage II-IIIA, PD-L1+, 21 Jan 2021 Data-Cut, BSC Arm)

Figure 3: DFS – KM cumulative hazard and parametric fits for atezolizumab arm

Figure 4: DFS – KM cumulative hazard and parametric fits for BSC arm

Figure 5: DFS – KM cumulative hazard and Exponential fit for atezolizumab arm

Figure 6: DFS – KM cumulative hazard and Weibull fit for atezolizumab arm

Figure 7: DFS – KM cumulative hazard and Log-Normal fit for atezolizumab arm

Figure 8: DFS – KM cumulative hazard and Generalised Gamma fit for atezolizumab arm

Figure 9: DFS – KM cumulative hazard and Log-Logistic fit for atezolizumab arm

Figure 10: DFS – KM cumulative hazard and Gompertz fit for atezolizumab arm

Figure 11: DFS – KM cumulative hazard and Gamma fit for atezolizumab arm

Figure 12: DFS – KM cumulative hazard and Exponential fit for BSC arm

Figure 13: DFS – KM cumulative hazard and Weibull fit for BSC arm

Figure 14: DFS – KM cumulative hazard and Log Normal fit for BSC arm

Figure 15: DFS – KM cumulative hazard and Generalised Gamma fit for BSC arm

Figure 16: DFS – KM cumulative hazard and Log-Logistic fit for BSC arm

Figure 17: DFS – KM cumulative hazard and Gompertz fit for BSC arm

Figure 18: DFS – KM cumulative hazard and Gamma fit for BSC arm

Figure 19: Q-Q plot (exponential) - Atezolizumab arm

Figure 20: Q-Q plot (Weibull) - Atezolizumab arm

Figure 21: Q-Q plot (Log-Logistic) - Atezolizumab arm

Figure 22: Q-Q plot (Log normal) - Atezolizumab arm

Figure 23: Q-Q plot (Gamma) - Atezolizumab arm

Figure 24: Q-Q plot (Gen Gamma) - Atezolizumab arm

Figure 25: Q-Q plot (Gompertz) - Atezolizumab arm

[redacted]

Figure 26: Q-Q plot (Exponential) - BSC arm[redacted]

Figure 27: Q-Q plot (Weibull) - BSC arm[redacted]

Figure 28: Q-Q plot (Log-logistic) - BSC arm[redacted]

Figure 29: Q-Q plot (Log normal) - BSC arm[redacted]

Figure 30: Q-Q plot (Gamma) - BSC arm[redacted]

Figure 31: Q-Q plot (Gen Gamma) - BSC arm

[redacted]

Figure 32: Q-Q plot (Gompertz) - BSC arm

[redacted]

B8. PRIORITY QUESTION. Following NICE Decision Support Unit Technical Support Documents 14, please provide parametric survival analysis of the IMpower010 DFS Stage II–IIIA PD-L1+ Overall Survival (OS) KM data.

Please see Figure 33 and Figure 34 below for the parametric survival plots showing the KM overlaid with the expected survival for each of the parametric functions using the IMpower010 OS and DFS Stage II-IIIA PD-L1+ KM data. The KM survival plots with the survival expected with log-logistic distribution (company base case) is shown separately in Figure 35 and Figure 36.

Figure 33: OS - KM and parametric fits for atezolizumab until 60 months

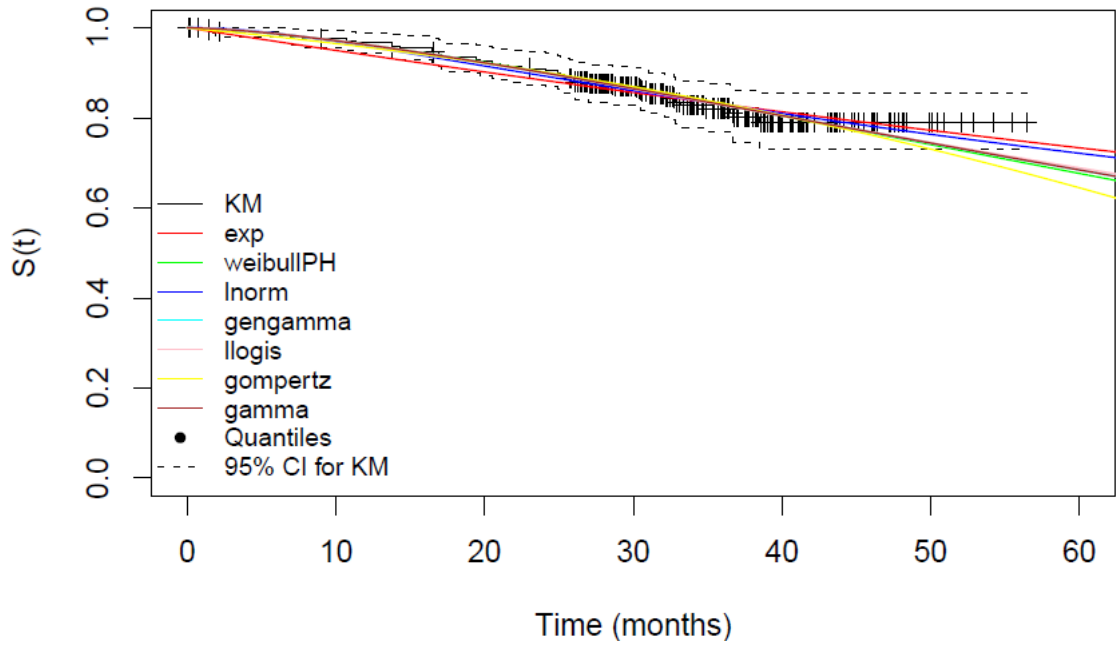


Figure 34: DFS - KM and parametric fits for BSC until 60 months

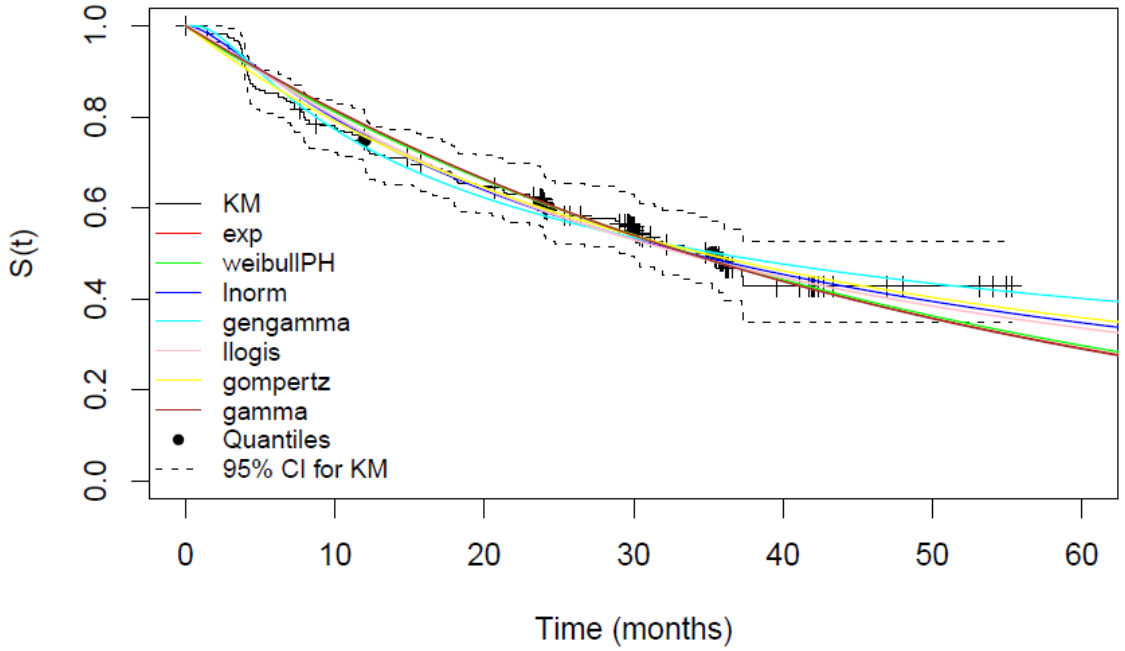


Figure 35: OS - KM and log-logistic fit for atezolizumab (base case)

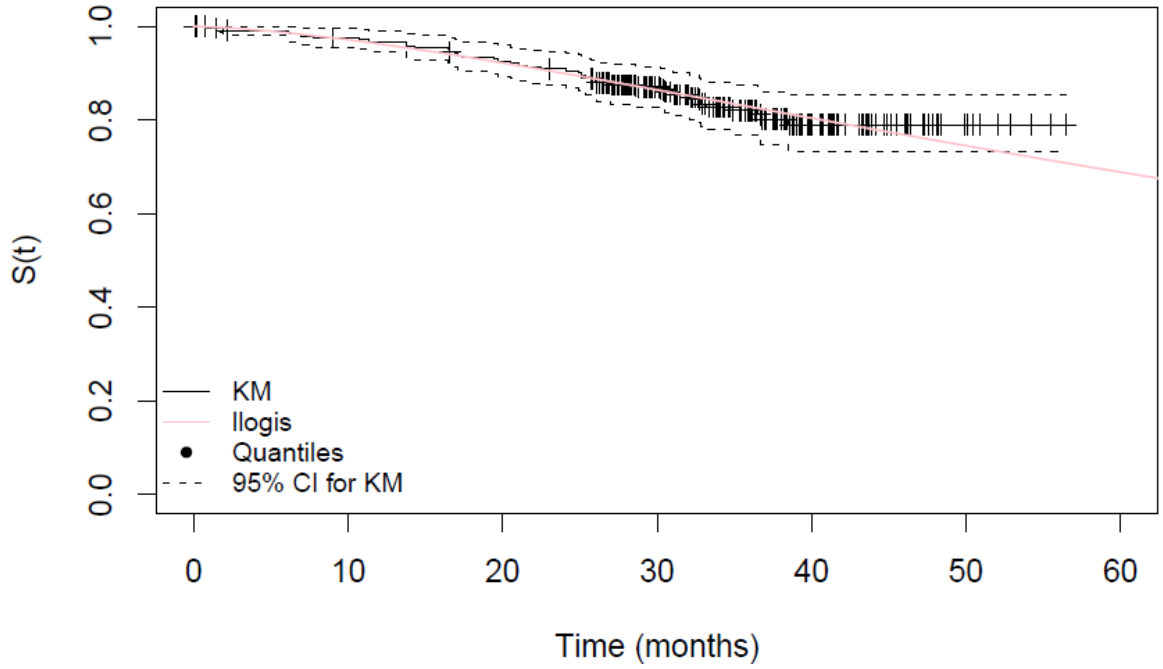
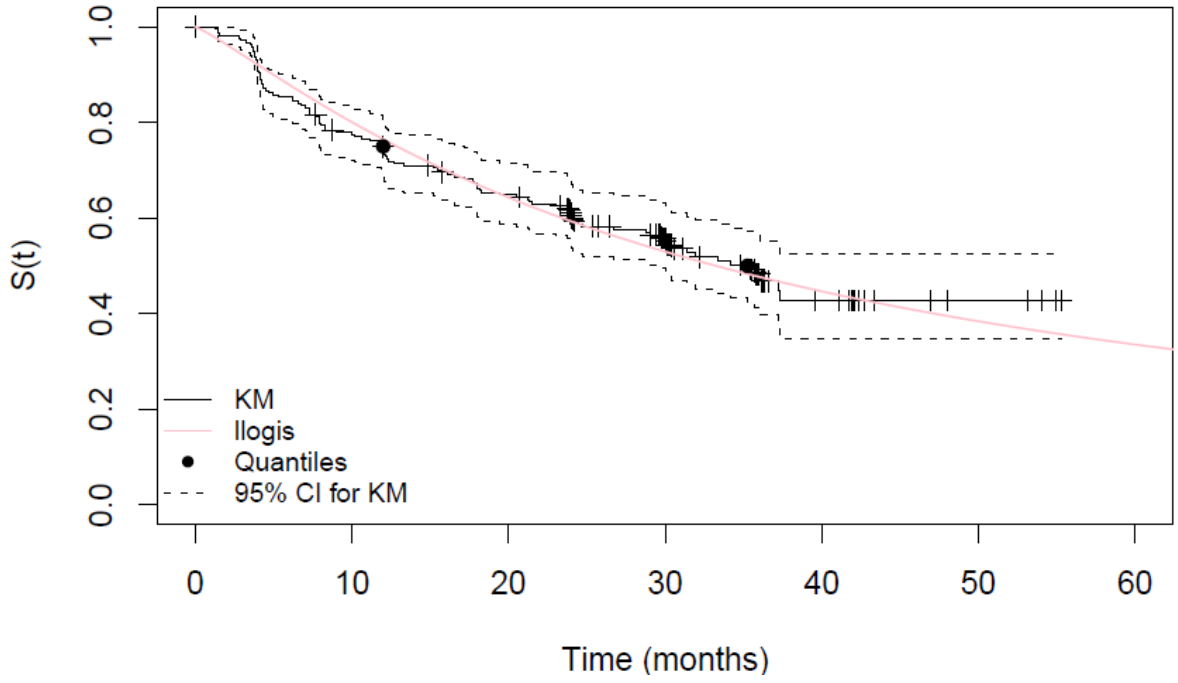


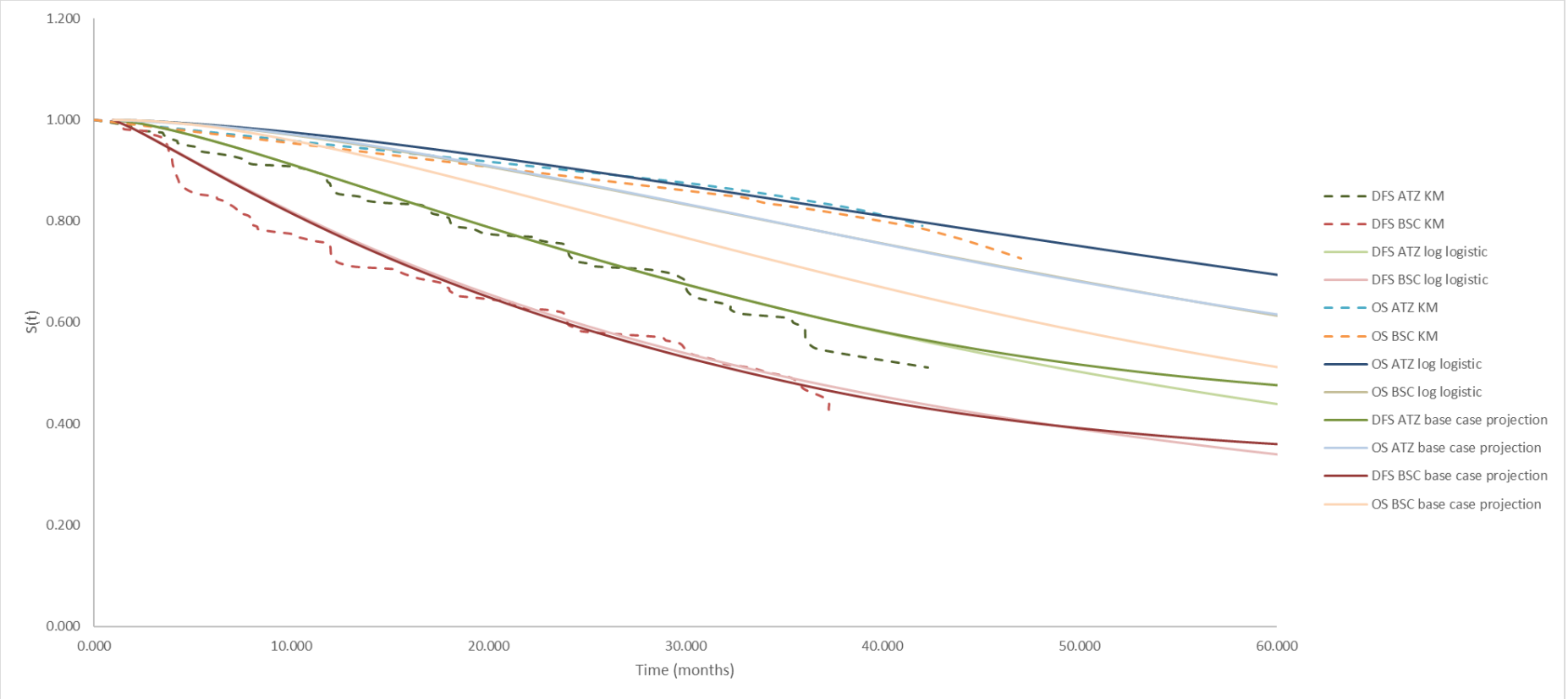
Figure 36: DFS - KM and log-logistic fit for BSC (base case)



B9. PRIORITY QUESTION. On one graph, please present all the IMpower010 DFS Stage II–IIIA PD-L1+ OS and DFS KM data. On this plot, please overlay (i) the respective (unadjusted) log-logistic model fit to each KM curve and (ii) the respective company submission base case projection for each endpoint.

Please see Figure 37 for the summary graph showing all the IMpower010 DFS Stage II–IIIA PD-L1+ OS and DFS KM data, with the respective unadjusted log-logistic model fit to each KM curve, and the company base case projection for each endpoint.

Figure 37: Summary of DFS and OS KM data with unadjusted log-logistic model fit plus the company base case projections (both arms)



B10. PRIORITY QUESTION. Please provide a cost-effectiveness scenario in which DFS and OS projections across model arms are driven by the respective Stage II–IIIA PD-L1+ KM data from the pivotal IMpower010 study.

This scenario has been included in an additional sheet 'OS Survival Analysis', outlining the calculations and drop down selections for the analysis. In this analysis, extrapolated OS and DFS KM data from IMpower010 is used. For the OS IMpower010 data, a background mortality calculation was implemented and all other mortality inputs (in 'Efficacy inputs' sheet) are set to zero so that the mortality inputs for the subsequent health states are 'background' mortality. In this scenario, mortality is assumed to be consistent across all health states.

Using this scenario, the ICER increases from £1,464 to £9,072 per QALY.

B11. Please analyse whether type of DFS event was significantly associated with treatment arm amongst Stage II–IIIA PD-L1+ patients in IMpower010

Given that the different types of DFS events are competing events (i.e. observing one of them precludes observing the other events, as the definition of DFS considers the first occurrence of any DFS event and no more tumour assessments are performed afterwards), we have analysed the time to metastatic recurrence as first DFS event, censoring the other recurrences at the time of the tumour assessment and censoring the deaths at the time of the last tumour assessment. We also compared the proportion of patients with metastatic recurrence (as first DFS event) until year 3.

The results are presented in Table 5 and indicate that the hazard of metastatic recurrences as the first DFS event is reduced by 48% in the atezolizumab compared to the BSC arm. Even if some of the assumptions beyond these analyses may be questionable (e.g. non-informative censoring), to our knowledge this is the best attempt to answer the question of treatment effect on the type of first recurrences in the context of competing events (9).

Table 5: Type of events for the Stage II-IIIA, SP263 TC ≥ 1% population (10)

Type of First Events	ATZ	BSC	Pooled
Total patients with DFS event	88	105	193
Number of Patients by Event			
Locoregional recurrence	35	42	77
Metastatic recurrence	37	57	94
Second Primary Lung Cancer	1	3	4
Death (without recurrence)	15	3	18
Proportion of Patients by Recurrence			
Locoregional Recurrence	48.6%	42.4%	45.0%
Metastatic Recurrence	51.4%	57.6%	55.0%

Table 6: Time to event summary of the first metastatic recurrence as DFS component – Stage II-IIIA patients, SP263 TC ≥ 1% (stratified analysis by sex, histology, tumour stage)

	Atezolizumab (N=248)	Best Supportive Care(BSC) (N=228)
Patients with event (%)	[redacted]	[redacted]
Earliest contributing event		
Metastatic Recurrence	[redacted]	[redacted]
Patients without event (%)	[redacted]	[redacted]
Time to event (months)		
Median	[redacted]	[redacted]
95% CI	[redacted]	[redacted]
25% and 75%-ile	[redacted]	[redacted]
Range	[redacted]	[redacted]
Stratified Analysis		
p-value (log-rank)	[redacted]	

Hazard Ratio	[redacted]
95% CI	[redacted]
Unstratified Analysis	
p-value (log-rank)	[redacted]
Hazard Ratio	[redacted]
95% CI	[redacted]
Time Point Analysis	
3 Years	
Patients remaining at risk	[redacted]
Event Rate (%)	[redacted]
95% CI	[redacted]
Difference in Event Rate	[redacted]
95% CI	[redacted]
p-value (Z-test)	[redacted]

B12. PRIORITY QUESTION. Please comment on the differences in prognostic factors across the Sonoda et al. 2019 patient cohort and IMpower10 patients, and the length of follow-up in Sonoda et al., and what these factors imply for the use of Sonoda et al. 2019 long-term remission estimates to inform lifetime cost-effectiveness estimates in this appraisal.

The sample of patients from Sonoda et al. 2019 (11) and the IMpower010 trial appear to be comparable in terms of patient characteristics (see Table 7 and Table 6 of the company submission). However, there appears to be a difference in the pathologic stage of the patients (~50% of patients in Sonoda et al. 2019 (11) have stage I NSCLC, whereas no patients in the IMpower010 population considered in the model have stage I NSCLC). This may imply that the value that was used to inform the proportion of patients potentially at risk of recurrence after 5 years may be biased downward, if we assume that a higher pathologic stage would result in a higher risk of recurrence. However, we can see from Table 1 in Sonoda et al. 2019 (11) that

while the proportion of recurrences that occur within 5 years increases with stage, the opposite is true for the proportion of recurrences that occur after 5 years (i.e. stage I: 21/114=2.7%; stage II: 14/133=10.5%; stage III: 5/229=2.2%). Thus, it may be the case that our estimated proportion of patients at risk of recurrence after 5 years is biased upward.

Table 7: Clinical characteristics of NSCLC cases examined in Sonoda et al. 2019 (11)

Characteristics	**Non-recurrence, n (%)**	**Early (≤5 years) recurrence, n (%)**	**Late (5–10 years) recurrence, n (%)**	**Ultra-late (≥10 years) recurrence, n (%)**
Overall	982	436	28	12
Age (years)				
Median	64	64	64	60
≥65	476 (48.5)	210 (48.2)	12 (42.9)	5 (41.7)
<65	506 (51.5)	226 (51.8)	16 (57.1)	7 (58.3)
Sex				
Male	582 (59.3)	275 (63.1)	18 (64.3)	5 (41.7)
Female	400 (40.7)	161 (36.9)	10 (35.7)	7 (58.3)
Smoking				
Index median	570	600	545	0
Non smoker	340 (34.6)	130 (29.8)	12 (42.9)	7 (58.3)
Smoker	642 (65.4)	306 (70.2)	16 (57.1)	5 (41.7)
Tumour size				
≤30	570 (58.0)	171 (39.2)	10 (35.7)	5 (41.7)
>30	412 (42.0)	265 (60.8)	18 (64.3)	7 (58.3)
p-N status				
N0	773 (78.7)	159 (36.5)	18 (64.3)	8 (66.7)
N1	123 (12.5)	99 (22.7)	6 (21.4)	4 (33.3)
N2	85 (8.7)	163 (37.4)	4 (14.3)	0
N3	1 (0.1)	15 (3.4)	0	0

p-stage				
I	654 (66.6)	93 (21.3)	15 (53.6)	6 (50.0)
II	203 (20.7)	119 (27.3)	8 (28.6)	6 (50.0)
III	125 (12.7)	224 (51.4)	5 (17.9)	0
Histologic type				
Adenocarcinoma	685 (69.8)	313 (71.8)	18 (64.3)	11 (91.7)
Squamous cell carcinoma	202 (20.6)	62 (14.2)	5 (17.9)	0
Adenosquamous carcinoma	20 (2.0)	26 (6.0)	0	0
Large cell carcinoma	49 (5.0)	25 (5.7)	3 (10.7)	0
Carcinoid	11 (1.1)	1 (0.2)	0	1 (8.3)
Others	15 (1.5)	9 (2.1)	2 (7.1)	0
Histologic differentiation				
Well	412 (42.0)	72 (16.5)	6 (21.4)	6 (50.0)
Moderate	316 (32.2)	220 (50.5)	14 (5.0)	3 (25.0)
Poor	149 (15.2)	78 (17.9)	4 (14.3)	2 (16.7)
Uncertain	105 (10.7)	66 (15.1)	4 (14.3)	1 (8.3)
Lymphatic invasion				
0	615 (62.6)	151 (34.6)	12 (42.9)	9 (75.0)
1	95 (9.7)	141 (32.3)	10 (35.7)	3 (25.0)
Uncertain	272 (27.7)	144 (33.0)	6 (21.4)	0
Vascular invasion				
0	417 (42.5)	65 (14.9)	7 (25.0)	6 (50.0)
1	295 (30.0)	229 (52.5)	15 (53.6)	6 (50.0)
Uncertain	270 (27.5)	142 (32.6)	6 (21.4)	0
Pleural invasion				
Absent	761 (77.5)	231 (53.0)	23 (82.1)	11 (91.7)
Present	221 (22.5)	205 (47.0)	5 (17.9)	1 (8.3)

Uncertain	0	0	0	0
Recurrence categories				
Local	0	105 (24.1)	6 (21.4)	6 (50.0)
Distant	0	331 (75.9)	22 (78.6)	6 (50.0)

B13. PRIORITY QUESTION. Independent clinical advice to the ERG suggests that the patient and NHS resource burden of adjuvant atezolizumab administration and management will not be limited to the cost of atezolizumab acquisition and administration described by Sections B.3.5.1 of Document B.

The ERG are informed that before each atezolizumab administration, a patient is expected to have clinical review, through either a doctor-led or nurse-led clinic, to ensure the patient can continue to tolerate treatment and has not developed any side effects or symptoms that suggest a recurrence. At each visit, this would involve a blood test, to ensure the patient is safe to proceed. The patient would then attend as a day case in a separate visit, to receive the treatment.

Please amend assumed adjuvant atezolizumab administration costs, to incorporate the cost of this expected clinical review at every administration. Please illustrate the impact of the amendment in a cost-effectiveness scenario.

From the clinical advice obtained by the ERG, a scenario has been included where the following costs have been included:

- Clinical review to ensure patient can continue to tolerate treatment - unit cost: £192.90, resource use: 13 (due to average no. of cycles in the trial) in first year (NHS Reference costs 2019/2020 Code 370 Outpatient visit)
- Complete blood count - unit cost: £2.58, resource use, 13 in first year (NHS Reference costs 2019/2020 Code DAPS05)
- We have not included another cost for patient attending as a day case to receive treatment, as this is already included in the administration cost of

£299.61 (NHS Reference Costs 2019/2020, SB12Z, day case and reg day/night)

In 'Cost Inputs' Sheet, cell F18, changing the input to include these costs (£299.61+£192.90+£2.58 = £495.09) increases the ICER from £1,464 to £3,856.

B14. PRIORITY QUESTION. The company assume no adverse event costs for adjuvant treatment with atezolizumab, "as the proportion of patients experiencing treatment-related AEs/SAEs of grade 3 and above were all below 2%" (Company submission, B.3.3.7.1).

Independent clinical advice to the ERG anticipates that patients and the healthcare system will bear an additional adverse event burden with the introduction of atezolizumab to the adjuvant setting, from experience using immunotherapy in adjuvant and metastatic settings.

It is anticipated that all Grade 2 and above events will require NHS resources, even if it is more regular clinical visits for a Grade 2 event. For example, patients may be put on steroids, which will then raise questions about bone health; other clinicians may then be involved.

Please amend adverse event management cost assumptions, to incorporate a relevant cost for all observed treatment-related Grade 2+ adverse events in IMpower010. Please illustrate the impact of the amendment in a cost-effectiveness scenario.

During the clarification questions call, it was agreed with the ERG to include AE costs for adjuvant treatment with atezolizumab as a cost-effectiveness scenario. However, as there are approximately 100 different Grade 2+ AEs, a pragmatic approach has been adopted to use a single AE cost from previous NSCLC trials (choosing the highest AE cost in each instance, i.e. £7,508 for unit cost of febrile neutropenia in IMpower150). This has been done to assess the impact of adverse events on the ICER and decision making and presents an extreme picture of the potential impact of adverse events. The results are presented in Table 8 (calculations are available in an additional sheet "AE ERG scenario").

Table 8: Cost-effectiveness scenario analysis – including Grade 2+ AE costs

	ATZ		BSC		ATZ vs BSC	
	Total cost	Total QALY	Total cost	Total QALY	Δ Cost	Δ QALY
Base case	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Including AE cost and disutilities	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Base case ICER	[redacted]					
ICER including AE cost from PACIFIC (TA578)	[redacted]					
ICER including AE cost from IMpower150 (TA584)	[redacted]					
ICER including AE cost from OAK (TA520)	[redacted]					

B15. The company assume no disutility from adverse events "to avoid double-counting" (Company submission, B.3.4). Yet, the utility values used are from published estimates, and there is no case-by-case justification of this assumption, with reference to data collection in the selected studies.

Please amend adverse event patient utility assumptions, to incorporate the expected utility impact of all observed treatment-related Grade 2+ adverse events in IMpower010. Please illustrate the impact of the amendment in a cost-effectiveness scenario.

The company agrees with the ERG to include disutility from adverse events for adjuvant treatment with atezolizumab, however, similar to the response for B14, as there are approximately 100 different Grade 2+ AEs, a pragmatic approach has been adopted to use a single disutility from the literature (-0.09 from Nafees et al. 2008) and a previous NSCLC appraisal (-0.11 from NICE appraisal TA578). This has been

done to assess the impact of adverse events on the ICER and decision making and presents an extreme picture of the potential impact of adverse events. The results are presented in Table 9 (calculations are available in an additional sheet “AE ERG scenario”).

Table 9: Cost-effectiveness scenario analysis – including Grade 2+ AE disutilities

	ATZ		BSC		ATZ vs BSC	
	Total cost	Total QALY	Total cost	Total QALY	∆ Cost	∆ QALY
Base case	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Including AE cost and disutilities	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Base case ICER	[redacted]					
ICER including disutility from PACIFIC (TA578, pg 334 of Committee papers)	[redacted]					
ICER including disutility from Nafees et al. 2008 (Table 2, febrile neutropenia)	[redacted]					

B16. Please analyse whether cause of death (all-cause versus disease-related) was significantly associated with treatment arm amongst relevant Stage II–IIIA PD-L1+ patients in IMpower010.

A competing risk is an event whose occurrence prevents the occurrence of the primary event of interest. For example, a patient who dies of a cardiovascular cause is no longer at risk of death attributable to progressive non-small cell lung cancer (NSCLC). In the IMpower010 study, given that the different causes of death are competing events (i.e. observing one of them precludes observing the other), time to

death due to progressive disease was analysed, censoring the other causes of death. The proportion of patients who died due to progressive disease until year 3 have also been compared.

The results are presented in the tables below. Table 10 presents the death and causes of death for the PD-L1 ≥ 1% TC Stage II–IIIA population, Table 11 presents the analysis of time to death due to progressive disease and the proportion of patients who died due to progressive disease until year 3. Table 11 indicates that the hazard of dying due to progressive disease is [redacted] by [redacted] in the atezolizumab arm compared to the BSC arm. Even if some of the assumptions beyond these analyses may not be realistic (i.e. it assumes that deaths from other causes do not occur), to our knowledge this is the best attempt to answer the question of treatment effect on cause-specific deaths in the context of competing risks (9).

Table 10: Death and Causes of Death for the PD-L1 ≥ 1% TC Stage II–IIIA population

	Atezolizumab (N=248)		Best Supportive Care (BSC) (N=228)	
	n	%	n	%
All Deaths	[redacted]	[redacted]	[redacted]	[redacted]
Adverse event	[redacted]	[redacted]	[redacted]	[redacted]
Progressive disease	[redacted]	[redacted]	[redacted]	[redacted]
Other	[redacted]	[redacted]	[redacted]	[redacted]

Table 11: Time to event summary of the time-to-death due to progressive disease and proportion of patients who died due to progressive disease until year 3 – Stage II-IIIA patients, SP263 TC ≥ 1% (stratified analysis by sex, histology, tumour stage)

	Atezolizumab (N=248)	Best Supportive Care (BSC) (N=228)
Patients with event (%)	[redacted]	[redacted]
Earliest contributing event		
Death due to progressive disease	[redacted]	[redacted]
Patients without event (%)	[redacted]	[redacted]
Time to event (months)		

Median	[redacted]	[redacted]
95% CI	[redacted]	[redacted]
25% and 75%-ile	[redacted]	[redacted]
Range	[redacted]	[redacted]
Stratified Analysis		
p-value (log-rank)	[redacted]	
Hazard Ratio	[redacted]	
95% CI	[redacted]	
Unstratified Analysis		
p-value (log-rank)	[redacted]	
Hazard Ratio	[redacted]	
95% CI	[redacted]	
Time Point Analysis		
3 Years		
Patients remaining at risk	[redacted]	
Event Rate (%)	[redacted]	
95% CI	[redacted]	
Difference in Event Rate	[redacted]	
95% CI	[redacted]	
p-value (Z-test)	[redacted]	

B17. PRIORITY QUESTION.

(a) Please could the company supply missing information in the table below, which shows the proportion of patients in each health state in IMpower010 at the datacut (21/1/21) (32-month median follow-up). Filled-in entries were obtained by the ERG from Document B Table 9.

	DFS	Locoregional	Metast. 1	Metast. 2	Dead
ATZ	1-88/248=0.65				42/248=0.17
BSC	1-105/228=0.54				48/228=0.21

Please see the response to (b)

(b) The table below shows the model-based proportions in these health states, also at 32 months (extracted from model datasheets). Please could the company comment on any differences between the model-based results in this table, and the trial results in the previous table.

	DFS	Locoregional	Metast. 1	Metast. 2	Dead
ATZ	0.64	0.079	0.065	0.023	0.189
BSC	0.498	0.095	0.100	0.04	0.262

In IMpower010, tumour assessment was not planned after first recurrence (see answer to question B6), therefore it is not possible to estimate the proportion of patients in the intermediate health states (i.e. Locoregional, Metastatic 1 and Metastatic 2). In addition, it is more appropriate to compare the KM estimates at month 32 for DFS and OS, given censoring. These are provided in Table 12 below.

Table 12: KM estimates at month 32 for DFS and OS

Treatment arm	DFS KM estimate at month 32 (95% confidence interval, CI)	OS KM estimate at month 32 (95% CI)	Estimated proportion of patients dead by month 32 (95% CI)
ATZ	[redacted]	[redacted]	[redacted]
BSC	[redacted]	[redacted]	[redacted]

Table 12 shows that the OS that we see in the trial is lower than what is seen in the current model at 32 months for patients that are dead. It is worth noting that changing how the transition probabilities are calculated (using digitised data rather than simple calculation, see 'Efficacy Inputs' sheet rows 105, 192, 249) results in the proportions dead at 32 months to be similar between the trial results and the model results (see Table 13).

Table 13: Model-based proportions in difference health states, at 32 months (extracted from model datasheets, using survival analysis rather than simple calculation for transition probability)

	DFS	Locoregional	Metast. 1	Metast. 2	Dead
ATZ	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
BSC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Probabilistic and deterministic analyses

B18. PRIORITY QUESTION. Many potentially important and uncertain parameters are held fixed in the company's probabilistic and deterministic sensitivity analyses. Other important and uncertain parameters are varied illogically in the company's probabilistic sensitivity analyses. For example, where transition probability parameters that must sum to one are varied, these parameters are varied independently (and not following a Dirichlet distribution as stated in Document B.3.6 and in the company's economic model) in the probabilistic analysis, leading to erroneous results.

Please provide revised probabilistic and deterministic sensitivity analysis in which all uncertain parameters are varied appropriately, including but not limited to all efficacy input parameters listed in Table 62 of the company's submission (Document B). Please justify each distributional choice explicitly.

For the proportion of patients transitioning to health states, (e.g. 'Efficacy inputs' sheet, rows 34–35), these are now varied using the Beta distribution in the model as opposed to fixed. In terms of the proportions which should sum up to one (e.g. 'Efficacy inputs' sheet, rows 80–81 or rows 157–160), this is accounted for within the cell formula, for example, cell H80: Parameters!L16/SUM(Parameters!$L$16:$L$18).

Table 62 from the company submission has been replicated and revised with justifications for each input in Table 14.

The Beta, Gamma, and Dirichlet distributions are used and the choice of distribution was made as follows:

- Beta was used where the value was a probability that needed to be bound between 0 and 1
- Gamma is used for costs as the distribution is bound by 0 to infinity and is often used for modelling individual costs
- Dirichlet was used where the proportions were split into more than two groups to enable the total proportions to equal 1.

Please refer to Appendix A (Table 24, Table 26, Figure 43) for the results from the revised probabilistic and sensitivity analysis.

Table 14: Summary of variables applied in the base case setting of the economic model

Variable	Value	Measurement of uncertainty and distribution: CI (distribution)	Justification	Reference to section in submission
General model parameters				
Time horizon	40 years	Fixed	Sufficiently long to capture all clinical and economic outcomes.	Section B.3.2
Discount rate – efficacy	3.5%	Fixed	As per reference case	
Discount – costs	3.5%	Fixed		
Population parameters				
Age	61.20 years	Fixed	As per IMpower010 trial	Baseline characteristics section
Body weight	74.07 kg	Fixed		
Height	169.00 cm	Fixed		
Body surface area	1.85 m^2	Fixed		
Proportion of males (%)	66.80%	Fixed		
Population in Analysis	PD-L1+ Stage II–IIIA	Fixed	[redacted]	
Efficacy inputs				

Disease-free survival				
Atezolizumab regimen	1,200 mg every 3 weeks	Fixed	As per IMpower010 trial	
Change in scanning schedule at month	24	Fixed	Clinical opinion	
Time to off treatment	Trial-observed	Fixed	As per IMpower010 trial	
Parametric distribution – atezolizumab arm	Log-logistic	Fixed	Clinically plausible option after considering statistical and visual fit, and clinical opinion	Section B.3.3.3
Parametric distribution – BSC arm	Log-logistic	Fixed		
First event occurrence by type – trial data to use to inform recurrence type split	Separate by arm	Fixed	We have sufficient trial data to inform this type by arm	
First event occurrence by type – Atezo arm: proportion of patients with locoregional recurrence	[redacted]	Beta	As per IMpower010 trial	
First event occurrence by type – Atezo arm: proportion of patients with first line metastatic recurrence	[redacted]	Beta		
First event occurrence by type – Atezo arm: Transition probability to death (monthly)	[redacted]	Beta		

First event occurrence by type – BSC arm: proportion of patients with locoregional recurrence	[redacted]	Beta		
First event occurrence by type – Atezo arm: proportion of patients with first line metastatic recurrence	[redacted]	Beta		
First event occurrence by type – Atezo arm: Transition probability to death (monthly)	[redacted]	Beta		
Treatment effect – Duration of atezo treatment effect	Limited to 60 months	Fixed	A five-year treatment effect was chosen as this aligns with previous NSCLC appraisals (see Table 63 in company submission for further information)	
Cured patients – maximum proportion of cured patients	91.5 %	Fixed	Informed by Sonoda et al. 2019 (11)	Section B.3.3.4
Cured patients – cure proportion starts to increase	36 months	Fixed	Pignon et al. 2008 (12) and Clinical opinion	
Cured patients – cure proportion maximum reached	72 months	Fixed	Pignon et al. 2008 (12) and Clinical opinion	

Excess mortality of long-term survivors – standardised mortality ratio	1.25	Fixed	Based on Janssen-Heijnen et al. 2012 (13) and Clinical validation	
Cost effectiveness analysis	Markov model	Fixed	See response to B1	
Locoregional recurrence				
Treatment setting - % of patients by treatment intent: curative treatment	80%	Dirichlet	Informed by Sonoda et al. 2020 (6)	Section B.3.3.7
Treatment setting - % of patients by treatment intent: palliative treatment	20%	Dirichlet		
Treatment setting - % of patients by treatment intent: no treatment	0%	Dirichlet		
Treatment setting - Curative treatment regimen: include radiotherapy	Yes	Fixed	Clinical opinion	
Treatment setting - Curative treatment regimen: include chemotherapy	Yes	Fixed		
Treatment setting - Curative treatment	Cisplatin	Fixed		

regimen: treatment regimen drug 1				
Treatment setting - Curative treatment regimen: treatment regimen drug 2	Vinorelbine	Fixed		
Treatment setting - Palliative treatment regimen: include radiotherapy	No	Fixed		
Treatment setting - Palliative treatment regimen: include chemotherapy	No	Fixed		
Efficacy by treatment intent - use result from survival analysis or calculation (based on median)	Simple calculation	Fixed	Based on the median results from the Nakamichi et al. 2017 study (14) due to the uncertainty from using the analysis of the digitised Kaplan-Meier plot.	
Efficacy by treatment intent - Transition probability to first line metastatic recurrence: curative treatment	0.036	Beta		
Efficacy by treatment intent - % progression to first line metastatic	81%	Beta	Informed by NICE TA578 - committee papers (15), Table 9, page 57	

recurrence as first event: curative treatment				
Efficacy by treatment intent –Use result from survival analysis or calculation (based on median)	Simple calculation	Fixed	Based on the median results from the Kruser et al. 2014 study (8) due to the uncertainty from using the analysis of the digitised Kaplan-Meier plot.	
Efficacy by treatment intent – Transition probability to Death: palliative treatment and no treatment	0.136	Beta		
First-line metastatic recurrence				
Treatment setting - % of patients by treatment intent – with treatment	[redacted]	Beta	Informed by clinical opinion	Section B.3.3.8
Treatment setting - % of patients by treatment intent – no treatment	[redacted]	Beta		
Treatment setting – limit treatment duration	Yes	Fixed	Informed by TA683 (16), TA600 (17), TA531 (18)	
Treatment setting – Treatment duration	24 months	Fixed		
Treatment setting – Treatment option 1	Pembrolizumab and pemetrexed	Fixed	Informed by clinical opinion. These market shares are not included in the PSA or deterministic analysis as	

Treatment market shares – atezo arm – treatment option 1	[redacted]	Dirichlet	patients cannot be rechallenged with imnmunotherapy, so 100% patients would receive treatment option 2 (pemetrexed and cisplatin)	
Treatment setting – Treatment option 2	Pemetrexed and cisplatin	Fixed		
Treatment market shares – atezo arm – treatment option 2	[redacted]	Dirichlet		
Treatment setting – Treatment option 3	Pembrolizumab	Fixed		
Treatment market shares – atezo arm – treatment option 3	[redacted]	Dirichlet		
Treatment setting – Treatment option 4	Pembrolizumab and carboplatin	Fixed		
Treatment market shares – atezo arm – treatment option 4	[redacted]	Dirichlet		
Treatment setting – Re-challenging with immunotherapy allowed after treatment initiation	12 months	Fixed	Clinical opinion was that re-challenge with immunotherapy would be unlikely, this setting does not affect the model as 100% patients are assumed to receive pemetrexed and cisplatin	
Treatment setting – Re-challenging with immunother	[redacted]	Dirichlet	Clinical opinion	

apy: BSC arm, option 1 with pembrolizumab and pemetrexed				
Treatment setting – Re-challenging with immunotherapy: BSC arm, option 2 with pemetrexed and cisplatin	[redacted]	Dirichlet		
Treatment setting – Re-challenging with immunotherapy: BSC arm, option 3 with pembrolizumab	[redacted]	Dirichlet		
Treatment setting – Re-challenging with immunotherapy: BSC arm, option 4 with pembrolizumab and carboplatin	[redacted]	Dirichlet		
Efficacy by treatment intent – Allow second line metastatic recurrence	Yes	Fixed	Validated by clinicians	
Efficacy by treatment intent – Survival analysis results	IMpower150 trial	Fixed		
Efficacy by treatment	0.05	These are indirectly	Informed by IMpower150	

intent – Transition probability to second line metastatic recurrence - Treatment option 1		varied from the treatment market shares		
Efficacy by treatment intent – Transition probability to second line metastatic recurrence - Treatment option 2	0.11	These are indirectly varied from the treatment market shares		
Efficacy by treatment intent – Transition probability to second line metastatic recurrence - Treatment option 3	0.05	These are indirectly varied from the treatment market shares		
Efficacy by treatment intent – Transition probability to second line metastatic recurrence - Treatment option 4	0.05	These are indirectly varied from the treatment market shares		
Efficacy by treatment intent – Transition probability to second line metastatic recurrence – Weighted average for atezo arm	0.11	These are indirectly varied from the treatment market shares	Clinical opinion on market shares	
Efficacy by treatment intent –	0.07	These are indirectly varied from		

Transition probability to second line metastatic recurrence – Weighted average for BSC arm		the treatment market shares		
Efficacy by treatment intent – Transition probability to second line metastatic recurrence - % progression as first event	82.20%	Beta	Informed by IMpower150 (Table 22 from CSR, data on file)	
Efficacy by treatment intent –Use result from survival analysis or calculation (based on median)	Simple calculation	Fixed	Based on the median results from the Wong et al. 2016 study (19) due to the uncertainty from using the analysis of the digitised Kaplan-Meier plot.	
Efficacy by treatment intent – Transition probability to death: no treatment	0.23	Beta		
Second-line metastatic setting				
Treatment setting - % of patients by treatment intent – with treatment	[redacted]	Beta	Clinical opinion. For the market shares in the atezolizumab arm, treatment option 4 (atezolizumab) is set to 0% and not included in the PSA as patients cannot rechallenge with atezolizumab. It is kept in the model for transparency.	Section B.3.3.9
Treatment setting - % of patients by treatment intent – no treatment	[redacted]	Beta		
Treatment setting –	Nintedanib and docetaxel	Fixed		

Treatment option 1				
Treatment setting – Treatment option 2	Pemetrexed and cisplatin	Fixed		
Treatment setting – Treatment option 3	Docetaxel	Fixed		
Treatment setting – Treatment option 4	Atezolizumab	Fixed		
Treatment setting – Atezolizumab arm, option 1 with nintedanib and docetaxel	[redacted]	Dirichlet		
Treatment setting – Atezolizumab arm, option 2 with pemetrexed and cisplatin	[redacted]	Dirichlet		
Treatment setting – Atezolizumab arm, option 3 with docetaxel	[redacted]	Dirichlet		
Treatment setting – Atezolizumab arm, option 4 with atezolizumab	[redacted]	Dirichlet		
Treatment setting – BSC arm, option 1 nintedanib and docetaxel	[redacted]	Dirichlet		

Treatment setting – BSC arm, option 2 with pemetrexed and cisplatin	[redacted]	Dirichlet		
Treatment setting – BSC arm, option 3 with docetaxel	[redacted]	Dirichlet		
Treatment setting – BSC arm, option 4 with atezolizumab	[redacted]	Dirichlet		
Efficacy by treatment intent – Transition probability to death, treatment option 1	0.07	These are indirectly varied from the treatment market shares	Informed by OAK	
Efficacy by treatment intent – Transition probability to death, treatment option 2	0.07	These are indirectly varied from the treatment market shares		
Efficacy by treatment intent – Transition probability to death, treatment option 3	0.07	These are indirectly varied from the treatment market shares		
Efficacy by treatment intent – Transition probability to death, treatment option 4	0.05	These are indirectly varied from the treatment market shares		
Efficacy by treatment	[redacted]	These are indirectly		

intent – Transition probability to death, weighted average for atezo arm		varied from the treatment market shares	Clinical opinion on market shares	
Efficacy by treatment intent – Transition probability to death, weighted average for BSC arm	[redacted]	These are indirectly varied from the treatment market shares		
Efficacy by treatment intent –Use result from survival analysis or calculation (based on median)	Simple calculation	Fixed	Based on the median results from the Wong et al. 2016 study (19) due to the uncertainty from using the analysis of the digitised Kaplan-Meier plot.	
Efficacy by treatment intent – Transition probability to death: no treatment	0.23	Beta		
Cost inputs				
Drug costs				
Drug costs - Proportion of vials that are shared across different patients	100%	Fixed	As per previous appraisal (IMpower110 -TA705 (20)	Section B.3.5.1
Drug costs - Proportion of new vial that should be used to justify opening	2%	Fixed	Company assumption	
Drug costs – Atezolizuma	£2665.38 [redacted])	Fixed	Sourced from BNF	

b: Composition (mg) = 840 – List Price (PAS price)				
Drug costs – Atezolizumab: Composition (mg) = 1200 - List Price (PAS price)	£3807 [redacted])	Fixed		
Radiotherapy – Cost per fraction	£144.54	Fixed	NHS reference costs 2019-2020, SC22Z	
CT scan	£119.01	Fixed	NHS Reference Costs 2019-2020, Diagnostic Imaging, Outpatient, HRG code RD24Z (two areas with contrast)	
Administration costs				
IV administration cost	£299.61	Gamma	Administration costs NHS Reference Costs 2019-2020, SB12Z, daycase and reg day/night	Section B.3.5.2
Disease-free survival cost and resource use				
Follow-up costs – CT scans: change in scanning schedule	24 months	Fixed	Clinical opinion	Section B.3.5.2
Follow-up costs – CT scans: Interval between scans in months (first 24 months)	6 months	Fixed		
Follow-up costs – CT scans: Interval between scans in months (after 24 months)	12 months	Fixed		

Follow-up costs – CT scans: Month at which CT scans cease	60 months	Fixed		
Follow-up costs – Include other healthcare resource costs	Yes	Fixed		
Follow-up costs – Duration of healthcare resource use	60 months	Fixed		
Follow-up costs – Healthcare resource use cost (monthly)	£53.19	This is indirectly varied as this is a weighted cost and individual costs are varied using Gamma)	Costs sourced from NHS reference costs and PSSRU, resource use from clinical opinion	
One-off AE management cost	£0	Fixed	All Grade 3+ AEs were below 2%, therefore AE management costs were not considered	Section B.3.5.5
Locoregional recurrence cost and resource use				
Curative treatment – Chemotherapy drug 1	Cisplatin, 80 mg/m^2, once every 3 weeks for 4 cycles	Fixed	Clinical opinion	Section B.3.5.2
Curative treatment – Chemotherapy drug 2	Vinorelbine, 60 mg/m^2, once every 3 weeks for 4 cycles	Fixed		
Curative treatment – Radiotherapy	Total treatment dose 66 Gy, 5 fractions per week	Fixed		

Curative treatment – AE cost (monthly)	£14.05	Gamma	TA578 committee papers (21), Table 49, costs updated to NHS reference costs 2019/2020	
Curative treatment – Follow-up costs – Include other healthcare resource costs	Yes	Fixed	Costs sourced from NHS reference costs and PSSRU, resource use from clinical opinion	
Curative treatment follow-up costs – Healthcare resource use cost (monthly)	£161.57	This is indirectly varied as this is a weighted cost and individual costs are varied using Gamma		
Palliative treatment – AE cost	£0	Fixed	No treatment, therefore no treatment-related AEs	Section B.3.5.5
Palliative treatment – Follow-up costs – Include other healthcare resource costs	Yes	Fixed	Costs sourced from NHS reference costs and PSSRU, resource use from clinical opinion	
Palliative treatment – Healthcare resource use cost (monthly)	£161.57	This is indirectly varied as this is a weighted cost and individual costs are varied using Gamma		
First-line metastatic recurrence cost and resource use				
Drug option 1	Pembrolizumab, 200mg every 3	Fixed	Clinical opinion	Section B.3.5.3

	weeks and pemetrexed 500 mg/m^2 every 3 weeks			
Drug option 2	Pemetrexed 500 mg/m^2 every 3 weeks and cisplatin 75 mg/m^2 every 3 weeks	Fixed		
Drug option 3	Pembrolizumab, 200mg every 3 weeks	Fixed		
Drug option 4	Pembrolizumab, 200mg every 3 weeks and carboplatin 150 AUC every 3 weeks	Fixed		
Overall weighted average costs – Atezo arm: Treatment cost (monthly)	£2,090.39	This is indirectly varied as this is a weighted cost and market shares are varied using dirichlet	Clinical opinion on market shares	
Overall weighted average costs – Atezo arm: AE cost (monthly)	£87.07	This is indirectly varied as this is a weighted cost and AE management costs are varied using Gamma	AE management costs from IMpower150 UK cost-effectiveness model [TA584] (22)	
Overall weighted average costs – BSC arm:	£7,220.76	This is indirectly varied as this is a weighted	Clinical opinion on market shares	

Treatment cost (monthly)		cost and market shares are varied using dirichlet		
Overall weighted average costs – BSC arm: AE cost (monthly)	£93.45	This is indirectly varied as this is a weighted cost and AE management costs are varied using Gamma	AE management costs from IMpower150 UK cost-effectiveness model [TA584] (22)	
Follow-up care costs – Include other healthcare resource costs	Yes	Fixed	Costs sourced from NHS reference costs and PSSRU, resource use from clinical opinion	
Treatment follow-up – Healthcare resource use cost (monthly)	£352.11	This is indirectly varied as this is a weighted cost and individual costs are varied using Gamma)		
No treatment – Include other healthcare resource costs	Yes	Fixed		
No treatment follow-up – Healthcare resource use cost (monthly)	£352.11	This is indirectly varied as this is a weighted cost and individual costs are varied		

		using Gamma)		
Second-line metastatic recurrence cost and resource use				
Drug option 1	Nintedanib 300 mg every 3 weeks and docetaxel 75 mg/m^2 every 3 weeks	Fixed	Clinical opinion	Section B.3.5.3
Drug option 2	Pemetrexed 500 mg/m^2 every 3 weeks and cisplatin 75 mg/m^2 every 3 weeks	Fixed		
Drug option 3	Docetaxel 75 mg/m^2 every 3 weeks	Fixed		
Drug option 4	Atezolizumab 1200 mg every 3 weeks	Fixed		
Overall weighted average costs – Atezo arm: Treatment cost (monthly)	£1366.06	This is indirectly varied as this is a weighted cost and market shares are varied using dirichlet	Clinical opinion on market shares	
Overall weighted average costs – Atezo arm: AE cost (monthly)	£308.41	This is indirectly varied as this is a weighted cost and AE management costs are varied using Gamma	AE management costs from OAK UK cost-effectiveness model [TA520] (23)	
Overall weighted average	£3099.28	This is indirectly varied as	Clinical opinion on market shares	

costs – BSC arm: Treatment cost (monthly)		this is a weighted cost and market shares are varied using dirichlet		
Overall weighted average costs – BSC arm: AE cost (monthly)	£216.58	This is indirectly varied as this is a weighted cost and AE management costs are varied using Gamma)	AE management costs from OAK UK cost-effectiveness model [TA520] (23)	
Follow-up care costs – Include other healthcare resource costs	Yes	Fixed	Costs sourced from NHS reference costs and PSSRU, resource use from clinical opinion	
Treatment follow-up – Healthcare resource use cost (monthly)	£608.34	This is indirectly varied as this is a weighted cost and individual costs are varied using Gamma)		
No treatment – Include other healthcare resource costs	Yes	Fixed		
No treatment follow-up – Healthcare resource use cost (monthly)	£608.34	This is indirectly varied as this is a weighted cost and individual		

		costs are varied using Gamma)		
End of life costs				
Disease-related death	£4598.01	Gamma	Informed by NICE TA705 (20) (IMpower110), page 123	Section B.3.5.7
Utilities – base case				
Disease-free survival				
Utility calculation method	Calculated disutilities	Fixed	This approach ensured that all health state utility values remained below the general population utility and the progressed states aligned over time (see Section B.3.4.3.1)	
Literature source	Jang et al. 2010	Fixed	Jang et al. 2010 (24) as it provided the most clinically plausible values (see Section B.3.4.3.2)	Section B.3.4.3
On treatment disutility	0.03	Beta		
Off treatment disutility	0.03	Beta		
AE total disutility	0	Beta	All Grade 3+ AEs were below 2%, therefore AE disutilities were not considered	
Locoregional recurrence				
Literature source	Chouaid et al. 2013	Fixed	Chouaid et al. 2013 (25) was the only source available to inform the utility of patients within the locoregional recurrence health state	Section B.3.4.3
Curative treatment disutility	0.08	Beta		
Palliative treatment – no treatment disutility	0.17	Beta		
First-line metastatic recurrence				
Literature source	IMpower150	Fixed	IMpower150 was the source used due to the trial population aligning with the population of interest, first-line metastatic. Also it is more conservative than the other sources.	Section B.3.4.3
Treatment disutility	0.11	Beta		
No treatment disutility	0.17	Beta		

Second-line metastatic recurrence				
Literature source	IMpower150	Fixed	IMpower150 was the source used due to the trial population aligning with the population of interest, first-line metastatic. Also it is more conservative than the other sources.	Section B.3.4.3
Treatment disutility	0.13	Beta		
No treatment disutility	0.17	Beta		

Abbreviations: CI, confidence interval

B19. From the convergence plots in model sheet "Results Chart", the mean PSA ICER estimate does not yet appear stable by 1,000 PSA iterations (within the limited parameter uncertainty explored in the company's submission). After respecifying the PSA according to Priority Question B.18, please test the sensitivity of the mean PSA ICER to additional PSA iterations up to at least 5,000 iterations and amend your base case PSA specifications accordingly.

Revised probabilistic and deterministic sensitivity analysis results are presented in Appendix A, for the base case results and Appendix B for the subgroup results. In the PSA, 5,000 iterations were used to test the sensitivity of the mean PSA ICER (Figure 38).

Figure 38: Convergence plot for Stage II–IIIA NSCLC, PAS price

B20. Please explain why the FIXED function is used in range CR8:EL10 in sheet "Simulation".

The FIXED function is used to round the numbers to two decimal places and was part of the model to limit run time of sensitivity analyses. This has been removed from the updated company model.

B21. In Section B.3.8.2 of the company's submission, the company state the following: "The base case values of most parameters were varied using 20%

and 80% confidence intervals for the variables". Please justify this choice, versus testing to upper and lower limits of 95% confidence intervals.

See Appendix A (Figure 43) and Appendix B (Figure 49) for the revised deterministic sensitivity analysis using the upper and lower limits of 95% confidence intervals from the PSA output. In the company submission, 20% and 80% confidence intervals were used due to the uncertainty in the parameters (transition probabilities, market shares, and utilities). These parameters were based on clinical opinion and literature whereby 95% confidence intervals were unavailable and therefore a 20% variation either way to test parameter sensitivity was deemed appropriate.

Justification of modelling assumptions

B22. For every clinical effectiveness, health-related quality of life and treatment and resource use assumption in sections B.3.3 to B.3.5 of the Company Submission that is not based on IMpower010 evidence, justify the assumption with reference to the corresponding assumption used for decision making in the most recent relevant NICE Single Technology Appraisal.

For assumptions in the adjuvant setting, refer to committee-preferred assumptions in the Appraisal Committee Document of the ongoing appraisal of osimertinib (NICE ID3835) where possible, accounting for prognostic differences in the affected patient population in that appraisal versus this appraisal, if the Final Appraisal Determination has not yet been published. For assumptions in the metastatic setting, refer to NICE TA705 "Atezolizumab monotherapy for untreated advanced non-small-cell lung cancer".

Please see Table 15 below with justification for the assumptions and reference to the Final Appraisal document from the osimertinib (ID3835) appraisal for the adjuvant setting and the atezolizumab (TA705) appraisal for the metastatic setting.

Table 15: HRQoL, treatment and resource use assumptions with justifications from previous appraisals

Variable	Value	Measurement of uncertainty	Justification	Committee preferred assumptions

		and distribution: CI (distribution)		from previous appraisals
Disease-free survival cost and resource use				
Follow-up costs – CT scans: change in scanning schedule	24 months	Fixed	Clinical opinion	No comment from the committee on the resource use in the osimertinib appraisal (ID3835) (26) for the DFS state. From the company Document A, "All other cost inputs for drug acquisition costs, administration costs, follow-up and monitoring costs, and AE costs are based on published sources. Resource use was also sourced from published sources and validated by clinicians." The osimertinib appraisal is for patients with stage Ib to IIIa NSCLC after tumour resection and whose tumours have EGFR exon 19 deletions or exon 21
Follow-up costs – CT scans: Interval between scans in months (first 24 months)	6 months	Fixed		
Follow-up costs – CT scans: Interval between scans in months (after 24 months)	12 months	Fixed		
Follow-up costs – CT scans: Month at which CT scans cease	60 months	Fixed		
Follow-up costs – Include other healthcare resource costs	Yes	Fixed		
Follow-up costs – Duration of healthcare resource use	60 months	Fixed		
Follow-up costs – Healthcare resource use cost (monthly)	£53.19	This is indirectly varied as this is a weighted cost and AE management costs are varied using Gamma	Costs sourced from NHS reference costs and PSSRU, resource use from clinical opinion	
One-off AE management cost	£0	Fixed	All Grade 3+ AEs were below 2%, therefore AE management costs were not considered	

				substitution mutations.
Locoregional recurrence cost and resource use				
Curative treatment –Chemotherapy drug 1	Cisplatin, 80 mg/m^2, once every 3 weeks for 4 cycles	Fixed	Clinical opinion	No comment from the committee on the resource use in the osimertinib appraisal (ID3835) (26) for the LRR state.
Curative treatment –Chemotherapy drug 2	Vinorelbine, 60 mg/m^2, once every 3 weeks for 4 cycles	Fixed		
Curative treatment –Radiotherapy	Total treatment dose 66 Gy, 5 fractions per week	Fixed		
Curative treatment – AE cost (monthly)	£14.05	Gamma	TA578 committee papers (21), Table 49, costs updated to NHS reference costs 2019/2020	
Curative treatment – Follow-up costs – Include other healthcare resource costs	Yes	Fixed	Costs sourced from NHS reference costs and PSSRU, resource use from clinical opinion	
Curative treatment follow-up costs – Healthcare resource use cost (monthly)	£161.57	This is indirectly varied as this is a weighted cost and AE management costs are varied using Gamma		
Palliative treatment – AE cost	£0	Fixed	No treatment, therefore no treatment-related AEs	
Palliative treatment – Follow-up costs – Include other healthcare resource costs	Yes	Fixed	Costs sourced from NHS reference costs and PSSRU, resource use from clinical opinion	
Palliative treatment – Healthcare	£161.57	This is indirectly		

resource use cost (monthly)		varied as this is a weighted cost and AE management costs are varied using Gamma		
First-line metastatic recurrence cost and resource use				
Drug option 1	Pembrolizumab, 200mg every 3 weeks and pemetrexed 500 mg/m^2 every 3 weeks	Fixed	Clinical opinion	No comment from the committee on the cost and resource use from atezolizumab [TA705] (27). In Document B of the TA705 submission, the source of costs and resource use were: NHS reference costs; PSSRU; BNF; eMIT; published literature, resource utilisation and costs accepted in previous NICE submissions, in particular TA584 (22) and TA531 (18). AEs were taken from the IMpower110 trial and NHS reference costs and PSSRU were
Drug option 2	Pemetrexed 500 mg/m^2 every 3 weeks and cisplatin 75 mg/m^2 every 3 weeks	Fixed		
Drug option 3	Pembrolizumab, 200mg every 3 weeks	Fixed		
Drug option 4	Pembrolizumab, 200mg every 3 weeks and carboplatin 150 AUC every 3 weeks	Fixed		
Overall weighted average costs – Atezo arm: Treatment cost (monthly)	£2,090.39	This is indirectly varied as this is a weighted cost and market shares are varied using dirichlet	Clinical opinion on market shares	
Overall weighted average costs – Atezo arm: AE cost (monthly)	£87.07	This is indirectly varied as this is a weighted cost and AE management costs are varied using Gamma	AE management costs from IMpower150 UK cost-effectiveness model [TA584] (22)	
Overall weighted average costs – BSC arm:	£7,220.76	This is indirectly varied as this is a weighted	Clinical opinion on market shares	

Treatment cost (monthly)		cost and market shares are varied using dirichlet		used to estimated costs. The TA705 guidance (27) is for patients with first-line metastatic tumours that have at least 50% of tumour cell or 10% of tumour-infiltrating immune cells and do not have EGFR or ALK mutations.
Overall weighted average costs – BSC arm: AE cost (monthly)	£93.45	This is indirectly varied as this is a weighted cost and AE management costs are varied using Gamma	AE management costs from IMpower150 UK cost-effectiveness model [TA584] (22)	
Follow-up care costs – Include other healthcare resource costs	Yes	Fixed	Costs sourced from NHS reference costs and PSSRU, resource use from clinical opinion	
Treatment follow-up – Healthcare resource use cost (monthly)	£352.11	This is indirectly varied as this is a weighted cost and AE management costs are varied using Gamma		
No treatment – Include other healthcare resource costs	Yes	Fixed		
No treatment follow-up – Healthcare resource use cost (monthly)	£352.11	This is indirectly varied as this is a weighted cost and AE management costs are varied using Gamma		
Second-line metastatic recurrence cost and resource use				
Drug option 1	Nintedanib 300 mg every 3 weeks and docetaxel 75 mg/m^2 every 3 weeks	Fixed	Clinical opinion	No comment from the committee on the cost and resource use from atezolizumab [TA705] (27). In document B, the source
Drug option 2	Pemetrexed 500 mg/m^2 every 3 weeks and cisplatin 75	Fixed		

	mg/m^2 every 3 weeks			of costs and resource use were: NHS reference costs; PSSRU; BNF; eMIT; published literature, resource utilisation and costs accepted in previous NICE submissions, in particular TA584 (22) and TA531 (18).
Drug option 3	Docetaxel 75 mg/m^2 every 3 weeks	Fixed		
Drug option 4	Atezolizumab 1200 mg every 3 weeks	Fixed		
Overall weighted average costs – Atezo arm: Treatment cost (monthly)	£1366.06	This is indirectly varied as this is a weighted cost and market shares are varied using dirichlet	Clinical opinion on market shares	
Overall weighted average costs – Atezo arm: AE cost (monthly)	£308.41	This is indirectly varied as this is a weighted cost and AE management costs are varied using Gamma	AE management costs from OAK UK cost-effectiveness model [TA520] (28)	
Overall weighted average costs – BSC arm: Treatment cost (monthly)	£3099.28	This is indirectly varied as this is a weighted cost and market shares are varied using dirichlet	Clinical opinion on market shares	
Overall weighted average costs – BSC arm: AE cost (monthly)	£216.58	This is indirectly varied as this is a weighted cost and AE management costs are varied using Gamma	AE management costs from OAK UK cost-effectiveness model [TA520] (28)	
Follow-up care costs – Include other healthcare resource costs	Yes	Fixed	Costs sourced from NHS reference costs and PSSRU, resource use from clinical opinion	
Treatment follow-up – Healthcare resource use cost (monthly)	£608.34	Gamma (this is indirectly varied as this is a weighted		

		cost and individual costs are varied using Gamma)		
No treatment – Include other healthcare resource costs	Yes	Fixed		
No treatment follow-up – Healthcare resource use cost (monthly)	£608.34	Gamma (this is indirectly varied as this is a weighted cost and individual costs are varied using Gamma)		
End of life costs				
Disease-related death	£4598.01	Gamma	Informed by NICE TA705 (27) (IMpower110), page 123	End of life costs and resource use from NICE TA705 were calculated from NICE TA531 and NICE guidance CG121
Utilities – base case				
Disease-free survival				
Utility calculation method	Calculated disutilities	Fixed	This approach ensured that all health state utility values remained below the general population utility and the progressed states aligned over time (see Section B.3.4.3.1)	In the osimertinib appraisal (ID3835) (26), utilities were based on EQ-5D-3L from the ADAURA trial.
Literature source	Jang et al. 2010	Fixed	Jang et al. 2010 (24) as it provided the	
On treatment disutility	0.03	Beta		

Off treatment disutility	0.03	Beta	most clinically plausible values (see Section B.3.4.3.2)	
AE total disutility	0	Beta	All Grade 3+ AEs were below 2%, therefore AE disutilities were not considered	
Locoregional recurrence				
Literature source	Chouaid et al. 2013	Fixed	Chouaid et al. 2013 (25) was the only source available to inform the utility of patients within the locoregional recurrence health state	The health state utility in the LRR health state was set equal to the DF state value due to a lack of data in patients with LRR in the ADAURA trial (26). The committee concluded that the company's utility values were acceptable for decision making
Curative treatment disutility	0.08	Beta		
Palliative treatment – no treatment disutility	0.17	Beta		
First-line metastatic recurrence				
Literature source	IMpower150	Fixed	IMpower150 was the source used due to the trial population aligning with the population of interest, first-line metastatic. Also, it is more conservative than the other sources.	In the atezolizumab appraisal [TA705] (27), utilities were based on EQ-5D-3L from the IMpower110 trial. There were no comments from the committee
Treatment disutility	0.11	Beta		
No treatment disutility	0.17	Beta		

				regarding the utilities.
Second-line metastatic recurrence				
Literature source	IMpower150	Fixed	IMpower150 was the source used due to the trial population aligning with the population of interest, first-line metastatic. Also, it is more conservative than the other sources.	In the atezolizumab appraisal [TA705] (27), utilities were based on EQ-5D-3L from the IMpower110 trial. There were no comments from the committee regarding the utilities.
Literature source	IMpower150	Fixed	IMpower150 was the source used due to the trial population aligning with the population of interest, first-line metastatic. Also, it is more conservative than the other sources.	
Treatment disutility	0.13	Beta		
No treatment disutility	0.17	Beta		

B23. Throughout Document B, the company references discussions with experts that informed or validated assumptions in the company's approach, but provides no details or documentation from these discussions beyond footnote descriptions such as "Four oncologists were consulted in April 2021". Please provide further details of each meeting, including but not limited to: attendees, agenda, any materials shared in advance, any minutes taken.

Documentation of discussions with experts have been provided in a confidential folder (File name: ERG Request for Expert Opinion Documents).

B24. The company indicates (section B3.3.3.1), based on clinical opinion and a published meta-analysis, that 'DFS is a suitable surrogate for OS'. But the ERG expects the DFS survival curve to decrease more rapidly than the OS survival curve (since DFS indicates the waiting time for death *or* progression), and observes this in the curves shown in Document B Figures 20 and 21. In light of this, please comment further on the idea that DFS is a surrogate for OS.

The company agrees with the ERGs expectation that the DFS survival curve will decrease more rapidly than the OS survival curves, as observed in Document B Figure 20 and 21, as DFS events such as first recurrence of NSCLC or occurrence of new primary NSCLC will not impact OS curve.

In the company submission, when DFS was discussed as a surrogate endpoint to OS, it was not in terms of the survival curves, but in relation to the use of DFS as a surrogate endpoint to OS as an earlier indicator of efficacy.

With surrogate endpoints, there is a correlation to the outcome of other clinically meaningful endpoints, with the added benefit that the surrogate endpoint is more readily obtainable in the clinical trial setting. Though OS is the gold standard in oncology clinical trials, its evaluation can take a long time and can be influenced by subsequent lines of therapy. DFS requires a shorter duration of follow-up, and is unaffected by crossover between study arms or subsequent therapies (29).

DFS has been shown to be a valid surrogate endpoint for OS in studies of adjuvant chemotherapy in early-stage NSCLC (29). A meta-analysis of 7,626 patients across 24 trials investigating postoperative chemotherapy ± radiotherapy versus no postoperative chemotherapy ± radiotherapy, for resectable NSCLC found a high correlation between DFS and OS (R^2 = 0.92 without RT; R^2 = 0.99 with RT) (29).

Additionally, DFS has been an accepted regulatory endpoint in solid tumours for two decades, across a wide range of cancers and therapy types (see Table 16). This now includes early NSCLC, with the recent FDA approval of atezolizumab in the adjuvant setting for patients with PD-L1 ≥ 1% Stage II–IIIA NSCLC (7th ed. TNM staging classification) and adjuvant osimertinib approved by the FDA and EMA for

patients with early stage EGFR+ NSCLC, both of which were approved based on a demonstrated DFS benefit (30).

DFS is being increasingly used as a surrogate for OS in studies of adjuvant systemic therapy in lung cancer (e.g. IMpower010 (31), ANVIL (1); KEYNOTE-091/PEARLS (5); BR.31 (32); ALCHEMIST Chemo-IO (2); MERMAID-1 (33); MERMAID-2 (34) in order to speed up evaluation of new therapies and bring effective treatments into the clinic more rapidly.

With regard to the IMpower010 trial, the proven DFS benefit and survival advantage for PD-L1 ≥ 1% TC Stage II–IIIA patients remained statistically significant after a median follow up of 32.8 months. Which according to clinical experts, indicate a positive impact on long-term survival.

Additionally, in the absence of mature OS data in the IMpower010 trial, extending the disease free survival period and delaying progression to advanced disease is clinically meaningful and provides long-term benefit to the patient.

Table 16: Non-exhaustive list of oncology EMA drug approvals given based on DFS data

Indication	Therapy	First approval (European Commission decision)	DFS/RFS HR
Early breast cancer	Anastrozole	2011 (35)	DFS HR 0.83
	Letrozole	2012 (36)	DFS HR 0.87 & 0.89
	Trastuzumab + chemotherapy	2011 (37)	DFS HR 0.48
	Neratinib	2018 (38)	iDFS HR 0.66
	Pertuzumab + trastuzumab + chemotherapy	2018 (39)	iDFS HR 0.82
	Ado-trastuzumab emtansine	2019 (40)	iDFS HR 0.50
Gastrointestinal stromal tumour	Imatinib	2009 (41)	RFS HR 0.40
Melanoma	Nivolumab	2018 (42)	RFS HR 0.65
NSCLC	Osimertinib	2021 (43)	DFS HR 0.20

iDFS, invasive DFS; NS, not significant; RFS: recurrence free survival.

B25. In Section B.3.4.2 Chouaid et al. 2013 and Nafees et al. 2008 are referenced in relation to health-related quality of life but they are not included in Appendix K, where details of HRQoL relevant studies identification is summarised. Please clarify how the Chouaid et al. 2013 and Nafees et al. 2008 studies were identified.

The SLR presented in Appendix K focussed on identifying studies that provided evidence on the health related quality of life of patients with early NSCLC. Chouaid et al. 2013 (44) and Nafees et al. 2008 (45) focus on patients with metastatic NSCLC. These studies were identified when looking at accepted NICE HTA submissions for NSCLC in progressive states (20, 22, 23).

B26.

[redacted]

Please see Table 17 and Table 18 for the requested additional details on the included HRQoL studies.

Table 17: Recruitment data from included HRQoL studies

Study	Recruitment process; no. contacted	Recruitment process; no. enrolled	Recruitment process; no. analysed
Andreas et al. (2018)	N=868	N=831	N=306
Bendixen et al. (2019)	N=361	N=206	N=201
Black et al. (2014)	Not available	Not available	Not available
Blom et al. (2020)	Not available	Not available	N = 5100
Brocki et al. (2018)	Not available	N=68	N=66
Grutters et al. (2010)	N=374	N=260	N=245
Ilonen et al. (2010)	Not available	N=53	N=48
Jang et al. (2009)	Not available	N=482	N=359
Jang et al. (2010)	N=172	N=172	N=172
Jeppesen et al. (2018)	N=63	N=51	N=51

Khan et al. (2016)	Not available	N=100	N=98
Kim et al. (2018)	Not available	N=515	N=515
Koide et al. (2019)	Not available	N=24	N=24
Manser et al. (2006)	Not available	N=116	N=92
Naik et al. (2017)	N=3019	N=1929	N=1759
Rauma et al. (2019)	N=456	N=199	N=180
Sharples et al. (2012)	Not available	N=241	N=144
Swan et al. (2018)	N=343	N=237	N=236
Tramontano et al. (2015)	Not available	N=5015	N=2396
Trippoli et al. (2001)	Not available	N=95	N=92
Vogel et al. (2019)	Not available	N=43	N=43
Witlox et al. (2020)	Not available	N=175	N=174
Wolff et al. (2018)	Not available	N=306	N=302
Yang et al. (2014)	Not available	N=2045	N=518
Yang et al. (2019)	Not available	N=1715	N=1715

Table 18: Intervention and comparators, response rates and adverse reactions from included HRQoL studies

Study	Interventions and comparators	Response Rates	Adverse Reactions
Andreas et al. (2018)	Not available	36%	Unclear if analysed for impact on HRQoL
Bendixen et al. (2019)	1) VATS 2) Anterior thoracotomy	Not available	Unclear if analysed for impact on HRQoL
Black et al. (2014)	1) Spiral CT 2) X-ray	Not available	Unclear if analysed for impact on HRQoL
Blom et al. (2020)	Not available	Not available	Unclear if analysed for impact on HRQoL
Brocki et al. (2018)	1) Inspiratory muscle training (intervention group) 2) Control group	Not available	Unclear if analysed for impact on HRQoL
Grutters et al. (2010)	Not available	70%	"Because the current study focuses on long-term follow-up, we examined the adverse event of dyspnoea. Severe adverse events are defined as

			grade ≥3"
Ilonen et al. (2010)	Lobectomy or bilobectomy (non-comparative)	Not available	Unclear if analysed for impact on HRQoL
Jang et al. (2009)	1) Vinorelbine + cisplatin (adjuvant therapy) 2) Observation	74%	Unclear if analysed for impact on HRQoL
Jang et al. (2010)	Not available	Not available	Unclear if analysed for impact on HRQoL
Jeppesen et al. (2018)	1) SBRT + CGA 2) SBRT alone	"CGA Group 5 weeks: 96% 5 weeks + 3 months: 64% 5 weeks + 6 months: 86% 5 weeks + 9 months: 53% 5 weeks + 12 months: 83% Non-CGA Group 5 weeks: 95% 5 weeks + 3 months: 81% 5 weeks + 6 months: 100% 5 weeks + 9 months: 62% 5 weeks + 12 months: 75%"	Unclear if analysed for impact on HRQoL
Khan et al. (2016)	Not available	Baseline: 99% 3 months: 79% 6 months: 55%	Unclear if analysed for impact on HRQoL
Kim et al. (2018)	Not available	Not available	Unclear if analysed for impact on HRQoL
Koide et al. (2019)	VATS	Not available	Unclear if analysed for impact on HRQoL

Manser et al. (2006)	Not available	79%	Unclear if analysed for impact on HRQoL
Naik et al. (2017)	Not available	64%	Unclear if analysed for impact on HRQoL
Rauma et al. (2019)	1) VATS lobectomy 2) Thoracotomy lobectomy	90%	Unclear if analysed for impact on HRQoL
Sharples et al. (2012)	1) EUS/EBUS 2) Surgical staging	Baseline: 100% At end of staging: 97% 2 months post-randomisation: 92% 6 months post-randomisation: 86%	Unclear if analysed for impact on HRQoL
Swan et al. (2018)	Not available	70%	Unclear if analysed for impact on HRQoL
Tramontano et al. (2015)	Not available	EQ-5D: 47.8% SF-12v2: 46.7%	Unclear if analysed for impact on HRQoL
Trippoli et al. (2001)	Not available	97%	Unclear if analysed for impact on HRQoL
Vogel et al. (2019)	Chemoradiation	100%	Unclear if analysed for impact on HRQoL
Witlox et al. (2020)	1) Prophylactic cranial irradiation 2) Observation	Prophylactic cranial irradiation arm: 80.2% Observation arm: 84.1%	Unclear if analysed for impact on HRQoL
Wolff et al. (2018)	1) SBRT 2) Surgery	Surgery: 0 months: 100% 3 months: 61% 6 months: 66% 12 months: 54%	Unclear if analysed for impact on HRQoL

		Propensity score matched (SBRT): 0 months: 98% 3 months: 78% 6 months: 68% 12 months: 56% Stratification based match: 0 months: 98% 3 months: 83% 6 months: 68% 12 months: 49%	
Yang et al. (2014)	Not available	Unclear	Unclear if analysed for impact on HRQoL
Yang et al. (2019)	Not available	Not available	Do not directly model impact on HRQoL

[redacted] Table 19 [redacted] All of the inputs presented in the table are varied at the same time when the model sub-group is changed, linked to cell F34 (named range “pop”) within the ‘Model Settings’ sheet. Thus, the effect that any one of the inputs may have on the results, may be confounded by the other inputs.

In the Table 19, we refer to the sub-group PD-L1+ Stage II-IIIA as (A), and the sub-group PD-L1+ Stage II-IIIA, excluding ALK+/EGFR as (B).

Table 19: The effects on the variables with the subgroup analysis for the PD-L1+ Stage II-IIIA, excluding ALK+/EGFR subgroup

Variable	Sheet	Cells	Effect	Interpretation
Time-to-off treatment (ttot_atz)	Atezolizumab in DFS Tx Schedule	C31:N46	If option_ttot_atz is set to 'observed in trial', a change in the time-to-off treatment has an effect on the atezolizumab treatment cost in the DFS health state.	<u>Completed 16 cycles of treatment (ATZ arm):</u> (A) [redacted] < (B) [redacted] This implies that the treatment cost should be higher in (B), which is realised: (A) [redacted] < (B) [redacted]
Number of patients experiencing locoregional and metastatic recurrence as first DFS event	DFS Events	E23:T24	A change in the number of patients who experience locoregional and metastatic recurrence has an effect on the proportion of patients who experience these recurrences (cells E30:T31 and variables p_dfs_lr_atz, p_dfs_mr_atz, p_dfs_lr_bsc, p_dfs_mr_bsc). As a consequence, this has an effect on the costs, quality-life year gains, and life-year gains for the locoregional recurrence and metastatic recurrence health states.	<u>% locoregional recurrences (ATZ arm):</u> (A) [redacted] < (B) [redacted] <u>% locoregional recurrences (BSC arm):</u> (A) [redacted] > (B) [redacted] The % of locoregional recurrences is greater in (B) than in (A) for the ATZ arm. The change appears insignificant for the BSC arm. Thus, we only interpret the effect that a change in this input has on the ATZ arm given the issue of confounding effects mentioned above. As more patients transition first to the locoregional recurrence health state, and as less patients may make it to the metastatic recurrence health states due to dying in the locoregional recurrence health state in (B), locoregional recurrence health state costs and QALYs should

				be higher, and metastatic recurrence health state costs and QALYs should be lower in (B). The below results show that this is realised: <u>Locoregional health state:</u> Cost: (A) = [redacted] < (B) = [redacted] QALY: (A) = [redacted] < (B) = [redacted] <u>Metastatic health states:</u> Cost: (A) = [redacted] > (B) = [redacted] QALY: (A) = [redacted] > (B) = [redacted]
Number of patients experiencing death as a first DFS event	DFS Events	E26:T26	A change in the number of patients who experience death as a first DFS event has an effect on the transition probability from the DFS health state to Death (cells C37:T38 and variables dfs_death_atz and dfs_death_bsc). A change in this transition probability would impact the costs, quality-life year gains and life year gains of all health states.	Transition probability to death: <u>Transition probability to death (ATZ arm):</u> (A) [redacted] > (B) [redacted] <u>Transition probability to death (ATZ arm):</u> (A) [redacted] < (B) [redacted] Due to the insignificant change in the transition probabilities, an interpretation of the results will not be conducted as changes in the other inputs may confound the effect that we can expect this input to have.

Number of patients experiencing each grade 3+ treatment emergent adverse event (atezolizumab arm only)	DFS Events	E50:S89	If the costs and disutilities of adverse events are considered by the model, a change in the number of patients experiencing each adverse event has an effect on the adverse event management costs and quality-life year gains in the DFS health state for the atezolizumab arm (refer to variables c_ae_atz and u_ae_atz).	This is not currently considered in the model.
Kaplan-Meier statistics	DFS Kaplan-Meier	C15:X177; C190:X416	If the model uses the Kaplan-Meier curve + parametric tail to model DFS, a change in these statistics affects the proportion of patients who are in the DFS health state in each cycle and, consequently, costs, quality-life year gains, and life-year gains of all health states. Moreover, if option_ttot_atz is set to 'until progression or death', a change in these statistics has an effect on the atezolizumab treatment cost in the DFS health state.	This input is not currently used to model DFS or time-to-off treatment.
Estimated parameters from survival analysis (DFS)	DFS Survival Analysis	C16:AW29; C38:AW51	A change in these estimates affects the extrapolation of DFS (proportion of patients in DFS in each cycle) and, consequently, the costs, quality-life year gains and life-year gains of all health states.	The analysis of DFS for the subgroup of patients that do not have ALK+/EGFR mutation shows that the hazard ratio decreases (refer to company submission Section B.2.7.2). Thus, an even greater improvement of DFS in this subgroup of patients should result in a greater difference in the overall costs and QALYs across the ATZ and BSC arms. In relative terms, even less patients in the ATZ arm vs. the BSC

				arm would experience recurrence. The results below show that this expectation is realised. <u>Cost Difference:</u> (A) [redacted] > (B) [redacted] <u>QALY Difference:</u> (A) [redacted] < (B) [redacted]

B28. When cell F49 in sheet "Efficacy Inputs", (mis?)named "list" is set to "Limited in Time", and the below cells "effect_dec_atz" and "effect_max_atz" are toggled, the predicted cost-effectiveness of atezolizumab improves as time to treatment effect decreases and time to treatment effect cessation is reduced. This counterintuitive relationship is also illustrated in the company's submitted scenario analyses, Document B Table 69.

Please describe and justify the company's approach to "limit the duration of atezolizumab treatment effect", and interpret the counterintuitive results produced by the company's model.

F49 in 'Efficacy Inputs' is named both "list" and "options_effect_atz" with the latter named range used throughout the model.

When the dropdown is set to "Limited in Time" with "effect_dec_atz" and "effect_max_atz" both set to 60 months, in line with the base case settings. The "ATZ" engine uses the between cycle (monthly) difference in selected parametric curve to generate a probability of having an event in the current cycle. Up to prespecified month 60, the ATZ engine uses the atezolizumab arm selected parametric curve to calculate the probability. Beyond month 60, the ATZ engine uses the BSC arm selected parametric curve to calculate the probability. This is in line with the treatment waning assumptions previously implemented for atezolizumab in other indications, in the absence of evidence on treatment waning.

A limitation of this switching approach is that each probability is independent of the last. The BSC arm based curves have a larger number of events in earlier cycles meaning there are fewer patients remaining to inform the probability beyond 60 months. In the base case, the log-logistic is used for the DFS parametric curve in both arms; this incorporates decreasing hazard functions. As a result, over time and as the number of patients falls the probability of an event between each cycle falls. For the "Limited in Time" scenario, this leads to a negligible drop in the probability of event beyond month 60 when reverting to BSC probabilities.

Roche agree that the impact on the results of switching to "Maintained over Time" is currently illogical due to the cumulative effect of the small differences in probabilities when reverting to BSC. This is exacerbated to the point where the overall direction of

change in results is illogical due to the DFS characteristics of eNSCLC patients: assuming a “cure” effect beyond 5 years of DFS.

[redacted]

There is a mistake in the equation in section B.3.3.5; the equation should read that the model uses the higher of the two values to model probability of death (health state vs general population). The model does not use the same adjustment for the post-DFS health states as the health state related probability of death is larger than the general population probability of death for the large majority of cycles. Using this adjustment (replacing “t_mort” to “t_mort_dfs”) for the post-DFS health states has minimal impact on the model results (a £2 increase to the ICER). The change has been incorporated in the updated model (see “Life Tables’ tab, cell F15 for switch between “t_mort” and “t_mort_dfs”), however, as this question was not a high priority and therefore implemented last, it is not included in the results tables in Appendix A and Appendix B.

B30. Please explain the partitioning of Metastatic Recurrence (1L and 2L) columns CG-CT in sheet “ATZ” between “On Treatment – Early” and “On Treatment – Late”, and the related use of variable “c_c_month_1lmtx” in column EN and c_c_month_2lmtx in column EX.

The model designates separate columns in the Markov trace (sheet ‘ATZ’) for patients who can and cannot re-challenge with immunotherapy when receiving 1L and 2L metastatic treatment for transparency. The monthly cost of 1L and 2L metastatic treatment for patients in the atezolizumab arm who can re-challenge with immunotherapy is based on the market shares of treatments captured by the following variables (tr1_c_ms_1lmtx- tr4_c_ms_1lmtx and tr1_c_ms_2lmtx- tr4_c_ms_2lmtx). These are the same market shares that the model uses to calculate the monthly cost of 1L and 2L metastatic treatment for patients in the BSC

arm. Since the monthly metastatic treatment costs for patients in the atezolizumab arm who can re-challenge, and the BSC arm are the same (unadjusted for proportion of patients in health state), the model uses c_c_month_1lmtx in column EM and c_c_month_2lmtx in column EW.

B31. Please confirm the source of the adverse event data in rows 49-89 of sheet "DFS Events". Are these all-Grade, restricted to treatment-emergent events, etc?

The source of the adverse event data is from IMpower010 and captures grade 3+ treatment emergent and treatment related adverse events.

B32. Please document your approach to calculate monthly transition probability estimates from published Kaplan-Meier plots, both "Using Median" and "Using Analysis", as described across sheets "LR Survival Analysis", "1L Met. Rec. Survival Analysis" and "2L Met. Rec. Survival Analysis". Explain and justify each step, from identification of each publication, through to the use of calculated transition probability estimates in the model.

The model uses two approaches to calculate the transition probabilities with evidence found in the literature. The first approach involves the digitisation of the Kaplan-Meier curve and reconstruction of the data with the algorithm presented in Guyot, Ades, Ouwens and Welton (2012) (46). The data is then analysed with a parametric survival model (exponential distribution used, this was a simplifying assumption as using a different parametric distribution would make it time varying) to estimate the parameters required to calculate the transition probabilities. The second approach uses the median statistic provided (progression-free survival or overall survival) to calculate the transition probability assuming an exponential survival function. Table 20 presents the rationale for choosing certain literature to estimate the transition probabilities. In addition to the rationale presented in the table, the use of the transition probabilities estimated with the first approach allow the proportion of patients who are in the death health state at month 32 to equal what is observed in the trial (please refer to question B17).

Table 20: Sources used for transition probabilities and the rationale for each source

Transition Probability	Source	Rationale
Locoregional recurrence health state to 1L metastatic recurrence health state and death (patients who treat with curative intent)	Nakamichi et al. 2017 (14)	This study was identified through the RWE SLR (Appendix M of company submission). It was used because, unlike the other studies that were also identified, it separates patients by type of treatment received in their analysis, and analyses a sample of patients who appear to be more comparable to the IMpower010 population of interest. The choice of study is not expected to have a significant impact on the results of the model as they all report similar median progression free survival estimates.
Locoregional recurrence health state to death (patients who treat with palliative intent or do not treat)	Kruser et al. 2014 (8)	This study was identified through a focused literature search. It was used because it used a large sample size to analyse overall survival and provided relatively recent evidence. The choice of study is not expected to not significantly impact the results of the model as they all report similar median overall survival estimates.
1L/2L metastatic recurrence health state to death (patients who do not treat)	Wong et al. 2016 (19)	This study was identified through a focused literature search. No other studies were identified in this search.

Section C: Textual clarification and additional points

C1. Are the operators in the equation in Document B Section 3.3.5 written the wrong way around?

This is indeed the case and we acknowledge this was an error.

References

1. ClinicalTrials.gov. Nivolumab After Surgery and Chemotherapy in Treating Patients With Stage IB-IIIA Non-small Cell Lung Cancer (An ALCHEMIST Treatment Trial) (ANVIL). 2021.
2. ClinicalTrials.gov. Testing the Addition of a Type of Drug Called Immunotherapy to the Usual Chemotherapy Treatment for Non-small Cell Lung Cancer, ALCHEMIST Chemo-IO Study. 2021.
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4. ClinicalTrials.gov. A Study of Neoadjuvant Chemotherapy Plus Nivolumab Versus Neoadjuvant Chemotherapy Plus Placebo, Followed by Surgical Removal and Adjuvant Treatment With Nivolumab or Placebo for Participants With Surgically Removable Early Stage Non-small Cell Lung Cancer. 2021.
5. ClinicalTrials.gov. Study of Pembrolizumab (MK-3475) vs Placebo for Participants With Non-small Cell Lung Cancer After Resection With or Without Standard Adjuvant Therapy (MK-3475-091/KEYNOTE-091) (PEARLS). 2020.
6. Sonoda D, Matsuura Y, Kondo Y, Ichinose J, Nakao M, Ninomiya H, et al. Characteristics of surgically resected non-small cell lung cancer patients with post-recurrence cure. Thorac Cancer. 2020;11(11):3280-8.
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Appendix A – Base case results

Summary of base-case cost effectiveness results

- **Cost effectiveness results are presented with and without confidential PAS for atezolizumab (list price for all other drugs) for the following population:**
    - **Stage II–IIIA patients following resection and platinum-based chemotherapy with NSCLC whose tumours have PD-L1 expression on ≥ 1% TC, with EGFR mutant or ALK-positive**
- **In this population, the resulting base case incremental cost effectiveness ratio (ICER) when comparing atezolizumab to BSC was:**
    - [redacted] **per quality-adjusted life year (QALY) gained at PAS price**
    - **£35,250 per QALY gained at list price**
- **A limitation of the with-PAS analysis is that confidential discounts are in place for other therapies in the pathway, which Roche are unable to account for. This analysis is also limited by the availability of relevant data which introduces a degree of uncertainty into the analysis**

A.1 Base-case incremental cost effectiveness analysis results

Base case results of the economic model are presented in Table 21 (list price) and Table 22 (PAS price; [redacted] discount) for the Stage II–IIIA patients following resection and platinum-based chemotherapy with NSCLC whose tumours have PD-L1 expression on ≥ 1% TC. In these comparisons, all comparators (and therapies included in the treatment pathway) are at list price.

Table 21: Base case cost effectiveness results – Stage II–IIIA population – list price

Technologies	Total costs	Total LYG	Total QALYs	Incremental costs	Incremental LYG	Incremental QALYs	ICER incremental (£/QALY)
Atezolizumab	[redacted]	8.65	[redacted]	[redacted]	1.36	[redacted]	£35,250
BSC	[redacted]	7.29	[redacted]				

Table 22: Base case cost effectiveness results – Stage II–IIIA population – PAS price

Technologies	Total costs	Total LYG	Total QALYs	Incremental costs	Incremental LYG	Incremental QALYs	ICER incremental (£/QALY)
Atezolizumab	[redacted]	8.65	[redacted]	[redacted]	1.36	[redacted]	[redacted]
BSC	[redacted]	7.29	[redacted]				

In the Stage II–IIIA population at list price, atezolizumab provided [redacted] QALYs and 8.65 life years at a total overall cost of [redacted]. In contrast, BSC provided [redacted] QALYs and 7.29 life years, at a total cost of [redacted]. The resulting base ICER when comparing atezolizumab to BSC was £35,250 per QALY gained.

Results of the with-PAS analysis showed that adjuvant atezolizumab treatment resulted in reduced total costs in the atezolizumab arm of [redacted] and reduced total costs in the BSC arm, due to atezolizumab being used in metastatic states, of [redacted]. This resulted in an ICER of [redacted], significantly below the cost effectiveness threshold, for the Stage II-IIIA population.

A.2 Sensitivity analyses

Summary of sensitivity analyses results

- **Extensive sensitivity and scenario analyses were conducted in the economic model to demonstrate the uncertainty around the parameters used, assess the plausibility of different scenarios and approaches, and help understand what key variables and assumptions potentially have a major impact on cost effectiveness results**
- **The PSA ICER results when comparing atezolizumab with PAS to BSC was £[redacted] per QALY gained, consistent with the deterministic base case**
    - **The one-way sensitivity analyses showed that at PAS price, the proportion of patients in the 1L metastatic state who receive treatment, proportion of patients in the DFS state in the BSC arm who have metastatic recurrence, the market share of patients who receive pemetrexed and cisplatin in the BSC arm for 1L metastatic treatment, and the transition probability to death from DFS health state, are the most influential parameters on the ICER**
- **These results help to quantify and understand the impact of the uncertainty in the analysis on cost effectiveness and decision-making. Overall. The results show that the model results are robust and are cost-effective in all scenarios presented**

A.2.1 Probabilistic sensitivity analysis

To assess the uncertainty surrounding the variables included in the cost effectiveness model, a PSA was undertaken using 5,000 iterations to ensure results had converged. Results of the PSA compared to deterministic results at list price are presented in Table 23. The with-PAS equivalent comparison is presented in Table

24. Deterministic and probabilistic results are similar, therefore not indicating any signs of non-linearity in the model.

Table 23: PSA results compared to base-case (list price)

	Costs		QALYs		ICERs	
	Deterministic base case	PSA	Deterministic base case	PSA	Deterministic base case	PSA
Stage II-IIIA population						
Atezolizumab	[redacted]	[redacted]	[redacted]	[redacted]	£35,250	£35,708
BSC	[redacted]	[redacted]	[redacted]	[redacted]	-	-

Table 24: PSA results compared to base-case (with PAS)

	Costs		QALYs		ICERs	
	Deterministic base case	PSA	Deterministic base case	PSA	Deterministic base case	PSA
Stage II-IIIA population						
Atezolizumab	[redacted]	£50,880	[redacted]	6.44	[redacted]	[redacted]
BSC	[redacted]	£49,129	[redacted]	5.42	-	-

The incremental cost effectiveness planes in Figure 39 and Figure 40 show the individual PSA iterations for the comparisons of atezolizumab to BSC in the Stage II–IIIA populations at list and PAS price, respectively. At PAS price, atezolizumab was dominant in 33% of the simulations; supporting the view that atezolizumab is a cost-effective option for the NHS in patients with Stage II–IIIA NSCLC. Cost effectiveness acceptability curves for the comparisons of atezolizumab to BSC in the Stage II–IIIA populations at list and PAS price are presented in Figure 41 and Figure 42. At PAS price, atezolizumab is deemed the most likely cost-effective treatment option beyond a willingness-to-pay (WTP) of approximately [redacted] per QALY. At a £20,000 and £30,000 WTP, the likelihood of atezolizumab being the most cost-effective treatment option rises to [redacted] and [redacted], respectively.

Figure 39: Incremental cost effectiveness plane – atezolizumab vs BSC in Stage II–IIIA NSCLC, list price

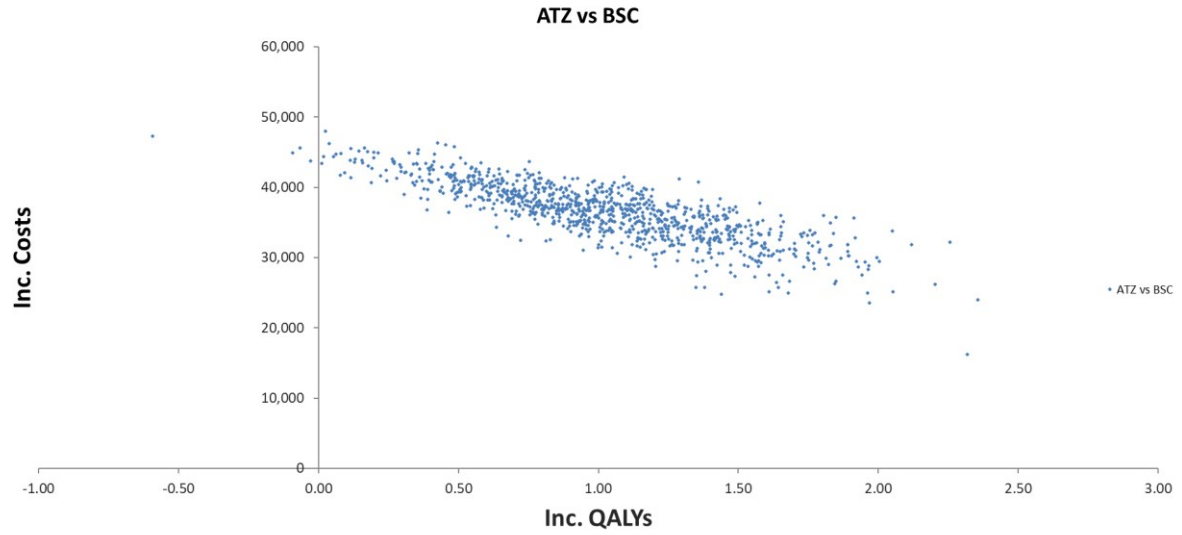


Figure 40: Incremental cost effectiveness plane – atezolizumab vs BSC in Stage II–IIIA NSCLC, PAS price

[redacted]

Figure 41: Cost effectiveness acceptability curve – atezolizumab vs BSC in Stage II–IIIA NSCLC, list price

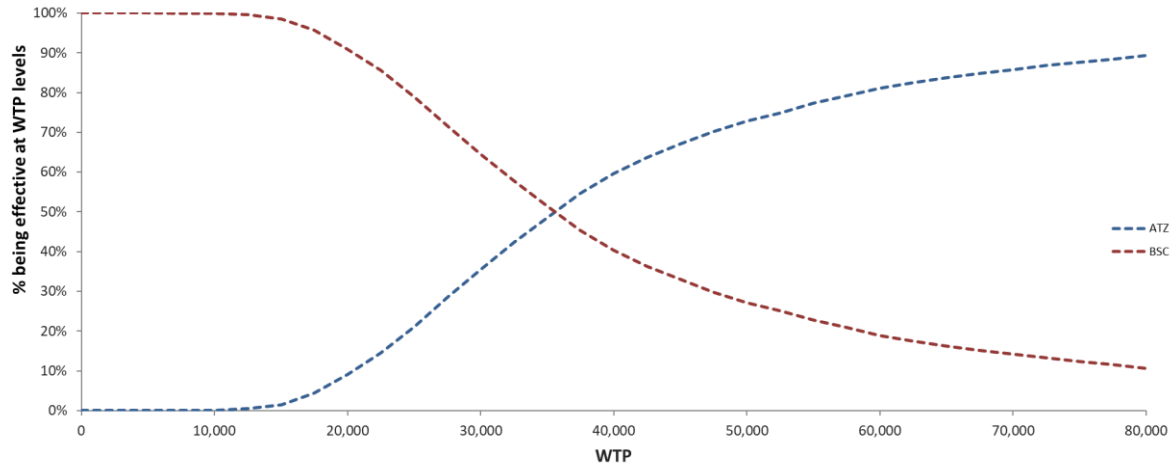


Figure 42: Cost effectiveness acceptability curve – atezolizumab vs BSC in Stage II–IIIA NSCLC, PAS price

[redacted]

A.2.2 Deterministic sensitivity analysis

The parameters to include in the deterministic sensitivity analysis (DSA) were taken from Table 14 (with additional parameters compared to the company submission). The parameter values used are presented in Table 25 below. The base case values of most parameters were varied using upper and lower limits of the 95% confidence intervals for the variables (from the PSA output), with the exception of discount rates, which were varied from 1.5% to 5.0%. Key remaining model parameters were tested in scenario analyses (see Appendix A.2.3).

Table 25: Parameter values for univariate sensitivity analysis

Parameter	Base case value	PAS price		List price	
		Lower value	Higher value	Lower value	Higher value
Proportion of patients who have metastatic recurrence as recurrence - ATZ Arm	[redacted]	0.42	0.61	0.42	0.61
Proportion of patients who have metastatic recurrence as recurrence - BSC Arm	[redacted]	0.50	0.66	0.49	0.66
Proportion of patients with Locoregional Recurrence - ATZ arm	[redacted]	0.39	0.58	0.39	0.58

Proportion of patients with Locoregional Recurrence - BSC arm	[redacted]	0.34	0.50	0.34	0.51
Transition probability to death from DFS health state - ATZ Arm	[redacted]	0.0016	0.0022	0.0016	0.0022
Transition probability to death from DFS health state - BSC Arm	[redacted]	0.0003	0.0005	0.0003	0.0005
% on Curative Treatment - Locoregional Recurrence	0.80	0.72	0.85	0.72	0.85
% on Palliative Treatment - Locoregional Recurrence	0.20	0.14	0.27	0.14	0.27
Transition probability (PFS - LR CT)	0.04	0.03	0.04	0.03	0.04
% have Progression as first Event - Locoregional Recurrence	0.81	0.66	0.93	0.66	0.93
Transition probability (OS - LR PT)	0.14	0.11	0.16	0.11	0.16
% on 1L metastatic Treatment - 1L Metastatic	[redacted]	0.56	0.79	0.56	0.79
Treatment Option 1 - Market Share - 1L Metastatic Treatment - BSC Arm	[redacted]	0.21	0.35	0.21	0.35
Treatment Option 2 - Market Share - 1L Metastatic Treatment - BSC Arm	[redacted]	0.17	0.30	0.17	0.30
Treatment Option 3 - Market Share - 1L Metastatic Treatment - BSC Arm	[redacted]	0.25	0.40	0.25	0.40
% have Progression as first Event - 1L Metastatic Recurrence	[redacted]	0.67	0.94	0.67	0.94
Transition probability (1LMNTx)	0.23	0.19	0.27	0.19	0.27
% on 2L metastatic Treatment - 2L Metastatic	[redacted]	0.42	0.58	0.42	0.58
Treatment Option 1 - Market Share - 2L Metastatic Treatment - Atezolizumab Arm	[redacted]	0.00	0.03	0.00	0.03
Treatment Option 2 - Market Share - 2L Metastatic Treatment - Atezolizumab Arm	[redacted]	0.46	0.62	0.46	0.62

Treatment Option 1 - Market Share - 2L Metastatic Treatment - BSC Arm	[redacted]	0.22	0.36	0.22	0.37
Treatment Option 2 - Market Share - 2L Metastatic Treatment - BSC Arm	[redacted]	0.16	0.29	0.16	0.29
Treatment Option 3 - Market Share - 2L Metastatic Treatment - BSC Arm	[redacted]	0.12	0.24	0.13	0.25
Transition probability (2LMNTx)	[redacted]	0.20	0.27	0.19	0.27
Discount costs	0.04	0.02	0.05	0.02	0.05
Discount effects	0.04	0.02	0.05	0.02	0.05
Administration cost	299.61	251.12	350.48	253.56	349.92
Other healthcare resource use (DFS)	53.19	48.69	57.76	48.69	57.83
Total AE management cost - LRR	14.05	11.86	16.34	11.85	16.45
Other healthcare resource use (LR - CT)	161.57	145.91	177.89	145.59	177.84
Other healthcare resource use (LR - PT)	161.57	146.22	177.89	146.34	178.10
Total AE management cost - 1L Met Atezo	87.07	73.98	101.22	73.76	101.11
Total AE management cost - 1L Met BSC	93.45	85.52	101.85	85.44	101.87
Other healthcare resource use (1LM - Tx)	352.11	321.89	382.42	322.98	384.03
Other healthcare resource use (1LM - NTx)	352.11	322.07	383.64	322.38	382.61
Total AE management cost - 2L Met Atezo	308.41	273.13	344.64	273.19	344.89
Total AE management cost - 2L Met BSC	216.58	187.36	248.81	187.35	248.37
Other healthcare resource use (2LM - Tx)	608.34	562.04	657.45	560.97	656.52
Other healthcare resource use (2LM - NTx)	608.34	562.24	657.42	561.42	657.09
End of life cost - disease death	4598.01	3878.35	5405.51	3879.41	5360.52
Utility treatment (DFS)	0.03	-0.03	0.11	-0.03	0.10
Utility no treatment (DFS)	0.03	-0.03	0.11	-0.03	0.10
Utility treatment (LR - CT)	0.08	0.01	0.15	0.01	0.16
Utility treatment (LR - PT)	0.17	0.12	0.22	0.13	0.22

Utility treatment (1LM)	0.11	0.10	0.12	0.10	0.12
Utility no treatment (1LM)	0.17	0.12	0.22	0.13	0.22
Utility treatment (2LM)	0.13	0.10	0.15	0.10	0.15
Utility no treatment (2LM)	0.17	0.13	0.22	0.12	0.22

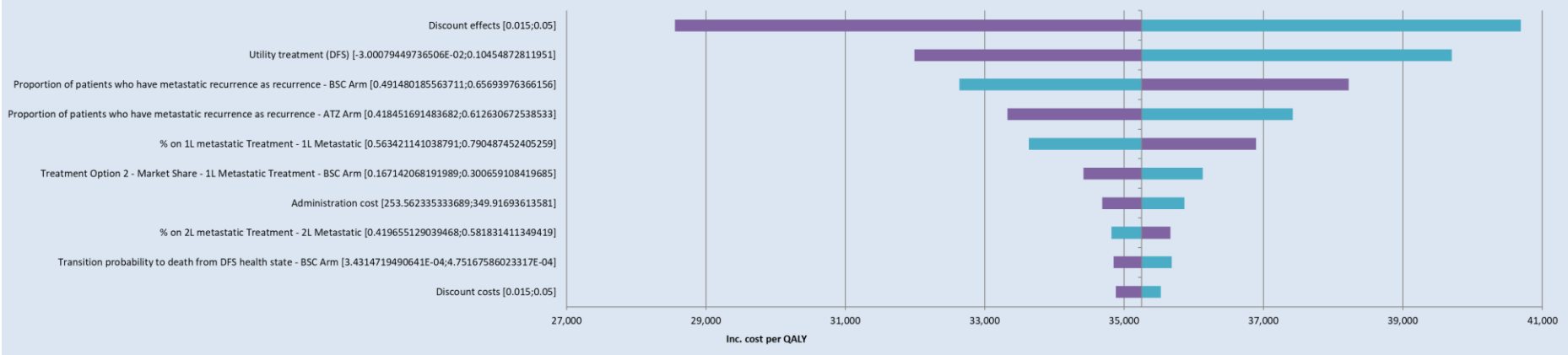
Deterministic sensitivity analyses with-PAS results for the Stage II–IIIA population are presented in Figure 43.

Based on the deterministic sensitivity analyses at PAS price, the most influential parameters appear to be the proportion of patients in the 1L metastatic state who receive treatment, proportion of patients in the DFS state in the BSC arm who have metastatic recurrence, the market share of patients who receive pemetrexed and cisplatin in the BSC arm for 1L metastatic treatment, and the transition probability to death from DFS health state. Using the upper value for the proportion of patients in the 1L metastatic state who receive treatment, resulted in a negative ICER, meaning atezolizumab was dominating. All results remained significantly below the cost effectiveness 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. This is further evidenced by discount rates being included in the top 10 most sensitive inputs, as discount rates impact results more broadly throughout the model than any other input.

Figure 43: Tornado diagram – Stage II–IIIA, PAS price

Deterministic sensitivity analyses list price results for the Stage II–IIIA population are presented in Figure 44. Based on the deterministic sensitivity analyses at list price, the most influential parameters appear to be discount effects, utility in DFS state (on treatment), and the market share of patients who receive pemetrexed and cisplatin in the BSC arm for 1L metastatic treatment. 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. This is further evidenced by discount rates being included in the top 10 most sensitive inputs, as discount rates impact results more broadly throughout the model than any other input.

Figure 44: Tornado diagram – Stage II–IIIA, list price


Discount effects [0.015;0.05]
Utility treatment (DFS) [-3.00079449736506E-02;0.10454872811951]
Proportion of patients who have metastatic recurrence as recurrence - BSC Arm [0.491480185563711;0.65693976366156]
Proportion of patients who have metastatic recurrence as recurrence - ATZ Arm [0.418451691483682;0.612630672538533]
% on 1L metastatic Treatment - 1L Metastatic [0.563421141038791;0.790487452405259]
Treatment Option 2 - Market Share - 1L Metastatic Treatment - BSC Arm [0.167142068191989;0.300659108419685]
Administration cost [253.562335333689;349.91693613581]
% on 2L metastatic Treatment - 2L Metastatic [0.419655129039468;0.581831411349419]
Transition probability to death from DFS health state - BSC Arm [3.4314719490641E-04;4.751675860233l7E-04]
Discount costs [0.015;0.05]
27,000
29,000
31,000
33,000
35,000
37,000
39,000
41,000
Inc. cost per QALY

A.2.3 Scenario analysis

Scenario analyses were conducted to assess uncertainty around remaining parameter inputs and structural assumptions in the model. Additional scenarios have been included from ERG clarification questions:

- OS survival analysis (DFS and OS projections driven by the respective KM data) – Question B10
- Additional administration costs – Question B13
- Incorporate costs for grade 2+ adverse events in IMpower010 – Question B14
- Incorporate disutilities for grade 2+ adverse events in IMpower010 – Question B15

Results of the scenario analyses are presented in Table 26 for the Stage II–IIIA population at PAS price for atezolizumab (results at list price are presented in Table 27).

All scenario results remain cost-effective and below [redacted], with the most sensitive scenarios based on the DFS distribution selection. Sensitivity to these scenarios are expected as they determine early movements from the DFS health state, impacting downstream costs and outcomes in progressive states. It should be noted that, whilst sensitive to distribution choice, all distributions explored were judged to be conservative during validation with UK clinical experts.

Table 26: Results from scenario analyses – Stage II–IIIA NSCLC population (PAS price for atezolizumab)

Parameter	Value	Atezolizumab			Best Supportive Care			ATZ vs. BSC	
		Life Years	QALYS	Costs	Life Years	QALYS	Costs	Inc. costs per LY gained	Inc. costs per QALY gained
Base case		8.65	[redacted]	[redacted]	7.29	[redacted]	[redacted]	[redacted]	[redacted]
DFS distributions	Exponential	8.33	[redacted]	[redacted]	6.78	[redacted]	[redacted]	[redacted]	[redacted]
	Weibull	8.06	[redacted]	[redacted]	6.84	[redacted]	[redacted]	[redacted]	[redacted]
	Log-normal	8.88	[redacted]	[redacted]	7.38	[redacted]	[redacted]	[redacted]	[redacted]
	Generalized Gamma	8.63	[redacted]	[redacted]	7.87	[redacted]	[redacted]	[redacted]	[redacted]
	Gompertz	8.30	[redacted]	[redacted]	7.55	[redacted]	[redacted]	[redacted]	[redacted]
	Gamma	8.07	[redacted]	[redacted]	6.76	[redacted]	[redacted]	[redacted]	[redacted]
Trial data used to inform recurrence type split	Pool across Arms	8.70	[redacted]	[redacted]	7.41	[redacted]	[redacted]	[redacted]	[redacted]
Treatment effect	Maintained over Time	8.63	[redacted]	[redacted]	7.29	[redacted]	[redacted]	[redacted]	[redacted]
Standardised mortality rate	1.50	8.41	[redacted]	[redacted]	7.05	[redacted]	[redacted]	[redacted]	[redacted]
	2.00	8.00	[redacted]	[redacted]	6.65	[redacted]	[redacted]	[redacted]	[redacted]
Atezolizumab treatment schedule	1, 680mg/ every 4 weeks	8.65	[redacted]	[redacted]	7.29	[redacted]	[redacted]	[redacted]	[redacted]
LRR: Efficacy by treatment intent	Digitised Data	8.99	[redacted]	[redacted]	7.68	[redacted]	[redacted]	[redacted]	[redacted]

Metastatic recurrence 1L: Efficacy by treatment intent	Digitised Data	8.71	[redacted]	[redacted]	7.36	[redacted]	[redacted]	[redacted]	[redacted]
Metastatic recurrence 1L: allow metastatic recurrence 2L	No	8.98	[redacted]	[redacted]	7.73	[redacted]	[redacted]	[redacted]	[redacted]
Metastatic recurrence 1L - Efficacy source	IMpower110	8.63	[redacted]	[redacted]	7.26	[redacted]	[redacted]	[redacted]	[redacted]
Metastatic recurrence 2L - Efficacy by treatment intent	Digitised Data	8.70	[redacted]	[redacted]	7.35	[redacted]	[redacted]	[redacted]	[redacted]
DFS cost inputs: scanning schedule	36.00	8.65	[redacted]	[redacted]	7.29	[redacted]	[redacted]	[redacted]	[redacted]
Time-to-off treatment	Until Progression or Death	8.65	[redacted]	[redacted]	7.29	[redacted]	[redacted]	[redacted]	[redacted]
Utility method	Source utilities	8.65	[redacted]	[redacted]	7.29	[redacted]	[redacted]	[redacted]	[redacted]
DFS utility source input	Grutters et al. (2010)	8.65	[redacted]	[redacted]	7.29	[redacted]	[redacted]	[redacted]	[redacted]
	Manser et al. (2006)	8.65	[redacted]	[redacted]	7.29	[redacted]	[redacted]	[redacted]	[redacted]
	Black, Keeler and Soneji (2014)	8.65	[redacted]	[redacted]	7.29	[redacted]	[redacted]	[redacted]	[redacted]
	Yang et al. (2014)	8.65	[redacted]	[redacted]	7.29	[redacted]	[redacted]	[redacted]	[redacted]
	IMpower110	8.65	[redacted]	[redacted]	7.29	[redacted]	[redacted]	[redacted]	[redacted]

Metastatic recurrence 1L utility source input	Chouaid et al. (2013)	8.65	[redacted]	[redacted]	7.29	[redacted]	[redacted]	[redacted]	[redacted]
Metastatic recurrence 2L utility source input	IMpower110	8.65	[redacted]	[redacted]	7.29	[redacted]	[redacted]	[redacted]	[redacted]
	Chouaid et al. (2013)	8.65	[redacted]	[redacted]	7.29	[redacted]	[redacted]	[redacted]	[redacted]
	Nafees et al. (2008)	8.65	[redacted]	[redacted]	7.29	[redacted]	[redacted]	[redacted]	[redacted]
Allow vial sharing	No	8.65	[redacted]	[redacted]	7.29	[redacted]	[redacted]	[redacted]	[redacted]
End of Life costs	Exclude	8.65	[redacted]	[redacted]	7.29	[redacted]	[redacted]	[redacted]	[redacted]
Time horizon	10.00	5.83	[redacted]	[redacted]	5.15	[redacted]	[redacted]	[redacted]	[redacted]
	20.00	7.92	[redacted]	[redacted]	6.74	[redacted]	[redacted]	[redacted]	[redacted]
	30.00	8.59	[redacted]	[redacted]	7.25	[redacted]	[redacted]	[redacted]	[redacted]
"Cure" proportion implementation	5 years	8.42	[redacted]	[redacted]	7.07	[redacted]	[redacted]	[redacted]	[redacted]
	6 years	8.04	[redacted]	[redacted]	6.76	[redacted]	[redacted]	[redacted]	[redacted]
	Ramp up 2–8 years	9.28	[redacted]	[redacted]	7.84	[redacted]	[redacted]	[redacted]	[redacted]
	Ramp up 3–8 years	8.93	[redacted]	[redacted]	7.51	[redacted]	[redacted]	[redacted]	[redacted]
Maximum "cure" proportion	20%	7.25	[redacted]	[redacted]	6.10	[redacted]	[redacted]	[redacted]	[redacted]
	40%	7.53	[redacted]	[redacted]	6.35	[redacted]	[redacted]	[redacted]	[redacted]
	60%	7.88	[redacted]	[redacted]	6.66	[redacted]	[redacted]	[redacted]	[redacted]
	80%	8.33	[redacted]	[redacted]	7.03	[redacted]	[redacted]	[redacted]	[redacted]
Additional results									

OS survival analysis	Use DFS and OS KM data	8.73	[redacted]	[redacted]	7.46	[redacted]	[redacted]	[redacted]	[redacted]
Additional admin costs	Add £192.90 and £2.58	8.65	[redacted]	[redacted]	7.29	[redacted]	[redacted]	[redacted]	[redacted]
Including AE costs for DFS state	IMpower150	8.65	[redacted]	[redacted]	7.29	[redacted]	[redacted]	[redacted]	[redacted]
Including disutility from AEs	PACIFIC (TA578, pg 334 of committee papers)	8.65	[redacted]	[redacted]	7.29	[redacted]	[redacted]	[redacted]	[redacted]

Table 27: Results from scenario analyses – Stage II–IIIA NSCLC population (list price for atezolizumab)

Parameter	Value	Atezolizumab			Best Supportive Care			ATZ vs. BSC	
		Life Years	QALYS	Costs	Life Years	QALYS	Costs	Inc. costs per LY gained	Inc. costs per QALY gained
Base case		8.65	[redacted]	[redacted]	7.29	[redacted]	[redacted]	£26,579	£35,250
DFS distributions	Exponential	8.33	[redacted]	[redacted]	6.78	[redacted]	[redacted]	£21,907	£29,122
	Weibull	8.06	[redacted]	[redacted]	6.84	[redacted]	[redacted]	£30,664	£40,553
	Log-normal	8.88	[redacted]	[redacted]	7.38	[redacted]	[redacted]	£23,137	£30,750
	Generalized Gamma	8.63	[redacted]	[redacted]	7.87	[redacted]	[redacted]	£53,532	£69,891
	Gompertz	8.30	[redacted]	[redacted]	7.55	[redacted]	[redacted]	£54,017	£70,545

	Gamma	8.07	[redacted]	[redacted]	6.76	[redacted]	[redacted]	£28,079	£37,186
Trial data used to inform recurrence type split	Pool across Arms	8.70	[redacted]	[redacted]	7.41	[redacted]	[redacted]	£30,722	£40,818
Treatment effect	Maintained over Time	8.63	[redacted]	[redacted]	7.29	[redacted]	[redacted]	£27,299	£36,172
Standardised mortality rate	1.50	8.41	[redacted]	[redacted]	7.05	[redacted]	[redacted]	£26,853	£35,501
	2.00	8.00	[redacted]	[redacted]	6.65	[redacted]	[redacted]	£27,314	£35,938
Atezolizumab treatment schedule	1, 680mg/ every 4 weeks	8.65	[redacted]	[redacted]	7.29	[redacted]	[redacted]	£29,321	£38,885
LRR: Efficacy by treatment intent	Digitised Data	8.99	[redacted]	[redacted]	7.68	[redacted]	[redacted]	£27,739	£36,734
Metastatic recurrence 1L: Efficacy by treatment intent	Digitised Data	8.71	[redacted]	[redacted]	7.36	[redacted]	[redacted]	£26,893	£35,597
Metastatic recurrence 1L: allow metastatic recurrence 2L	No	8.98	[redacted]	[redacted]	7.73	[redacted]	[redacted]	£26,206	£34,510
Metastatic recurrence 1L - Efficacy source	IMpower110	8.63	[redacted]	[redacted]	7.26	[redacted]	[redacted]	£26,758	£35,502
Metastatic recurrence 2L - Efficacy by treatment intent	Digitised Data	8.70	[redacted]	[redacted]	7.35	[redacted]	[redacted]	£26,793	£35,473
DFS cost inputs: scanning schedule	36.00	8.65	[redacted]	[redacted]	7.29	[redacted]	[redacted]	£26,591	£35,265

Time-to-off treatment	Until Progression or Death	8.65	[redacted]	[redacted]	7.29	[redacted]	[redacted]	£33,455	£44,367
Utility method	Source utilities	8.65	[redacted]	[redacted]	7.29	[redacted]	[redacted]	£26,579	£35,627
DFS utility source input	Grutters et al. (2010)	8.65	[redacted]	[redacted]	7.29	[redacted]	[redacted]	£26,579	£53,549
	Manser et al. (2006)	8.65	[redacted]	[redacted]	7.29	[redacted]	[redacted]	£26,579	£37,134
	Black, Keeler and Soneji (2014)	8.65	[redacted]	[redacted]	7.29	[redacted]	[redacted]	£26,579	£41,604
	Yang et al. (2014)	8.65	[redacted]	[redacted]	7.29	[redacted]	[redacted]	£26,579	£32,666
Metastatic recurrence 1L utility source input	IMpower110	8.65	[redacted]	[redacted]	7.29	[redacted]	[redacted]	£26,579	£35,504
	Chouaid et al. (2013)	8.65	[redacted]	[redacted]	7.29	[redacted]	[redacted]	£26,579	£35,252
Metastatic recurrence 2L utility source input	IMpower110	8.65	[redacted]	[redacted]	7.29	[redacted]	[redacted]	£26,579	£35,272
	Chouaid et al. (2013)	8.65	[redacted]	[redacted]	7.29	[redacted]	[redacted]	£26,579	£35,107
	Nafees et al. (2008)	8.65	[redacted]	[redacted]	7.29	[redacted]	[redacted]	£26,579	£35,087
Allow vial sharing	No	8.65	[redacted]	[redacted]	7.29	[redacted]	[redacted]	£26,532	£35,187
End of Life costs	Exclude	8.65	[redacted]	[redacted]	7.29	[redacted]	[redacted]	£27,905	£37,008
Time horizon	10.00	5.83	[redacted]	[redacted]	5.15	[redacted]	[redacted]	£52,596	£65,820
	20.00	7.92	[redacted]	[redacted]	6.74	[redacted]	[redacted]	£30,523	£39,794
	30.00	8.59	[redacted]	[redacted]	7.25	[redacted]	[redacted]	£26,863	£35,557

"Cure" proportion implementation	5 years	8.42	[redacted]	[redacted]	7.07	[redacted]	[redacted]	£26,811	£35,546
	6 years	8.04	[redacted]	[redacted]	6.76	[redacted]	[redacted]	£28,539	£37,775
	Ramp up 2–8 years	8.49	[redacted]	[redacted]	7.18	[redacted]	[redacted]	£28,014	£37,104
	Ramp up 3–8 years	8.24	[redacted]	[redacted]	6.96	[redacted]	[redacted]	£28,497	£37,722
Maximum "cure" proportion	20%	7.25	[redacted]	[redacted]	6.10	[redacted]	[redacted]	£32,265	£42,517
	40%	7.53	[redacted]	[redacted]	6.35	[redacted]	[redacted]	£31,629	£41,709
	60%	7.88	[redacted]	[redacted]	6.66	[redacted]	[redacted]	£30,366	£40,099
	80%	8.33	[redacted]	[redacted]	7.03	[redacted]	[redacted]	£28,261	£37,407
Additional results									
OS survival analysis	Use DFS and OS KM data	8.73	[redacted]	[redacted]	7.46	[redacted]	[redacted]	£34,870	£47,165
Additional admin costs	Add £192.90 and £2.58	8.65	[redacted]	[redacted]	7.29	[redacted]	[redacted]	£28,383	£37,642
Including AE costs for DFS state	IMpower150	8.65	[redacted]	[redacted]	7.29	[redacted]	[redacted]	£29,161	£38,571
Including disutility from AEs	PACIFIC (TA578, pg 334 of committee papers)	8.65	[redacted]	[redacted]	7.29	[redacted]	[redacted]	£26,649	£37,053

Appendix B – Subgroup analysis results

Summary of base-case cost effectiveness results

- **Cost effectiveness results are presented with and without confidential PAS for atezolizumab (list price for all other drugs) for the following population:**
  - **PD-L1 ≥ 1% Stage II–IIIA NSCLC population, <u>excluding EGFR mutant or ALK-positive</u>**
- **In this population, the resulting incremental cost effectiveness ratio (ICER) when comparing atezolizumab to BSC was:**
  - **[redacted] per QALY gained at PAS price**
  - **£29,353 per QALY gained at list price**
- **A limitation of the with-PAS analysis is that confidential discounts are in place for other therapies in the pathway which Roche are unable to account for. This analysis is also limited by the availability of relevant data which introduces a degree of uncertainty into the analysis**

B.1 Subgroup incremental cost effectiveness analysis results

Subgroup results of the economic model are presented in Table 21 (list price) and Table 22 (PAS price; [redacted] discount) for the Stage II–IIIA patients following resection and platinum-based chemotherapy with NSCLC whose tumours have PD-L1 expression on ≥ 1% TC, <u>excluding EGFR mutant or ALK-positive</u>. In these comparisons, all comparators (and therapies included in the treatment pathway) are at list price.

Table 28: Subgroup cost effectiveness results – PD-L1 ≥ 1% Stage I – IIIA NSCLC, excluding EGFR mutant or ALK-positive - list price

Technologies	Total costs	Total LYG	Total QALYs	Incremental costs	Incremental LYG	Incremental QALYs	ICER incremental (£/QALY)
Atezolizumab	[redacted]	9.16	[redacted]	[redacted]	1.62	[redacted]	£29,353
BSC	[redacted]	7.54	[redacted]				

Table 29: Subgroup cost effectiveness results – PD-L1 ≥ 1% Stage II – IIIA NSCLC, excluding EGFR mutant or ALK-positive – PAS price

Technologies	Total costs	Total LYG	Total QALYs	Incremental costs	Incremental LYG	Incremental QALYs	ICER incremental (£/QALY)
Atezolizumab	[redacted]	9.16	[redacted]	[redacted]	1.62	[redacted]	[redacted]
BSC	[redacted]	7.54	[redacted]				

In the Stage II–IIIA population, excluding EGFR mutant or ALK-positive at list price, atezolizumab provided [redacted] QALYs and 9.16 life years at a total overall cost of [redacted]. In contrast, BSC provided [redacted] QALYs and 7.54 life years, at a total cost of [redacted]. The resulting base ICER when comparing atezolizumab to BSC was £29,353 per QALY gained.

Results of the with-PAS analysis showed that adjuvant atezolizumab treatment resulted in reduced total costs in the atezolizumab arm of [redacted] and reduced total costs in the BSC arm, due to atezolizumab being used in metastatic states, of [redacted]. This resulted in an ICER of [redacted], significantly below the cost effectiveness threshold, for the Stage II-IIIA population, excluding EGFR mutant or ALK-positive.

However, it should be noted that the with-PAS analysis does not account for confidential discounts of therapies used in the treatment pathway, pembrolizumab for first-line metastatic NSCLC and nintedanib for second-line metastatic NSCLC.

B.2 Subgroup sensitivity analyses

Summary of sensitivity analyses results

- **The PSA ICER results when comparing atezolizumab with PAS to BSC was [redacted] per QALY gained, consistent with the deterministic base case**
- **The one-way sensitivity analyses showed that proportion of patients on 1L metastatic treatment, market share of patients in the BSC arm that receive pemetrexed and cisplatin in the 1L metastatic state, and proportion of patients who have metastatic recurrence as a first event recurrence in the BSC arm, are the most influential parameters on the ICER**

B.2.1 Subgroup probabilistic sensitivity analysis

To assess the uncertainty surrounding the variables included in the cost effectiveness model, a PSA was undertaken using 5,000 iterations to ensure results had converged. Results of the PSA compared to deterministic results at list price are presented in Table 23. The with-PAS equivalent comparison is presented in Table 24. Deterministic and probabilistic results are similar, therefore not indicating any signs of non-linearity in the model.

Table 30: Subgroup PSA results compared to DSA, PD-L1 ≥ 1% Stage II – IIIA NSCLC, excluding EGFR mutant or ALK-positive (list price)

	Costs		QALYs		ICERs	
	Deterministic	PSA	Deterministic base case	PSA	Deterministic	PSA
PD-L1 ≥ 1% Stage II-IIIA NSCLC, excluding EGFR mutant or ALK-positive						
Atezolizumab	[redacted]	[redacted]	[redacted]	[redacted]	£29,353	£30,218
BSC	[redacted]	[redacted]	[redacted]	[redacted]	-	-

Table 31: Subgroup PSA results compared to DSA, PD-L1 ≥ 1% Stage II – IIIA NSCLC, excluding EGFR mutant or ALK-positive (with PAS)

	Costs		QALYs		ICERs	
	Deterministic	PSA	Deterministic	PSA	Deterministic	PSA
PD-L1 ≥ 1% Stage II-IIIA NSCLC, excluding EGFR mutant or ALK-positive						
Atezolizumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
BSC	[redacted]	[redacted]	[redacted]	[redacted]	-	-

The incremental cost effectiveness planes in Figure 39 and Figure 40 show the individual PSA iterations for the comparisons of atezolizumab to BSC in the PD-L1 ≥ 1% Stage II – IIIA NSCLC, excluding EGFR mutant or ALK-positive populations at list and PAS price, respectively. At PAS price, atezolizumab was dominant in 41% of the simulations; supporting the view that atezolizumab is a cost-effective option for the NHS in patients with PD-L1 ≥ 1% Stage II – IIIA NSCLC, excluding EGFR mutant or ALK-positive. Cost effectiveness acceptability curves for the comparisons of atezolizumab to BSC in the Stage II–IIIA populations at list and PAS price are presented in Figure 41 and Figure 42. At PAS price, atezolizumab is deemed the most likely cost-effective treatment option beyond a willingness-to-pay (WTP) of approximately £2,500 per QALY. At a £20,000 and £30,000 WTP, the likelihood of atezolizumab being the most cost-effective treatment option rises to 97% and 98%, respectively.

Figure 45: Incremental cost effectiveness plane – atezolizumab vs BSC in PD-L1 ≥ 1% Stage II – IIIA NSCLC, excluding EGFR mutant or ALK-positive, list price

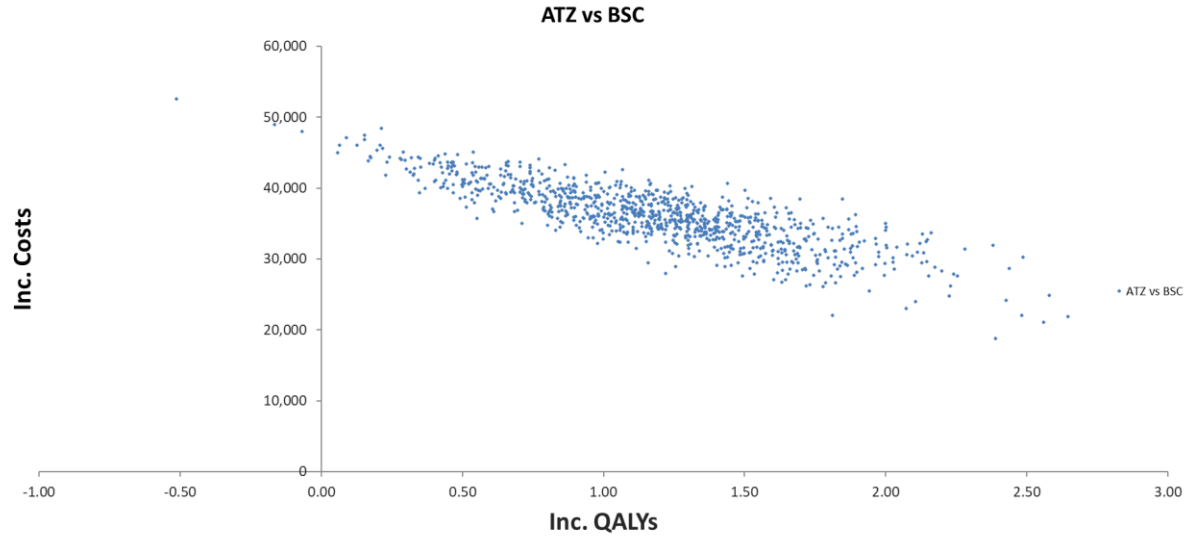


Figure 46: Incremental cost effectiveness plane – atezolizumab vs BSC in PD-L1 ≥ 1% Stage II – IIIA NSCLC, excluding EGFR mutant or ALK-positive, PAS price

[redacted]

Figure 47: Cost effectiveness acceptability curve – atezolizumab vs BSC in PD-L1 ≥ 1% Stage II – IIIA NSCLC, excluding EGFR mutant or ALK-positive, list price

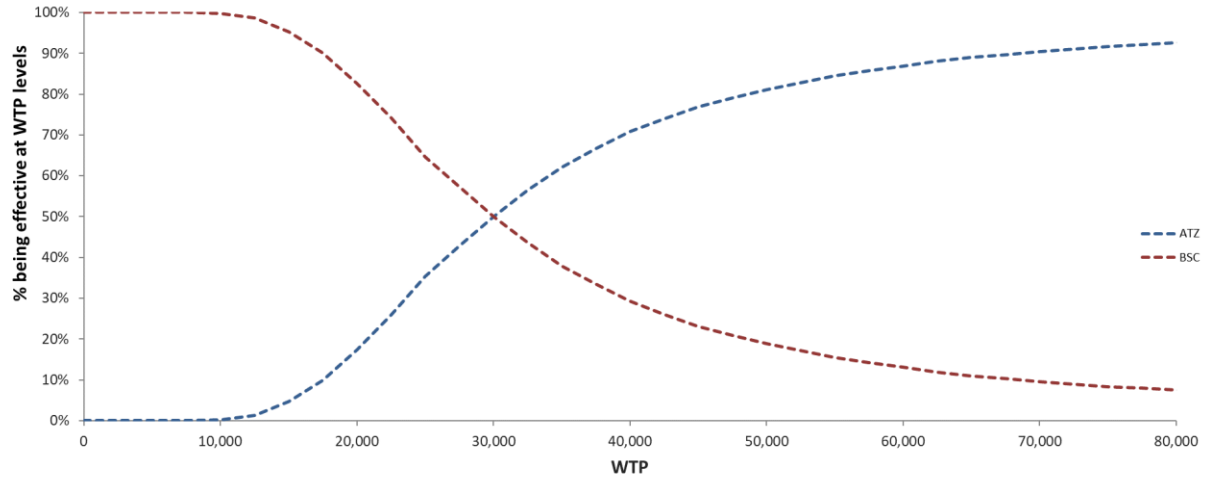


Figure 48: Cost effectiveness acceptability curve – atezolizumab vs BSC in PD-L1 ≥ 1% Stage II – IIIA NSCLC, excluding EGFR mutant or ALK-positive, PAS price

[redacted]

B.2.2 Subgroup deterministic sensitivity analysis

The parameters to include in the deterministic sensitivity analysis (DSA) were taken from Table 14 (with additional parameters compared to the company submission). The parameter values used are presented in Table 32 below. The base case values of most parameters were varied using upper and lower limits of the 95% confidence intervals for the variables (from the PSA output), with the exception of discount rates, which were varied from 1.5% to 5.0%. Key remaining model parameters were tested in scenario analyses (see Section B.2.3).

Table 32: Parameter values for univariate sensitivity analysis, in patients with PD-L1 ≥ 1% Stage II – IIIA NSCLC, excluding EGFR mutant or ALK-positive

Parameter	Base case value	PAS price		List price	
		Lower value	Higher value	Lower value	Higher value
Proportion of patients who have metastatic recurrence as recurrence - ATZ Arm	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Proportion of patients who have metastatic recurrence as recurrence - BSC Arm	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Proportion of patients with Locoregional Recurrence - ATZ arm	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Proportion of patients with Locoregional Recurrence - BSC arm	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Transition probability to death from DFS health state - ATZ Arm	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Transition probability to death from DFS health state - BSC Arm	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
% on Curative Treatment - Locoregional Recurrence	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
% on Palliative Treatment - Locoregional Recurrence	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Transition probability (PFS - LR CT)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
% have Progression as first Event - Locoregional Recurrence	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Transition probability (OS - LR PT)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
% on 1L metastatic Treatment - 1L Metastatic	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Treatment Option 1 - Market Share - 1L Metastatic Treatment - BSC Arm	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Treatment Option 2 - Market Share - 1L Metastatic Treatment - BSC Arm	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Treatment Option 3 - Market Share - 1L Metastatic Treatment - BSC Arm	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
% have Progression as first Event - 1L Metastatic Recurrence	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Transition probability (1LMNTx)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
% on 2L metastatic Treatment - 2L Metastatic	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Treatment Option 1 - Market Share - 2L Metastatic Treatment - Atezolizumab Arm	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Treatment Option 2 - Market Share - 2L Metastatic Treatment - Atezolizumab Arm	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Treatment Option 1 - Market Share - 2L Metastatic Treatment - BSC Arm	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Treatment Option 2 - Market Share - 2L Metastatic Treatment - BSC Arm	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Treatment Option 3 - Market Share - 2L Metastatic Treatment - BSC Arm	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Transition probability (2LMNTx)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Discount costs	0.04	0.02	0.05	0.02	0.05
Discount effects	0.04	0.02	0.05	0.02	0.05
Administration cost	299.61	249.58	350.53	250.99	350.78
Other healthcare resource use (DFS)	53.19	48.77	57.78	48.72	57.75
Total AE management cost - LRR	14.05	11.83	16.40	11.81	16.36
Other healthcare resource use (LR - CT)	161.57	146.08	178.74	145.77	177.91
Other healthcare resource use (LR - PT)	161.57	146.34	177.86	146.27	177.03
Total AE management cost - 1L Met Atezo	87.07	73.66	101.35	73.77	101.71
Total AE management cost - 1L Met BSC	93.45	85.35	101.96	85.41	101.84
Other healthcare resource use (1LM - Tx)	352.11	322.50	382.91	321.88	383.28
Other healthcare resource use (1LM - NTx)	352.11	321.26	382.86	322.68	382.73
Total AE management cost - 2L Met Atezo	308.41	273.31	345.82	272.91	345.95
Total AE management cost - 2L Met BSC	216.58	187.99	248.30	186.18	248.62
Other healthcare resource use (2LM - Tx)	608.34	562.64	657.37	561.07	656.50
Other healthcare resource use (2LM - NTx)	608.34	561.00	654.72	561.40	656.24
End of life cost - disease death	4598.01	3849.71	5376.64	3882.03	5398.89
Utility treatment (DFS)	0.03	-0.03	0.11	-0.03	0.11
Utility no treatment (DFS)	0.03	-0.03	0.11	-0.03	0.11

Utility treatment (LR - CT)	0.08	0.01	0.16	0.01	0.16
Utility treatment (LR - PT)	0.17	0.13	0.22	0.13	0.22
Utility treatment (1LM)	0.11	0.10	0.12	0.10	0.12
Utility no treatment (1LM)	0.17	0.12	0.22	0.13	0.22
Utility treatment (2LM)	0.13	0.10	0.15	0.10	0.15
Utility no treatment (2LM)	0.17	0.13	0.22	0.12	0.22

Deterministic sensitivity analyses with-PAS results for the PD-L1 ≥ 1% Stage II – IIIA NSCLC, excluding EGFR mutant or ALK-positive population are presented in Figure 49 (see Figure 50 for list price results).

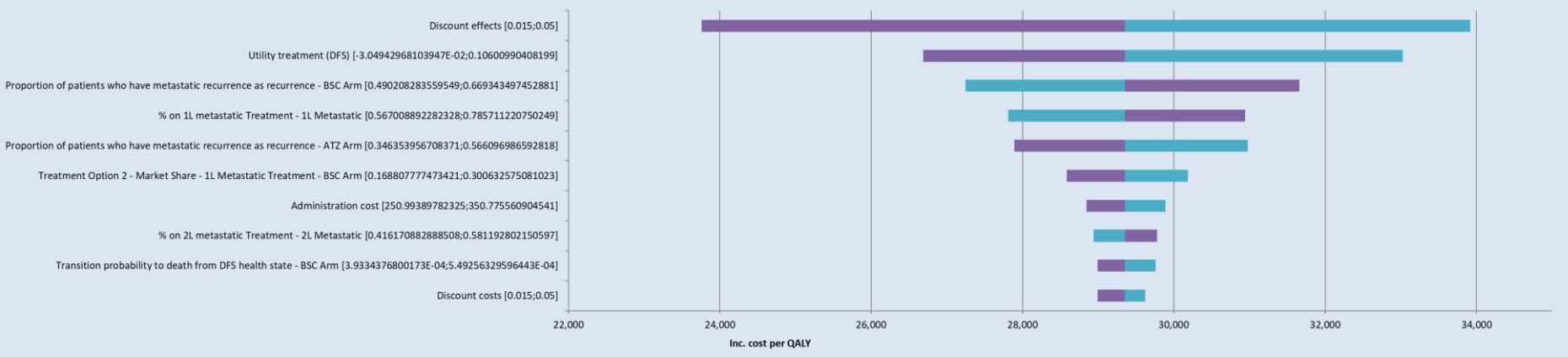
Based on the deterministic sensitivity analyses at PAS price, the most influential parameters appear to be the proportion of patients on 1L metastatic treatment, market share of patients in the BSC arm that receive pemetrexed and cisplatin in the 1L metastatic state, and proportion of patients who have metastatic recurrence as a first event recurrence in the BSC arm. All results remained significantly below the cost effectiveness 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.

Figure 49: Tornado diagram – in patients with PD-L1 ≥ 1% Stage II – IIIA NSCLC, excluding EGFR mutant or ALK-positive, PAS price

[redacted]

Based on the deterministic sensitivity analyses at list price, the most influential parameters appear to be the discount effects, disutility source for DFS, and proportion of patients who have metastatic recurrence as a first event recurrence in the BSC arm. All results remained significantly below the cost effectiveness 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. This is further evidenced by discount rates being included in the top 10 most sensitive inputs, as discount rates impact results more broadly throughout the model than any other input

Figure 50: Tornado diagram – in patients with PD-L1 ≥ 1% Stage II – IIIA NSCLC, excluding EGFR mutant or ALK-positive, list price



B.2.3 Subgroup scenario analysis

Scenario analyses were conducted to assess uncertainty around remaining parameter inputs and structural assumptions in the model.

Results of the scenario analyses are presented in Table 33 for the PD-L1 ≥ 1% Stage II – IIIA NSCLC, excluding EGFR mutant or ALK-positive at PAS price for atezolizumab (results at list price are presented in Table 34).

All scenario results remain cost-effective and [redacted], with the most sensitive scenarios based on the DFS distribution selection. Sensitivity to these scenarios are expected as they determine early movements from the DFS health state, impacting downstream costs and outcomes in progressive states.

Table 33: Subgroup results from scenario analyses – PD-L1 ≥ 1% Stage II – IIIA NSCLC, excluding EGFR mutant or ALK-positive population (PAS price for atezolizumab)

Parameter	Value	Atezolizumab			Best Supportive Care			ATZ vs. BSC	
		Life Years	QALYS	Costs	Life Years	QALYS	Costs	Inc. costs per LY gained	Inc. costs per QALY gained
Base case		9.16	[redacted]	[redacted]	7.54	[redacted]	[redacted]	[redacted]	[redacted]
DFS distributions	Exponential	8.76	[redacted]	[redacted]	7.00	[redacted]	[redacted]	[redacted]	[redacted]
	Weibull	8.65	[redacted]	[redacted]	7.16	[redacted]	[redacted]	[redacted]	[redacted]
	Log-normal	9.38	[redacted]	[redacted]	7.64	[redacted]	[redacted]	[redacted]	[redacted]
	Generalized Gamma	9.22	[redacted]	[redacted]	8.16	[redacted]	[redacted]	[redacted]	[redacted]
	Gompertz	9.00	[redacted]	[redacted]	7.97	[redacted]	[redacted]	[redacted]	[redacted]

	Gamma	8.62	[redacted]	[redacted]	7.07	[redacted]	[redacted]	[redacted]	[redacted]
Trial data used to inform recurrence type split	Pool across Arms	9.17	[redacted]	[redacted]	7.68	[redacted]	[redacted]	[redacted]	[redacted]
Treatment effect	Maintained over Time	9.16	[redacted]	[redacted]	7.54	[redacted]	[redacted]	[redacted]	[redacted]
Standardised mortality rate	1.50	8.88	[redacted]	[redacted]	7.28	[redacted]	[redacted]	[redacted]	[redacted]
	2.00	8.42	[redacted]	[redacted]	6.86	[redacted]	[redacted]	[redacted]	[redacted]
Atezolizumab treatment schedule	1, 680mg/ every 4 weeks	9.16	[redacted]	[redacted]	7.54	[redacted]	[redacted]	[redacted]	[redacted]
LRR: Efficacy by treatment intent	Digitised Data	9.50	[redacted]	[redacted]	7.91	[redacted]	[redacted]	[redacted]	[redacted]
Metastatic recurrence 1L: Efficacy by treatment intent	Digitised Data	9.20	[redacted]	[redacted]	7.61	[redacted]	[redacted]	[redacted]	[redacted]
Metastatic recurrence 1L: allow metastatic recurrence 2L	No	9.45	[redacted]	[redacted]	7.96	[redacted]	[redacted]	[redacted]	[redacted]
Metastatic recurrence 1L - Efficacy source	IMpower110	9.14	[redacted]	[redacted]	7.51	[redacted]	[redacted]	[redacted]	[redacted]
Metastatic recurrence 2L - Efficacy by treatment intent	Digitised Data	9.20	[redacted]	[redacted]	7.60	[redacted]	[redacted]	[redacted]	[redacted]

DFS cost inputs: scanning schedule	36.00	9.16	[redacted]	[redacted]	7.54	[redacted]	[redacted]	[redacted]	[redacted]
Time-to-off treatment	Until Progression or Death	9.16	[redacted]	[redacted]	7.54	[redacted]	[redacted]	[redacted]	[redacted]
Utility method	Source utilities	9.16	[redacted]	[redacted]	7.54	[redacted]	[redacted]	[redacted]	[redacted]
DFS utility source input	Grutters et al. (2010)	9.16	[redacted]	[redacted]	7.54	[redacted]	[redacted]	[redacted]	[redacted]
	Manser et al. (2006)	9.16	[redacted]	[redacted]	7.54	[redacted]	[redacted]	[redacted]	[redacted]
	Black, Keeler and Soneji (2014)	9.16	[redacted]	[redacted]	7.54	[redacted]	[redacted]	[redacted]	[redacted]
	Yang et al. (2014)	9.16	[redacted]	[redacted]	7.54	[redacted]	[redacted]	[redacted]	[redacted]
Metastatic recurrence 1L utility source input	IMpower110	9.16	[redacted]	[redacted]	7.54	[redacted]	[redacted]	[redacted]	[redacted]
	Chouaid et al. (2013)	9.16	[redacted]	[redacted]	7.54	[redacted]	[redacted]	[redacted]	[redacted]
Metastatic recurrence 2L utility source input	IMpower110	9.16	[redacted]	[redacted]	7.54	[redacted]	[redacted]	[redacted]	[redacted]
	Chouaid et al. (2013)	9.16	[redacted]	[redacted]	7.54	[redacted]	[redacted]	[redacted]	[redacted]
	Nafees et al. (2008)	9.16	[redacted]	[redacted]	7.54	[redacted]	[redacted]	[redacted]	[redacted]
Allow vial sharing	No	9.16	[redacted]	[redacted]	7.54	[redacted]	[redacted]	[redacted]	[redacted]
End of Life costs	Exclude	9.16	[redacted]	[redacted]	7.54	[redacted]	[redacted]	[redacted]	[redacted]
Time horizon	10.00	6.07	[redacted]	[redacted]	5.26	[redacted]	[redacted]	[redacted]	[redacted]
	20.00	8.37	[redacted]	[redacted]	6.96	[redacted]	[redacted]	[redacted]	[redacted]

	30.00	9.10	[redacted]	[redacted]	7.50	[redacted]	[redacted]	[redacted]	[redacted]
“Cure” proportion implementation	5 years	8.96	[redacted]	[redacted]	7.332296778	[redacted]	[redacted]	[redacted]	[redacted]
	6 years	8.58	[redacted]	[redacted]	7.027284005	[redacted]	[redacted]	[redacted]	[redacted]
	Ramp up 2–8 years	8.99	[redacted]	[redacted]	7.435424834	[redacted]	[redacted]	[redacted]	[redacted]
	Ramp up 3–8 years	8.76	[redacted]	[redacted]	7.217861659	[redacted]	[redacted]	[redacted]	[redacted]
Maximum “cure” proportion	20%	7.76	[redacted]	[redacted]	6.353454739	[redacted]	[redacted]	[redacted]	[redacted]
	40%	8.04	[redacted]	[redacted]	6.60764444	[redacted]	[redacted]	[redacted]	[redacted]
	60%	8.39	[redacted]	[redacted]	6.914639301	[redacted]	[redacted]	[redacted]	[redacted]
	80%	8.84	[redacted]	[redacted]	7.288979274	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]									
OS survival analysis	Use DFS and OS KM data	8.72	[redacted]	[redacted]	7.45	[redacted]	[redacted]	[redacted]	[redacted]
Additional admin costs	Add £192.90 and £2.58	9.16	[redacted]	[redacted]	7.54	[redacted]	[redacted]	[redacted]	[redacted]
Including AE costs for DFS state	IMpower150	9.13	[redacted]	[redacted]	7.53	[redacted]	[redacted]	[redacted]	[redacted]
Including disutility from AEs	PACIFIC (TA578, pg 334	9.13	[redacted]	[redacted]	7.53	[redacted]	[redacted]	[redacted]	[redacted]

	of committee papers)								

Table 34: Subgroup results from scenario analyses – PD-L1 ≥ 1% Stage II – IIIA NSCLC, excluding EGFR mutant or ALK-positive population (list price for atezolizumab)

Parameter	Value	Atezolizumab			Best Supportive Care			ATZ vs. BSC	
		Life Years	QALYS	Costs	Life Years	QALYS	Costs	Inc. costs per LY gained	Inc. costs per QALY gained
Base case		9.16	[redacted]	[redacted]	7.54	[redacted]	[redacted]	£22,088	£29,353
DFS distributions	Exponential	8.76	[redacted]	[redacted]	7.00	[redacted]	[redacted]	£19,453	£25,886
	Weibull	8.65	[redacted]	[redacted]	7.16	[redacted]	[redacted]	£24,719	£32,796
	Log-normal	9.38	[redacted]	[redacted]	7.64	[redacted]	[redacted]	£19,852	£26,420
	Generalized Gamma	9.22	[redacted]	[redacted]	8.16	[redacted]	[redacted]	£37,647	£49,592
	Gompertz	9.00	[redacted]	[redacted]	7.97	[redacted]	[redacted]	£38,582	£50,821
	Gamma	8.62	[redacted]	[redacted]	7.07	[redacted]	[redacted]	£23,310	£30,949
Trial data used to inform recurrence type split	Pool across Arms	9.17	[redacted]	[redacted]	7.68	[redacted]	[redacted]	£26,300	£34,970
Treatment effect	Maintained over Time	9.16	[redacted]	[redacted]	7.54	[redacted]	[redacted]	£22,111	£29,379
Standardised mortality rate	1.50	8.88	[redacted]	[redacted]	7.28	[redacted]	[redacted]	£22,431	£29,711
	2.00	8.42	[redacted]	[redacted]	6.86	[redacted]	[redacted]	£23,134	£30,483
Atezolizumab treatment schedule	1, 680mg/ every 4 weeks	9.16	[redacted]	[redacted]	7.54	[redacted]	[redacted]	£24,376	£32,394
LRR: Efficacy by treatment intent	Digitised Data	9.50	[redacted]	[redacted]	7.91	[redacted]	[redacted]	£22,510	£29,916

Metastatic recurrence 1L: Efficacy by treatment intent	Digitised Data	9.20	[redacted]	[redacted]	7.61	[redacted]	[redacted]	£22,333	£29,623
Metastatic recurrence 1L: allow metastatic recurrence 2L	No	9.45	[redacted]	[redacted]	7.96	[redacted]	[redacted]	£21,309	£28,129
Metastatic recurrence 1L - Efficacy source	IMpower110	9.14	[redacted]	[redacted]	7.51	[redacted]	[redacted]	£22,281	£29,622
Metastatic recurrence 2L - Efficacy by treatment intent	Digitised Data	9.20	[redacted]	[redacted]	7.60	[redacted]	[redacted]	£22,248	£29,517
DFS cost inputs: scanning schedule	36.00	9.16	[redacted]	[redacted]	7.54	[redacted]	[redacted]	£22,099	£29,367
Time-to-off treatment	Until Progression or Death	9.16	[redacted]	[redacted]	7.54	[redacted]	[redacted]	£27,445	£36,472
Utility method	Source utilities	9.16	[redacted]	[redacted]	7.54	[redacted]	[redacted]	£22,088	£29,655
DFS utility source input	Grutters et al. (2010)	9.16	[redacted]	[redacted]	7.54	[redacted]	[redacted]	£22,088	£43,965
	Manser et al. (2006)	9.16	[redacted]	[redacted]	7.54	[redacted]	[redacted]	£22,088	£30,877
	Black, Keeler and Soneji (2014)	9.16	[redacted]	[redacted]	7.54	[redacted]	[redacted]	£22,088	£34,473
	Yang et al. (2014)	9.16	[redacted]	[redacted]	7.54	[redacted]	[redacted]	£22,088	£27,256
Metastatic recurrence 1L utility source input	IMpower110	9.16	[redacted]	[redacted]	7.54	[redacted]	[redacted]	£22,088	£29,554
	Chouaid et al. (2013)	9.16	[redacted]	[redacted]	7.54	[redacted]	[redacted]	£22,088	£29,355
Metastatic recurrence 2L utility source input	IMpower110	9.16	[redacted]	[redacted]	7.54	[redacted]	[redacted]	£22,088	£29,371
	Chouaid et al. (2013)	9.16	[redacted]	[redacted]	7.54	[redacted]	[redacted]	£22,088	£29,236
	Nafees et al. (2008)	9.16	[redacted]	[redacted]	7.54	[redacted]	[redacted]	£22,088	£29,220

Allow vial sharing	No	9.16	[redacted]	[redacted]	7.54	[redacted]	[redacted]	£22,047	£29,298
End of Life costs	Exclude	9.16	[redacted]	[redacted]	7.54	[redacted]	[redacted]	£23,196	£30,826
Time horizon	10.00	6.07	[redacted]	[redacted]	5.26	[redacted]	[redacted]	£43,819	£55,066
	20.00	8.37	[redacted]	[redacted]	6.96	[redacted]	[redacted]	£25,326	£33,104
	30.00	9.10	[redacted]	[redacted]	7.50	[redacted]	[redacted]	£22,315	£29,600
"Cure" proportion implementation	5 years	8.96	[redacted]	[redacted]	7.33	[redacted]	[redacted]	£21,753	£28,911
	6 years	8.58	[redacted]	[redacted]	7.03	[redacted]	[redacted]	£23,056	£30,604
	Ramp up 2–8 years	8.99	[redacted]	[redacted]	7.44	[redacted]	[redacted]	£23,238	£30,853
	Ramp up 3–8 years	8.76	[redacted]	[redacted]	7.22	[redacted]	[redacted]	£23,286	£30,907
Maximum "cure" proportion	20%	7.76	[redacted]	[redacted]	6.35	[redacted]	[redacted]	£26,119	£34,549
	40%	8.04	[redacted]	[redacted]	6.61	[redacted]	[redacted]	£25,683	£33,989
	60%	8.39	[redacted]	[redacted]	6.91	[redacted]	[redacted]	£24,789	£32,838
	80%	8.84	[redacted]	[redacted]	7.29	[redacted]	[redacted]	£23,289	£30,905
Additional results									
OS survival analysis	Use DFS and OS KM data	8.72	[redacted]	[redacted]	7.45	[redacted]	[redacted]	£32,527	£43,231
Additional admin costs	Add £192.90 and £2.58	9.16	[redacted]	[redacted]	7.54	[redacted]	[redacted]	£23,628	£31,399
Including AE costs for DFS state	IMpower150	9.12	[redacted]	[redacted]	7.54	[redacted]	[redacted]	£24,689	£32,160
Including disutility from AEs	PACIFIC (TA578, pg 334 of committee papers)	9.12	[redacted]	[redacted]	7.54	[redacted]	[redacted]	£22,534	£30,612

NICE National Institute for Health and Care Excellence

Professional organisation submission

Atezolizumab for adjuvant treatment of resected non-small-cell lung cancer [ID3852]

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.

About you	
1. Your name	[redacted]
2. Name of organisation	**British Thoracic Oncology Group (BTOG)**

3. Job title or position	[redacted]
4. Are you (please tick all that apply):	x☐ an employee or representative of a healthcare professional organisation that represents clinicians? x☐ a specialist in the treatment of people with this condition? x☐ a specialist in the clinical evidence base for this condition or technology? ☐ other (please specify):
5a. Brief description of the organisation (including who funds it).	**BTOG is a registered charity funded by registrations for our annual conference and pharmaceutical**
4b. 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.]	**No**

If so, please state the name of manufacturer, amount, and purpose of funding.	
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.)	To increase the chance of cure
7. What do you consider a clinically significant treatment response? (For example, a reduction in tumour size by	An increase in DFS or OS of 3 months compared with SOC

x cm, or a reduction in disease activity by a certain amount.)	
8. In your view, is there an unmet need for patients and healthcare professionals in this condition?	Yes – outcomes post surgical resection remain poor. There is a high unmet need for better adjuvant treatments
What is the expected place of the technology in current practice?	
9. How is the condition currently treated in the NHS?	Adjuvant chemotherapy – 4 cycles of platinum based treatment post surgery
• Are any clinical guidelines used in the treatment of the condition, and if so, which?	NICE, ESMO
• Is the pathway of care well defined? Does it vary or are there differences of opinion between professionals across the NHS? (Please	Well defined

state if your experience is from outside England.)	
• What impact would the technology have on the current pathway of care?	Would require longer systemic adjuvant treatment
10. Will the technology be used (or is it already used) in the same way as current care in NHS clinical practice?	Will be used as an adjunct to the current adjuvant chemotherapy practice
• How does healthcare resource use differ between the technology and current care?	Current adjuvant treatment is for 4 cycles of chemotherapy. The technology would add another 16 cycles of treatment (with Atezolizumab)
• In what clinical setting should the technology be used? (For example, primary or secondary care, specialist clinics.)	Secondary care (cancer units that are delivering SACT)
• What investment is needed to introduce the technology? (For example, for facilities, equipment, or training.)	There will be increased chair / chemotherapy time as patients will be receiving SACT for another 16 cycles (3weekly) Also there will be increased Oncology clinic appointments for toxicity checks. Potentially patients will require further input either as outpatient or inpatient for toxicity management

11. Do you expect the technology to provide clinically meaningful benefits compared with current care?	yes
• Do you expect the technology to increase length of life more than current care?	yes
• Do you expect the technology to increase health-related quality of life more than current care?	yes
12. Are there any groups of people for whom the technology would be more or less effective (or appropriate) than the general population?	As per the appraisal – this will be focussed on PDL1 positive patients
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.)	There will be increased chair / chemotherapy time as patients will be receiving SACT for another 16 cycles (3weekly) Also there will be increased Oncology clinic appointments for toxicity checks. Potentially patients will require further input either as outpatient or inpatient for toxicity management Monitoring and imaging maybe more frequent for the period patients are on active treatment than would otherwise be performed Paradoxically if the technology is approved and implemented potentially less patients would recur with advanced metastatic disease. This would therefore reduce somewhat the resource burden in that setting.
14. Will any rules (informal or formal) be used to start or stop treatment with the technology? Do these include any additional testing?	Treatment would continue for the specified number of cycles, unless stopped prematurely for toxicities or disease recurrence
15. Do you consider that the use of the technology will result in any substantial health-	n/a

related benefits that are unlikely to be included in the quality-adjusted life year (QALY) calculation?	
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?	
• Is the technology a 'step-change' in the management of the condition?	Yes – adjuvant treatment to date has added very minimal benefit. This would be a significant improvement to current SOC
• Does the use of the technology address any particular unmet need of the patient population?	As above

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?	Toxicity frequency will be as recorded in the study. The management of IO related toxicities is well establised
Sources of evidence	
18. Do the clinical trials on the technology reflect current UK clinical practice?	Yes
• 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?	Disease Free Survival (DFS)
• If surrogate outcome measures were used, do they adequately predict long-term clinical outcomes?	As above – DFS as a surrogate for Overall Survival

• Are there any adverse effects that were not apparent in clinical trials but have come to light subsequently?	no
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?	The SOC arm is reflective of real world treatment
Equality	
21a. Are there any potential equality issues that should be taken into account when considering this treatment?	no

21b. Consider whether these issues are different from issues with current care and why.	no

Key messages

22. In up to 5 bullet points, please summarise the key messages of your submission.

- Current SOC adjuvant treatment for resected NSCLC provides very minimal gains in DFS / OS
- This trial and appraisal represents a huge step forward in terms of clinical outcomes for these patients
- Although upfront it will require more resources, the fact that less patients will recur will somewhat reduce the resource burden of managing patients with advanced disease
-
-

Thank you for your time.

Please log in to your NICE Docs account to upload your completed submission.

……

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Atezolizumab for adjuvant treatment of resected non-small-cell lung cancer [ID3852]:

A Single Technology Appraisal

Produced by

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University of Exeter Medical School
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Date completed

4 April 2022

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Justin Matthews	Critical appraisal of the company submission, writing and editorial input.
Charlotte Day	Contributed to the critical appraisal of the cost effectiveness evidence and writing of the economic sections of the report.
Sophie Robinson	Critical appraisal of the literature search strategies, review of draft report.
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Nicole Dorey	Clinical advice and review of draft report.
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Abbreviations

AE	adverse event
AFT	accelerated failure time
AJCC	American Joint Committee on Cancer
ALK	anaplastic lymphoma kinase
ALT	alanine aminotransferase
AST	aspartate aminotransferase
ATA	anti-therapeutic antibodies
ATZ/Atezo	Atezolizumab
BNF	British National Formulary
BSC	best supportive care
CADTH	Canadian Agency for Drugs and Technologies in Health
CAES	company additional evidence submission (addendum submitted January 2021)
CCOD	clinical data cut-off date
CDF	Cancer Drugs Fund
CI	confidence interval
CNS	clinical nurse specialist
COVID-19	coronavirus disease
CS	company submission
CSR	clinical study report
CT	computed tomography
NCI CTCAE	National Cancer Institute Common Terminology Criteria for Adverse Events
DFS	disease free survival
DSA	deterministic sensitivity analysis
DSU	Decision Support Unit
EA	exploratory analysis
ECOG	Eastern Cooperative Oncology Group performance status
EGFR	epidermal growth factor receptor
EMA	European Medicines Agency
eNSCLC	early stage non-small cell lung cancer
EQ-5D	European Quality of Life-5 Dimensions
ERG	Evidence Review Group
FDA	Food and Drug Administration
GP	general practitioner
HR	hazard ratio
HRQL	health-related quality of life
HTA	health technology assessment

IA	interim analysis
IC	immune cells
ICER(s)	incremental cost-effectiveness ratio(s)
IHC	Immunohistochemistry
ITC	indirect treatment comparison
ITT	intent-to-treat
IV	Intravenous
KM	Kaplan-Meier
LY	life year
MHRA	Medicines and Healthcare products Regulatory Agency
N/A	not applicable
NE	not evaluable
NHS	National Health Service
NICE	National Institute for Health and Care Excellence
NIHR	National Institute for Health Research
NMB	net monetary benefit
NSCLC	non-small cell lung cancer
ONS	Office for National Statistics
OS	Overall survival
PAS	Patient access scheme
PD-1	programmed cell death 1
PD-LC	programmed cell death-ligand 1
PFS	progression-free survival
PH	proportional hazards
PICOS	Population, intervention, comparator, outcome, study design
PK	Pharmacokinetics
PLD	patient level data
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
PSA	probabilistic sensitivity analysis
PSS	Personal Social Services
QA	quality assessment
QALY	Quality adjusted life year
RCT	randomised controlled trial
SCLC	small cell lung cancer
SE	standard error
SIGN	Scottish Intercollegiate Guidelines Network
SLR	systematic literature review
SMR	standardised mortality ratio
STA	single technology appraisal
TA	technology appraisal

TC	tumour cells
TKI	tyrosine kinase inhibitor
TSD	Technical Support Document
TTO	time trade off
UICC	Union for International Cancer Control
UK	United Kingdom
US	United States

1. EXECUTIVE SUMMARY

This summary provides a brief overview of the key issues identified by the evidence review group (ERG) as being potentially important for decision making. It also includes the ERG's preferred assumptions and the resulting incremental cost-effectiveness ratios (ICERs).

Section 1.1 provides an overview of the key issues. Section 1.2 provides an overview of key model outcomes and the modelling assumptions that have the greatest effect on the ICER. Sections 1.3 to 1.6 explain the key issues in more detail. Background information on the condition, technology and evidence and information on non-key issues are in the main ERG report.

All issues identified represent the ERG's view, not the opinion of NICE.

1.1. Overview of the ERG's key issues

A brief overview of the key issues identified by the ERG in their appraisal of the company submission (CS) is provided in Table 1, Sections 1.3, 1.4, and 1.5.

The key clinical issue is the immaturity of clinical effectiveness data. In terms of cost effectiveness issues, the ERG noted key issues with various aspects of the company's approach to modelling lifetime patient outcomes, and further key issues in the company's metastatic treatment pathway assumptions and various cost assumptions.

Table 1. Summary of key issues

ID	Summary of issues	Report sections
#1	Immaturity of IMpower010 clinical effectiveness data	3.2.3.2
#2	Approach to model DFS patient outcomes	4.2.6.2, 4.2.6.3, 4.2.7, 4.2.8.1 and 6.2
#3	Approach to model post-DFS patient outcomes	4.2.6.3, 4.2.6.4 and 6.2
#4	Approach to capture lifetime treatment pathway expectations	4.2.8.3 and 6.2
#5	Approach to capture incremental cost differences aside from NSCLC treatment acquisition costs	4.2.3, 4.2.8.1, 4.2.8.2, 4.2.8.3, 4.2.8.4 and 6.2

Abbreviations: DFS, disease free survival; NSCLC, non-small cell lung cancer

The key differences between the company's preferred assumptions and the ERG's preferred assumptions are outlined in Table 2.

Table 2: Key differences between the company's preferred assumptions and ERG's preferred assumptions

	Company's preferred assumption	ERG preferred assumption	Report Sections
DFS modelling	91.5% of patients predicted to remain disease-free at 5 years assumed to be no longer at risk of disease recurrence. Various favourable post-hoc adjustments and assumptions.	Stress uncertainty around parametric survival model choice and timing and impact of "cure" assumptions, with a delay to 8 years and different underlying parametric model deemed equally plausible given availability of evidence Removal of various post-hoc inflationary adjustments and assumptions.	1.5, 4.2.6.2, 4.2.6.3, 4.2.7, 4.2.8.1 and 6.2
Treatment pathway	Company expert-informed approach to metastatic treatment availability and uptake assumptions.	ERG expert and NHS algorithm-informed approach to metastatic treatment availability and uptake assumptions.	1.5, 4.2.6.3, 4.2.6.4 and 6.2
Costs	Various favourable assumptions, including no metastatic treatment discontinuation and fewer atezolizumab arm patients incurring a £4,598.01 terminal care cost.	Removal or adaptation of favourable assumptions, to best available assumptions.	1.5, 4.2.3, 4.2.8.1, 4.2.8.2, 4.2.8.3, 4.2.8.4 and 6.2

Abbreviations: DFS, disease free survival; ERG, Evidence Review Group; NHS, National Health Service

1.2. Overview of key model outcomes

NICE technology appraisals compare how much a new technology improves length (overall survival) and quality of life in a quality-adjusted life year (QALY). An ICER is the ratio of the extra cost for every QALY gained.

Overall, the technology is modelled to affect QALYs by extending lifetime disease-free survival, and in doing so:

- Increasing the proportion of patients predicted to be disease-free at 5 years, who are assumed to be no-longer at risk of disease recurrence

- Improving expected lifetime patient health-related quality of life
- Increasing overall survival, with the expected disease-free survival benefit translating to a slightly smaller overall survival benefit, owing to the assumed availability of PD-L1 / PD-1 targeting immunotherapeutic treatments for metastatic recurrence on the comparator arm only

Overall, the technology is modelled to affect costs by:

- Introducing the cost of adjuvant atezolizumab acquisition and administration to the adjuvant post-resection setting
- Reducing the treatment options available at 1st metastatic recurrence

The modelling assumptions that have the greatest effect on the ICER are:

- Extrapolation assumptions for observed disease-free survival Kaplan-Meier data
- Whether and when it is appropriate to assume disease-free patients are no longer at risk of disease recurrence
- Metastatic recurrence treatment options, uptake, duration and effectiveness

The ERG noted that the overall survival implications of adjuvant atezolizumab are highly uncertain and believe that the economic analysis does not adequately capture this uncertainty. A key limitation of the company's economic analysis is that overall survival projections derived from the modelling do not match observed overall survival Kaplan-Meier data from the key trial. It should be noted however, that due to limitations on the model flexibility, data and time constraints, the ERG-preferred approaches also suffer from this limitation.

1.3. The decision problem: summary of the ERG's key issues

No key issues with the company's approach to addressing the decision problem were identified.

1.4. The clinical effectiveness evidence: summary of the ERG's key issues

One key issue with the company's clinical effectiveness evidence is highlighted for the committee's attention.

Key Issue 1. Immaturity of IMpower010 clinical effectiveness data

Report sections	3.2.3.2
Description of issue and why the ERG has identified it as important	OS data were immature in the pivotal IMpower trial. Median OS could not be estimated in either arm. Although OS data were presented, OS was not formally tested, and DFS was instead used as a surrogate outcome for clinical effectiveness in the health economic model. OS is the gold standard outcome for oncology trials. Moreover, in the PD-L1 ≥ 50% TC Stage II–IIIA population, DFS was also immature, due to the smaller sample size available compared to the company's original PD-L1 ≥ 1% TC Stage II–IIIA population, as reflected in the very small number of patients [redacted] remaining in the tail of the KM distribution.
What alternative approach has the ERG suggested?	Data immaturity is an intrinsic issue in the available evidence, which has been exacerbated through the narrowing of the population due to regulatory reasons, and the consequent reduction in the sample size. The ERG does not consider this issue can be resolved with the available evidence, although future data cuts may help resolve the uncertainty.
What is the expected effect on the cost-effectiveness estimates?	This issue increases uncertainty in the cost-effectiveness estimates. It is not known what the direction or magnitude of change in clinical effectiveness parameters in the health economic model would be if more mature clinical effectiveness data were available and used in the model.
What additional evidence or analyses might help to resolve this key issue?	The provision of future data cuts could help resolve this uncertainty.

Abbreviations: DFS, disease free survival; ERG, Evidence Review Group; KM, Kaplan-Meier; OS, overall survival; PD-L1, programmed cell death ligand 1; TC, tumour cells

1.5. The cost effectiveness evidence: summary of the ERG's key issues

Four multifaceted key issues with the cost-effectiveness evidence are highlighted for the committee's consideration.

Key Issue 2. Approach to model DFS patient outcomes

Report sections	4.2.6.2, 4.2.6.3, 4.2.7, 4.2.8.1 and 6.2
Description of issue and why the ERG has identified it as important	The ERG-corrected company-preferred analysis projects a substantial lifetime benefit (lifetime DFS

Report sections	4.2.6.2, 4.2.6.3, 4.2.7, 4.2.8.1 and 6.2
	extension of over 4 years, discounted DFS QALY benefit of [redacted] QALYs), from subgroup Kaplan-Meier data of a ~2-year data cut of the pivotal IMpower010 study, using various optimistic and poorly evidenced adjustments and assumptions.
What alternative approach has the ERG suggested?	The ERG's preferred optimistic analysis addresses several perceived biases in the company's preferred approach: removing a post-hoc "Ramping up" of DFS (Sections 4.2.6.2, 6.2.3); removing the "treatment effect waning" adjustment (Sections 4.2.6.2, 6.2.4); removing a selective assumption that adjuvant atezolizumab influences DFS event type (metastatic vs locoregional recurrence) as well as DFS event timing (Sections 4.2.6.3, 6.2.6); including an estimate of the expected effect of adjuvant atezolizumab adverse events upon patient utility and NHS costs (Sections 4.2.7, 4.2.8.1, 6.2.7). The ERG's alternative, less-optimistic preferred analysis uses different but similarly plausible assumptions around DFS parametric model type (Weibull rather than log-logistic) and timing of cure assumptions (8 years rather than 5 years).
What is the expected effect on the cost-effectiveness estimates?	Preferred optimistic changes to the ERG-corrected company base case, as described above, applied collectively, lead to a [redacted] reduction in predicted lifetime cost savings and [redacted] QALY fall in predicted incremental health benefits. Then applying alternative, less-optimistic though equally plausible parametric model type and cure assumptions causes a [redacted] increase in predicted lifetime cost savings and a further [redacted] QALY fall in predicted incremental health benefits.
What additional evidence or analyses might help to resolve this key issue?	Continued follow-up of PD-L1 ≥ 50% TC Stage II–IIIA IMpower010 patients could provide evidence on the likelihood of modelled DFS projections. Data collection from NHS England patients treated with adjuvant atezolizumab could help address uncertainty around the generalisability of observed IMpower010 PD-L1 ≥ 50% TC Stage II–IIIA DFS data to NHS England practice.

Abbreviations: DFS, disease free survival; ERG, Evidence Review Group; ICER, incremental cost-effectiveness ration; NHS, National Health Service; PD-L1, programmed cell death ligand 1; QALY, quality adjusted life year; TC, tumour cells

Key Issue 3. Approach to model post-DFS patient outcomes

Report sections	4.2.6.3, 4.2.6.4 and 6.2
Description of issue and why the ERG has identified it as important	In all but a few aspects of post-DFS health state transition modelling, the company draw on data from outside of IMpower010, without clearly stating or convincingly justifying either the choice to eschew the observed trial data or the data identification and selection processes employed. Company modelling choices in using selected data are then often similarly poorly justified, and in some cases introduce bias. For example, post-DFS health state transition probability estimates are assumed to be time-invariant, even when the underlying data imply the opposite. Reflecting the limitations of this approach, the implied OS projections are different to (lower than) observed OS KM data for PD-L1 ≥ 50% TC Stage II–IIIA IMpower010 patients, across model arms.
What alternative approach has the ERG suggested?	In lieu of sufficient information in the CS, the ERG asked the company to explain and justify each step of post-DFS transition probability estimation, from identification of each publication, through to the use of calculated transition probability estimates in the model. The company's explanation has not reassured the ERG that the best data available are being used in the most appropriate manner for decision-making. Within the framework of the company's model structure, the ERG has tested some model sensitivity to alternative assumptions (Section 6.2.10), but this remains an area of substantial and underexplored uncertainty. The ERG asked the company to provide a cost-effectiveness scenario in which DFS and OS projections across model arms are driven by the relevant IMpower010 KM data. The company provided a scenario in which relevant IMpower010 OS KM were used directly, but in which DFS projections no longer fitted the observed DFS KM data, and in which a lifetime survival benefit is predicted for the BSC arm. The ERG place little weight on this scenario.
What is the expected effect on the cost-effectiveness estimates?	The expected effect of uncertainty around post-DFS health state transition assumptions upon cost-effectiveness is largely unknown. To an extent, this is owing to unavoidable data limitations. The ERG is concerned that the company's approach is underestimating the expected benefit of pembrolizumab or atezolizumab to treat metastatic recurrence of NSCLC, relative to apparent decision-making assumptions in

Report sections	4.2.6.3, 4.2.6.4 and 6.2
	appraisals for those treatments (TA531 and TA705, respectively), and thus overestimating the incremental health benefit expected for adjuvant atezolizumab.
What additional evidence or analyses might help to resolve this key issue?	In the immediate term, the company and committee are practically limited by the company's chosen model structure and approach to implementation. The company could not verify the 1st metastatic recurrence treatment benefit the analysis assumes for PD-L1/-1 targeting immunotherapeutic treatment strategies, in relation to that assumed in TA705 (in which they are the submitting company). Longer-term, continued follow-up of PD-L1 ≥ 50% TC Stage II–IIIA IMpower010 patients could provide evidence on likely OS projections, and the company could revisit their approach to capture these data and relevant DFS data in a more appropriate model structure.

Abbreviations: BSC, best supportive care; CS, company submission; DFS, disease free survival; ERG, Evidence Review Group; KM, Kaplan-Meier; NSCLC, non-small cell lung cancer; OS, overall survival; PD-L1, programmed cell death ligand 1; TA, technology appraisal; TC, tumour cells

Key Issue 4. Approach to capture lifetime treatment pathway expectations

Report sections	4.2.8.3 and 6.2
Description of issue and why the ERG has identified it as important	The company assume adjuvant atezolizumab will preclude subsequent atezolizumab or pembrolizumab. In other words, that a patient will only receive one course of PD-L1/PD-1-targeting immunotherapy to treat NSCLC in their lifetime. The validity of this assumption is important for cost-effectiveness estimates, primarily for the cost differences implied by use of immunotherapy to treat metastatic recurrence in the comparator arm only. The company's treatment pathway assumptions are otherwise naïve to the complexity of the NHS treatment pathway at metastatic recurrence.
What alternative approach has the ERG suggested?	The ERG aligned with the company expectation that adjuvant atezolizumab will preclude subsequent atezolizumab or pembrolizumab in NHS England practice, though note the importance of this assumption for decision-making. The ERG has incorporated NHS-algorithm-informed metastatic treatment availability and uptake assumptions (Sections 4.2.8.3 and 6.2.12).

Report sections	4.2.8.3 and 6.2
What is the expected effect on the cost-effectiveness estimates?	If a patient could receive a second PD-L1/PD-1 targeting immunotherapeutic NSCLC treatment in their lifetime, this would increase costs associated with the intervention arm of this analysis, with an unevidenced QALY impact that may or may not justify the incremental cost, based on the NICE decision-making threshold range. Using treatment availability and uptake assumptions that reflect NHS practice at metastatic recurrence and best available patient characteristic assumptions at this stage causes the ERG-corrected, company-preferred deterministic predicted incremental costs to increase by [redacted], as an isolated effect (Section 6.2.12), with the implication in isolation that adjuvant atezolizumab is less cost saving than implied by company assumptions,
What additional evidence or analyses might help to resolve this key issue?	Clarity from NHS England that a patient will receive no more than one course of PD-L1/PD-1-targeting immunotherapy as NHS England treatment for NSCLC in their lifetime will help resolve this aspect of decision uncertainty.

Abbreviations: ERG, Evidence Review Group; ICER, incremental cost-effectiveness ratio; NHS, National Health Service; NICE, National Institute for Health and Care Excellence; NSCLC, non-small cell lung cancer; PD-1, programmed cell death 1; PD-L1, programmed cell death ligand 1; QALY, quality adjusted life year

Key Issue 5. Approach to capture incremental cost differences aside from NSCLC treatment acquisition costs

Report sections	4.2.3, 4.2.8.1, 4.2.8.2, 4.2.8.3, 4.2.8.4 and 6.2
Description of issue and why the ERG has identified it as important	The company's analysis includes assumptions around costs that the ERG feel bias the company-preferred analysis in favour of atezolizumab. As addressed within Key Issue 2, the company-preferred analysis assumes no AE costs associated with the introduction of atezolizumab to the adjuvant treatment setting. Elsewhere, • The company assume no treatment discontinuation within metastatic recurrence states. The ERG believe this is an implausible assumption that biases the company's analysis in favour of adjuvant atezolizumab (Sections 4.2.8.3 and 6.2.14) • The company assume only some patients will incur a terminal care cost, in a manner that favours the adjuvant atezolizumab arm of the analysis (Sections 4.2.8.4 and 6.2.11)

Report sections	4.2.3, 4.2.8.1, 4.2.8.2, 4.2.8.3, 4.2.8.4 and 6.2
	• The company assume a lower NHS and patient burden associated with adjuvant atezolizumab administration than that expected by the ERG expert (Sections 4.2.8.1 and 6.2.9) • The company assume the administration cost of doublet IV therapy is twice that of IV monotherapy, when the ERG's expert expects no meaningful additional cost of doublet versus monotherapy administration (Sections 4.2.8.2 and 6.2.13) • The company implicitly assume no atezolizumab batch remakes in practice, when evidence from an NHS pharmacist highlights this as a rare issue (Sections 4.2.3 and 6.2.8)
What alternative approach has the ERG suggested?	The ERG has attempted to relax or adapt the company assumptions described above in the ERG-preferred analyses, using the best data available (Sections 6.2). Specifically, the ERG prefer to assume: • Those assumed to receive treatment for metastatic recurrence are assumed to spend 50% of time before next recurrence or death receiving active treatment, in absence of data (Section 6.2.14) • All patients are assumed to incur a terminal care cost (Section 6.2.11) • ERG-expert-informed adjuvant atezolizumab administration resource burden (Section 6.2.9) • No additional administration cost for the second IV element of doublet IV therapy (Section 6.2.13) • A pharmacy-data informed batch-remake rate for adjuvant atezolizumab (Section 6.2.8)
What is the expected effect on the cost-effectiveness estimates?	Applying ERG-preferred adjustments to the stated assumptions in combination leads to a [redacted] increase in the ERG-corrected, company-preferred deterministic incremental cost prediction, producing an ICER of [redacted] /QALY gained.
What additional evidence or analyses might help to resolve this key issue?	The ERG's estimate of the expected proportion of time in 1st metastatic recurrence before 2nd recurrence or death and in 2nd recurrence before death spent on treatment by those expected to receive active treatment at these stages, is highly uncertain. However, it is not plausible that the proportion is 100%. Better-informed estimates

Report sections	4.2.3, 4.2.8.1, 4.2.8.2, 4.2.8.3, 4.2.8.4 and 6.2
	would lead to better-informed results to support decision-making.

Abbreviations: AE, adverse event; ERG, Evidence Review Group; ICER, incremental cost-effectiveness ratio; IV, intravenous; NHS, National Health Service

1.6. Other key issues: summary of the ERG's views

No other key issues were identified.

1.7. Summary of ERG's preferred assumptions and resulting ICERs

Table 3 presents the incremental and cumulative impact of the ERG's preferences.

Table 3. Summary of ERG's preferred assumptions and ICER

	Incremental		Cumulative ICER £/QALY
Description	Costs	QALYs	
Company base-case (det)	[redacted]	[redacted]	[redacted]
ERG-corrected company base case (det)	[redacted]	[redacted]	[redacted]
ERG-corrected company base case (det) + EA #3 = A *EA #3: Remove "ramping up" adjustment*	[redacted]	[redacted]	[redacted]
A + EA #4 = B *EA #4: Remove "treatment effect waning" adjustment*	[redacted]	[redacted]	[redacted]
B + EA #6 = C *EA #6: DFS event type not affected by treatment arm*	[redacted]	[redacted]	[redacted]
C + EA #7 = D *EA #7: Apply AE cost and HRQL effects for all active treatments*	[redacted]	[redacted]	[redacted]
D + EA #8 = E *EA #8: Assume some atezolizumab batch remakes*	[redacted]	[redacted]	[redacted]
E + EA #9 = F *EA #9: Capture adjuvant atezolizumab administration burden expectations*	[redacted]	[redacted]	[redacted]
F + EA #11 = G *EA #11: Terminal care costs for all patients*	[redacted]	[redacted]	[redacted]
G + EA #12 = H *EA #12: Capture expected metastatic treatment pathway*	[redacted]	[redacted]	[redacted]
H + EA #13 = I *EA #13: Assume one administration cost for combination IV therapy*	[redacted]	[redacted]	[redacted]
I + EA #14 = J = ERG-preferred optimistic base case (det) *EA #14: Relax assumption of no treatment discontinuation within metastatic recurrence health states*	[redacted]	[redacted]	[redacted]

	Incremental		Cumulative ICER £/QALY
Description	Costs	QALYs	
ERG-preferred optimistic base case (mean prob)	[redacted]	[redacted]	[redacted]
J + EA #2 = K *EA #2: Assume Weibull distribution for DFS*	[redacted]	[redacted]	[redacted]
K + EA #5 = L = ERG-preferred pessimistic base case (det) *EA #5: Delay cure assumption to 8 years*	[redacted]	[redacted]	[redacted]
ERG-preferred alternative base case (mean prob)	[redacted]	[redacted]	[redacted]

Abbreviations: AE, adverse event; DFS, disease free survival; det, deterministic; EA, exploratory analysis; ERG, Evidence Review Group; HRQL, health-related quality of life; ICER, incremental cost-effectiveness ratio; IV, intravenous; prob, probabilistic; QALY, quality adjusted life year

Note: "(£+)" entries indicate the change in deterministic ICER from the previous deterministic iteration, e.g. the "J" ICER is [redacted] than the "I" ICER.

Modelling errors identified and corrected by the ERG are described in Section 6.1. For further details of the exploratory analyses conducted by the ERG, see Section 6.2.

2. INTRODUCTION AND BACKGROUND

2.1. Introduction

In this report, the Evidence Review Group (ERG) provides a review of the evidence submitted by Roche in support of atezolizumab for adjuvant treatment of resected non-small-cell lung cancer (NSCLC).

The ERG noted that the initial submission to NICE in October 2021, covered the technology's full, proposed marketing authorisation for the indication at that time: Tecentriq® (atezolizumab) as monotherapy is indicated as adjuvant treatment following complete resection for adult patients with NSCLC whose tumour has PD-L1 expression of ≥ 1% of TCs and whose disease has not progressed following platinum-based adjuvant chemotherapy.

However, [redacted], the Medicine and Healthcare products Regulatory Agency (MHRA), restricted the indication to the PD-L1 ≥ 50% Stage II–IIIA population with the following proposed updated indication wording:

- Tecentriq® as monotherapy is indicated as adjuvant treatment following complete resection for adult patients with Stage II to IIIA (7th edition of the Union for International Cancer Control [UICC]/ American Joint Committee on Cancer [AJCC]-staging system) non-small cell lung cancer (NSCLC) whose tumours have PD-L1 expression on ≥50% of tumour cells (TC) and whose disease has not progressed following platinum-based adjuvant chemotherapy.

The company therefore submitted a supplementary data package in January 2022 presenting data in the PD-L1 ≥50% Stage II–IIIA population.

The ERG report refers to the addendum submitted by the company on 31 January 2022 reflecting changes in the target population following Medicine and Healthcare products Regulatory Agency (MHRA) review.

2.2. Critique of the company's description of the underlying health problem

The company's description of the underlying health problem, resected NSCLC, is summarised in the CS (Document B, Section B.1.3.1) of the CS. Lung cancer is the most prevalent form of cancer globally, contributing to around 12% of newly diagnosed cancer cases[1] and an estimated 1.8 million cancer-related deaths.[2] In the United Kingdom (UK), lung cancer is the third most prevalent form of cancer, accounting for approximately 47,800 new cases per annum and approximately 21% of all UK cancer deaths.[3] NSCLC is one of two primary categories of lung cancer and represents an estimated 88% of all lung cancer cases,[4] and can be further subdivided into non-squamous and squamous histology, the former accounting for approximately 70% of NSCLC cases.[5] In the UK, diagnosis of NSCLC is often late, with the modal stage at which diagnosis is made being Stage IIIA.[6] Based on clinical advice, the ERG agreed with the company's proposition that despite potentially curative surgical options, survival rates are likely to be highly dependent on disease stage, which is the key prognostic factor in this population. The ERG considered that the CS provided a generally acceptable description of the condition; its pathophysiology, natural course and epidemiology, and the current treatment options available. However, the ERG considered that the company did not provide sufficient information to substantiate its claim that the UK five-year survival estimates for NSCLC – based on clinical advice to the company – are comparable to published international estimates of 68-92% for Stage I disease, 53-60% for Stage II disease, and 13-36% for Stage III disease.[7] No epidemiological evidence was available specifically in the revised target population.

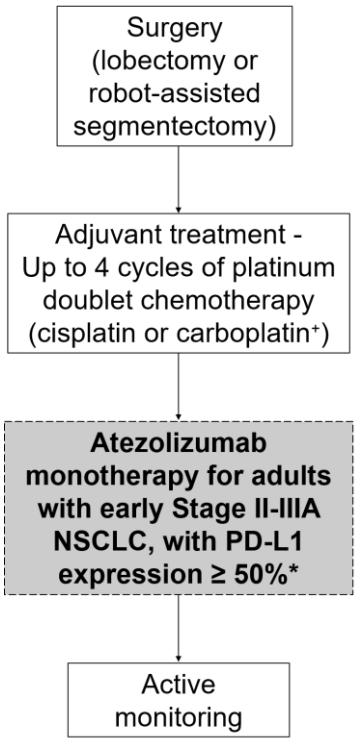
2.3. Critique of the company's overview of current service provision

The company's current care pathway is described in Section B.1.3.3 of the CS (Document B). The company depicted the treatment pathway for UK clinical practice, which clinical advice to the company indicated corresponds well to this Guideline, and the proposed positioning of atezolizumab, in a flowchart (Figure 1). NICE Guideline 122[8] was identified by the company as relevant to this appraisal.

Although historically the use of surgery for early NSCLC has been less common in the UK than in other countries, its use has risen in recent years[9]. NICE currently recommends the use of adjuvant cisplatin-based chemotherapy for Stage 1B to Stage III patients.[8] However, the use of adjuvant chemotherapy in this context remains limited in a UK context, being given to between 30 and 60% of Stage II patients.[10] While carboplatin is not currently recommended by NICE in

this context[8], the company reports clinical advice that carboplatin is used in clinical practice, although there is regional variation in its usage.

Figure 1. Current treatment pathway for early NSCLC adult patients (including atezolizumab positioning)



Source: CS Addendum #1, Figure 1, p.5

Clinical advice to the ERG also indicated that the treatment pathway presented by the company could be considered reflective of clinical practice in England and Wales.

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 and tumour-infiltrating immune cells. Atezolizumab is approved by the European Medicines Agency (EMA) for a range of treatment positions in NSCLC, urothelial carcinoma, hepatocellular carcinoma and triple-negative breast cancer, as outlined in the CS (Document B. Table 2, pp.17-18). The ERG considered that the company's intended positioning for atezolizumab, as compared to current standard of care, to be appropriate and generally well-described.

Clinical advice to the ERG indicated that atezolizumab would displace best supportive care (BSC), i.e. active monitoring without specific intervention, which would be moved later in the treatment pathway, i.e. to be only used after non-response to atezolizumab. The ERG was additionally advised that the narrowing of the company's target population to include only individuals with PD-L1 expression ≥50% was unlikely to have any material impact upon the anticipated treatment pathways.

In addition, the ERG noted that NICE has recently appraised osimertinib (TA761, January 2022[11]). Osimertinib was recommended for use within the Cancer Drugs Fund (CDF) as adjuvant treatment after complete tumour resection in adults with Stage IB to IIIA NSCLC whose tumours have epidermal growth factor receptor (EGFR) exon 19 deletions or exon 21 (L858R) substitution mutations. As such, osimertinib will not be available via routine commissioning.

2.4. Critique of the company's definition of decision problem

The company statement regarding the decision problem is presented in Section B1.1. of the CS, Table 1. The company position and the ERG response is provided in Table 4 below.

The ERG considered that the company decision problem generally corresponded well to the NICE final scope for this appraisal, with some exceptions. The ERG noted that the subgroup of interest (PD-L1 ≥50% TC Stage II–IIIA) was narrower than the population specified in the NICE scope but consistent with the marketing authorization. While clinical advice to the ERG agreed that the quality of life burden of this condition is likely to be low, the ERG did consider the non-collection of quality of life data in the IMpower010 trial to be a limitation in terms of clinical effectiveness data capture associated with the intervention and comparator in the target population, which necessitated the use of other data sources to inform quality of life estimates parameters in the model.

Table 4. Summary of decision problem

	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope	ERG comment
Population	Adults with fully resected NSCLC after adjuvant cisplatin-based chemotherapy	Adults with resected, Stage II–IIIA eNSCLC, expressing PD-L1 ≥50% of tumour cells.	The PD-L1 ≥50% population is in line with the marketing authorization following MHRA review.	The ERG noted that the subgroup of interest (PD-L1 ≥50% TC Stage II–IIIA) was narrower than the population specified in the NICE scope but consistent with the marketing authorization.
Intervention	Atezolizumab (as an adjuvant treatment).	Per final scope.	N/A.	N/A.
Comparator(s)	Established clinical management without atezolizumab (that is, active monitoring). For adults with EGFR mutation-positive NSCLC: Osimertinib (subject to NICE appraisal).	Established clinical management without atezolizumab (that is, active monitoring).	• Data from the IMpower010 trial demonstrated potential benefit from adjuvant atezolizumab after chemotherapy for some NSCLC patients (e.g., PD-L1+) with epidermal growth factor receptor (EGFR+) mutations. However, the sample size of EGFR/ALK+ NSCLC patients were small and insufficient to fully characterise the treatment effect and to draw conclusions on the risk/benefit profile for adjuvant atezolizumab in these populations. • In addition, based on results from the ADAURA trial, and recent FDA and EMA approvals, osimertinib is likely to become standard of care for EGFR+ NSCLC patients in the adjuvant setting. • Roche Products Ltd, along with clinical experts, do not expect the IMpower010	The CS stated that the comparator is established clinical management without atezolizumab (active monitoring, i.e. routine monitoring and follow-up). The ERG considered that the comparator in IMpower010 was consistent with the decision problem. In the IMpower010 trial, active monitoring comprised tumour assessment was carried out at baseline and every four months in Year 1, then every six months through Years 2-5, until disease recurrence, across both treatment arms. The ERG noted that NICE has recommended the use of osimertinib within the CDF and it is therefore not part of routine commissioning."[12] on this basis, the ERG concluded that osimertinib is not a relevant comparator for this appraisal. In addition, the ERG highlighted that its clinical advisor had indicated that atezolizumab was unlikely to displace osimertinib as it may not

	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope	ERG comment
			regimen to replace osimertinib for these patients and therefore, we do not consider osimertinib to be a relevant comparator.	be used to treat EGFR+/ALK+ disease, owing to concern that adjuvant immunotherapy may increase the risk of side effects from subsequent TKI treatment. The ERG was satisfied that the company's focus on established clinical management without atezolizumab (i.e. active monitoring) was appropriate.
Outcomes	The outcome measures to be considered include: • Overall survival • Disease-free survival • Response rate • Adverse effects of treatment • Health-related quality of life	The outcome measures to be considered include: • Overall survival • Disease-free survival • Adverse effects of treatment	Response rates and health-related quality of life were not measured. • Response rates are not measurable in resected NSCLC patients. • Patients with early NSCLC are generally asymptomatic, and their disease burden are relatively low when compared to patients in the metastatic setting. In addition, patients in the IMpower010 trial did not receive an active control therapy.	The ERG noted that the outcomes in the company's decision problem were broadly comparable with those in the NICE scope. Clinical advice to the ERG indicated that response rates were not a relevant outcome in a resected population. Patients receiving adjuvant therapy by definition have no measurable disease therefore unable to assess radiological response as for people who have recurrent or metastatic disease where the treatment intent would change from "adjuvant" to "palliative" or "radical" (if still able to offer potential curative intent salvage therapy). Clinical advice to the ERG indicated that the quality of life burden of this condition is likely to be low, the ERG did consider that the non-collection of HRQoL data in the IMpower010 trial to be a limitation in terms of clinical effectiveness data capture

	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope	ERG comment
				associated with the intervention and comparator in the relevant population, which necessitated the use of other data sources to inform HRQoL estimates parameters in the model. Data for disease relapse are also presented but are not a scoped outcome.
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 PSS perspective. The availability of any commercial arrangements for the intervention, comparator and subsequent treatment technologies will be taken into account. The availability of any managed access arrangement for the intervention will be taken into account.	• Cost per QALY • Time horizon suitably long to reflect differences • NHS PSS perspective PAS to be taken into account.	N/A	N/A
Subgroups	If evidence allows, subgroup analysis by level of PD-L1 expression will be considered. Guidance will only be issued in accordance with the marketing authorisation. Where the wording	Patients with resected, Stage II–IIIA eNSCLC, expressing PD-L1 ≥50% of tumour cells and without EGFR/ALK+ mutations.	• In the IMpower010 trial, NSCLC patients with ALK+ genetic alternations did not appear to benefit with atezolizumab compared with BSC.	The scope specified analysis by level of PD-L1 expression. However, the main population in the CS was PD-L1 ≥50% Stage 2 and Stage 3A in line with the indication wording. No further

	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope	ERG comment
	of the therapeutic indication does not include specific treatment combinations, guidance will be issued only in the context of the evidence that has underpinned the marketing authorisation granted by the regulator.		• Data from the IMpower010 trial demonstrated potential benefit from adjuvant atezolizumab after chemotherapy for some NSCLC patients (e.g., PD-L1+) with EGFR+ mutations. • The sample size of EGFR/ALK+ NSCLC patients were small and insufficient to fully characterise the treatment effect and to draw conclusions on the risk/benefit profile for adjuvant atezolizumab in these populations. • We do not expect the IMpower010 regimen to be used for these patients and have therefore presented DFS data excluding EGFR/ALK+ NSCLC patients.	analysis by PD-L1 expression was therefore presented in the CS Addendum. The ERG considered the subgroup presented by the company – excluding patients with EGFR/ALK+ mutations who are unlikely to be prescribed atezolizumab – to be appropriate as a subgroup analysis. However, the ERG also noted that this particular sub-group was not specified in the NICE scope. Given that clinical advice indicated that atezolizumab was unlikely to be used in this population, the ERG's review focuses on the company's evidence for the whole MHRA-approved population, including those patients with EGFR+/ALK+ disease. .
Special considerations including issues related to equity or equality	N/A	N/A	N/A	N/A

Abbreviations ALK, anaplastic lymphoma kinase; BSC, best supportive care; CS, company submission; DFS, disease free survival; EGFR, epidermal growth factor receptor; EMA, European Medicines Agency; eNSCLC, early non-small cell lung cancer; ERG, Evidence Review Group; FDA, Food and Drug Administration; MHRA, Medicines and Healthcare Regulatory Agency; N/A, Not applicable; NICE, National Institute for Health and Care Excellence; NSCLC, non-small-cell lung cancer; PAS, patient access scheme; PD-L1, programme death ligand 1; PSS, personal social services; QALY, quality-adjusted life year

3. CLINICAL EFFECTIVENESS

The sections below discuss the evidence submitted by the company in support of the clinical effectiveness of atezolizumab for adults with resected, Stage II–IIIA early non-small cell lung cancer (eNSCLC), expressing PD-L1 ≥50% of tumour cells.

The ERG reviewed the details provided on:

- Methods implemented to identify, screen, data extract and assess the risk of bias in relevant evidence.
- Clinical efficacy of atezolizumab.
- Safety profile of atezolizumab,
- Assessment of comparative clinical effectiveness of atezolizumab against relevant comparators.

A detailed description of an aspect of the CS is only provided where the ERG disagreed with the company's assessment or proposal, or where the ERG identified a particular area of concern that the ERG considered necessary to highlight for the Committee.

The ERG identified one key issue relating to the clinical effectiveness evidence:

- Immaturity of clinical effectiveness data in the key IMpower010 trial

Since in the CS, the company made a number of preferences and assumptions based on clinical expert opinion, the ERG requested a detailed set of materials from the advisory board meetings at the clarification stage. The company provided a list of attendees, the slides that were shown to attendees and a report of the meetings. Following a review of all the materials provided, the ERG noted that the discussion was set in context of the PD-L1 TC ≥1% Stage II–IIIA population aligned with the planned marketing authorisation. The ERG also noted that, subsequent to the change in marketing authorisation to limit to PD-L1 TC ≥50% Stage II–IIIA population, further discussions were conducted with clinicians to check validity in the PD-L1 TC ≥50% Stage II–IIIA population.

3.1. Critique of the methods of review(s)

In the CS submitted in November 2021 (Appendix D), the company reported a systematic review undertaken to identify relevant publications on the clinical efficacy and safety of atezolizumab as monotherapy as adjuvant treatment for adults with resected Stage II–IIIA eNSCLC, expressing PD-L1 ≥1% of tumour cells and whose disease has not progressed following platinum-based adjuvant chemotherapy.

In addition to best supportive care (BSC), the company considered direct comparisons between the intervention and comparators, with adjuvant chemotherapy, specifically platinum-based doublet regimens, and chemoradiotherapy delivered sequentially in the adjuvant setting as well as programmed death-1 (PD-1) or programmed death-ligand 1 (PD-L1) inhibitors considered to be relevant comparators.

While appropriate methods for study inclusion were employed by the company, poor reporting meant that the ERG could not evaluate the robustness of the data extraction processes conducted by the company.

No updated search or SLR was presented with the company's addendum; however, the ERG did not consider this to be an issue.

Table 5. Summary of ERG's critique of the methods implemented by the company to identify evidence relevant to the decision problem

Systematic review step	Section of CS in which methods are reported	ERG assessment of robustness of methods
Searches	Appendix D; Table 2, Table 3, Table 4.	The searches were adequate but not comprehensive (CS, Appendix D). Indexed terms (e.g. MeSH, Emtree) were not used to search for the intervention terms (the drug names); this is not best practice and it is certainly possible that some records were missed. Drug names are very well indexed in Embase in particular and indexed terms should be included with the other search terms as standard. The company did not carry out any clinical trials registry searches for ongoing trials. In clarification the company stated that the searches of trials in CENTRAL should be enough. This approach is not evidence based and research to-date suggests that searching CENTRAL alone is not enough, other clinical trials registries should be searched

Systematic review step	Section of CS in which methods are reported	ERG assessment of robustness of methods
		individually.[13] It is therefore highly possible that some trials were missed by the searches.
Inclusion criteria	Appendix D (Section D.1.4, Table 5)	Broadly appropriate. Broad criteria were applied. Clinical effectiveness of interventions aimed at managing early-stage NSCLC (Stage 2--3B) receiving treatment in the adjuvant or neoadjuvant treatment settings published in English language from Year 2004 to Year 2021 were included. No restrictions with regard to patient age or mutation status were applied.
Screening	Appendix D (page 15)	Unclear[a] whether screening was conducted to appropriate standards to minimise selection bias. Although dual screening of titles and abstracts was mentioned, it was unclear whether dual screening of full text articles was conducted. No mention of arbitration by a third reviewer at title/abstract and full-text stages.
Data extraction	Appendix D	Unclear. No methodological details were /provided in the CS.
Tool for quality assessment of included study or studies	Appendix D (Section D.3, Table 10)	Appropriate. A modified version of the Cochrane Risk of Bias tool to assess RCT quality was used.
Evidence synthesis	-	No evidence synthesis was conducted. The company justified this by saying that the Impower010 trial included the relevant intervention and comparator pairing, and no other suitable trials were available. The ERG considered this to be appropriate. The ERG's critique of the company's decision not to conduct an indirect treatment comparison is provided in Section 3.4.

Abbreviations: CS, company submission

Notes:

[a] Titles and abstracts were dual screened versus pre-defined eligibility criteria. A list of excluded studies was provided in Appendix D, Section D1.5, Table 7 of the CS together with reasons for exclusion

3.2. Critique of trials of the technology of interest, the company's analysis and interpretation (and any standard meta-analyses of these)

3.2.1. Studies included in the clinical effectiveness review

The company presented evidence from one Phase 3 RCT of atezolizumab – IMpower010.[14,15] This forms the pivotal trial in the context of this appraisal.

3.2.2. Description and critique of the design of the studies

3.2.2.1. IMpower010: Study design

The company's primary evidence for atezolizumab was derived from IMpower010[15] a global, randomised, Phase 3, multi-centre, open-label trial of atezolizumab compared to BSC following resection and cisplatin-based adjuvant chemotherapy.

The study was done in two phases: enrolment and randomisation. The second phase, randomised evaluation of atezolizumab versus best supportive care, started after completion of cisplatin-based chemotherapy (one to four cycles) in patients without disease recurrence who were still eligible.[15,16] Three to eight weeks after the last dose of adjuvant chemotherapy, participants were randomly assigned (1:1) by a permuted-block method with a block size of four to either the atezolizumab arm or BSC arm with an interactive voice-web response system. Randomisation was stratified by sex (female vs male), tumour histology (squamous vs non-squamous), extent of disease (Stage IB vs Stage II vs Stage IIIA), and PD-L1 expression status (tumour cell [TC] 2/3 and any tumour-infiltrating immune cells [IC] vs TC0/1 and IC2/3 vs TC0/1 and IC0/1 with the SP142 immunohistochemistry assay). Masking was not done as the study had an open-label design.

Participants entered the enrolment phase 28–84 days after complete resections of their NSCLC, and eligible patients received the investigator's choice of one of four adjuvant cisplatin-based chemotherapy regimens for up to four 21-day cycles: cisplatin 75 mg/m² intravenously on Day 1 of each cycle plus either vinorelbine 30 mg/m² intravenously on Days 1 and 8, docetaxel 75 mg/m² intravenously on Day 1, gemcitabine 1,250 mg/m² intravenously on Days 1 and 8, or, in the case of patients with non-squamous NSCLC, pemetrexed 500 mg/m² intravenously on Day 1. After randomisation, participants received either atezolizumab or best supportive care.

An overview of the trial design is provided in Table 6.

Table 6. Overview of IMpower010 trial design

Study name and acronym	Study design Phase	Population	Intervention (n)	Comparator (n)	Treatment duration	Stratification factors	Number of randomised participant by region
IMpower010 (NCT02486718)	Randomised, open-label, multicentre, placebo-controlled Phase 3	Adults (aged 18 years-plus) with ECOG PS 0 or 1, completely resected Stage IB to IIIA NSCLC[a], and able to receive cisplatin-based chemotherapy	Adjuvant atezolizumab 1,200 mg every 21 days for 16 cycles or 1 year (n=507[b])	BSC (observation and regular scans for disease recurrence) (n=498[b])	One year	Female vs male Squamous vs non-squamous Stage IB vs Stage II vs Stage IIIA PD-L1 expression status (TC 2/3 and any tumour-infiltrating IC vs TC0/1 and IC2/3 vs TC0/1 and IC0/1 with the SP142 immunohistochemistry assay).	European and Middle East: n=651 Asia-Pacific: n=235 North America: n=119

Abbreviations: BSC, best supportive care; ECOG PS, Eastern Cooperative Oncology Group Performance Status; IC, immune cells; NSCLC, non-small-cell lung cancer; PD-L1, programme death ligand 1; TC, tumour cells

Notes:

[a]Per the Union Internationale Contre le Cancer and American Joint Committee on Cancer staging system (7th edition); [b]intent-to-treat population

Source: Felip 2010[15]

Table 7. IMpower010 analysis populations

Analysis population	Atezolizumab	BSC	Total
Intent-to-treat	507	498	1,005
Intent-to-treat: Stage II–IIIA participants	442	440	882
Intent-to-treat: Stage II–IIIA + SP263 TC ≥1% participants	248	228	476
Randomised safety evaluable participants[a]	495	495	990
Marketing authorization: Stage II–IIIA + SP263 TC ≥50% participants	**115**	**114**	**229**

Abbreviations: BSC, best supportive care

Notes:

[a]Participants who received at least one dose of atezolizumab or who were randomized to BSC and had at least one post-baseline assessment

Source: IMpower010 CSR (adapted from Table 9 Analysis populations)[16]

Trial population

Eligible participants were adults (aged 18 years-plus) with completely resected Stage IB (tumours greater ≥4cm) to Stage IIIA (T2-3 N0, T1-3 N1, T1-3 N2, T4 N0-1) NSCLC (per UICC/AJCC staging system 7th edition), with an ECOG performance status of 0–1 and were able to receive cisplatin-based chemotherapy. Detailed inclusion and exclusion criteria were provided in the CS (Appendix E). It should be noted that the ECOG eligibility criteria for the trial were not included in either the NICE scope or the company decision problem.

There was a total of 1,280 participants recruited from 227 centres across 22 countries globally. A total of 1269 patients were enrolled and received up to four 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 1,005 patients were subsequently randomised in a 1:1 ratio to receive atezolizumab or BSC. Information about the country profile in the relevant subgroup was not provided, but in the trial ITT population, a total of [redacted] ([redacted]%) participants of the ITT population were from the United Kingdom (UK), while European centres were well represented. Clinical advice to the ERG indicated that the relative lack of UK participants was unlikely to be a major concern in terms of generalisability. While the report from the company's clinical advisory board meetings [redacted].

The population in the decision problem reflected a subgroup of the trial ITT population: participants with PD-L1 ≥50% TC Stage II–IIIA which reflected the [redacted]. A total of 229 participants were included in this subgroup (115 in the atezolizumab group and 114 in the BSC group). PD-L1 was pre-specified as a stratification factor for the secondary DFS endpoint, but not with this particular cut-off. The ERG noted that PD-L1 status was a pre-randomisation stratification factor in the trial, which the ERG considered to be a strength given the focus on a subgroup for this appraisal.

Interventions evaluated

The intervention in the IMpower010 trial was atezolizumab intravenously every 21 days (Day 1 of each 21-day cycle) for a total of 16 cycles, representing approximately one year of treatment. There are three different recommended dosing regimens for atezolizumab (CS, Document B,

Section B.1.2, Table 2, p18): 840 mg administered intravenously every two weeks; 1,200 mg administered intravenously every three weeks; or 1,680 mg administered intravenously every four weeks. The three-weekly dosing regimen corresponds to that used in the trial. Clinical advice to the ERG indicated that some centres currently have switched from a three-weekly to a four-weekly regimen, as this has advantages for day unit capacity. However, the selection of dosing regimen in clinical practice would be dictated by NHS England guidance upon routine commissioning, and this may favour a three-weekly dosing regimen as this was used in the trial. There therefore remains uncertainty about what the dosing regimen in clinical practice upon routine adoption of atezolizumab would be in England and Wales.

The comparator in the IMpower010 trial was BSC which included observation and regular scans for disease recurrence. No crossover BSC to atezolizumab was allowed. Based on clinical advice, the ERG considered this corresponded well to the decision problem; i.e. established clinical management without atezolizumab (active monitoring i.e. routine imaging and follow-up).

Outcomes

The outcomes covered in the IMpower010 trial were summarised in the CS Section B.2.3.3.

The primary efficacy outcome measure for this study was:

- disease-free survival (DFS)

  Disease-free survival (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. This efficacy outcome measure was added in the PD-L1 subpopulation TC ≥1% by the SP263 immunohistochemistry (IHC) assay within participants with Stage II–IIIA NSCLC, in all randomized patients with Stage II–IIIA NSCLC and in the ITT population.

  The company used DFS as the clinical input to the health-economic model, citing immaturity in the OS data (see Section 4.2.6.4). The company cited a meta-analysis (Mauguen et al. 2013) that showed DFS to be a valid surrogate endpoint in studies of adjuvant chemotherapy for NSCLC, but the ERG noted also the authors' caveat that '*Extrapolation to targeted treatments, however, is not automatically warranted*'.

The secondary efficacy outcome measures for the IMpower010 study were:

- overall survival (OS)

  OS was defined as the time from the date of randomisation to death by any cause.

- DFS rates at three years and five years in the PD-L1 subpopulation, in the Stage II-IIA population, and in the ITT population.

- DFS in the PD-L1 subpopulation TC ≥50% by the SP263 IHC assay within participants with Stage II–IIIA NSCLC.

Table 8. IMpower010: Efficacy outcomes assessed, pre-specified analyses

Analysis population	ITT	ITT: Stage II–IIIA participants	Intent-to-treat: Stage II–IIIA + SP263 TC ≥1% participants	Intent-to-treat: Stage II–IIIA + SP263 TC ≥50% participants	Subgroup analyses[b]
Primary outcome:					
DFS[a]	●	●	●		●
Secondary outcomes:					
OS	●				●
DFS				●	
3-year DFS[a]	●	●	●		
5-year DFS[a]	●	●	●		

Abbreviations: DFS, disease-free survival; ECOG PS, Eastern Cooperative Oncology Group Performance Status; ITT, intent-to-treat; OS, overall survival; PD-L1, programme death ligand 1; TC, tumour cell

Notes:

[a]Investigator-assessed DFS

[b]Age, sex, race, ethnicity, tumour stage, PD-L1 expression, chemotherapy regimen before randomization, histology, smoking history, & ECOG PS

Source: Felip 2021[15]

Safety outcome measures were:

- Incidence, nature, and severity of adverse events, serious adverse events, and adverse events of special interest graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) v4.0.

- Changes from baseline in vital signs, physical findings, and targeted clinical laboratory results.
- Incidence of anti-therapeutic antibodies (ATA) response to atezolizumab and potential correlation with pharmacokinetics (PK), safety, and efficacy parameters.

Data from IMpower010 were available for the following outcomes in the NICE scope:[17] OS, DFS, AEs. The IMpower010 trial did not collect data for response rates. Clinical advice to the ERG indicated that response rates were not a relevant outcome in a resected population, as once resection has occurred patients are assumed to be disease free and response is not assessed. Additionally, the IMpower010 trial did not collect HRQoL data. During clarification the ERG asked the company to comment on why HRQoL data had not been collected in the clinical trial (Clarification Question A3). The company commented that the assessment of HRQoL was not routine in the eNSCLC setting at the time of study design for IMpower010 and referenced other trials within the adjuvant eNSCLC setting that are not collecting HRQoL data (ANVIL [NCT02595944],[18] ALCHEMIST [NCT04267848],[19] Checkmate-816 [NCT02998528],[20] Checkmate-77T [NCT04025879],[21] and KEYNOTE-091/PEARLS [NCT02504372][22]). Additionally, the company speculated in its response that this could be because people with eNSCLC are generally asymptomatic and diagnosed incidentally and following surgery these patients are tumour-free and, therefore, considered disease-free. Nevertheless, the ERG noted that, while some studies suggest that HRQoL returns to baseline levels at six to nine months postoperatively, the evidence is uncertain.[14] Therefore the ERG considered the non-collection of HRQoL data in the IMpower010 trial to be a limitation in terms of clinical effectiveness data capture associated with the intervention and comparator in the relevant population, which necessitated the use of other data sources to inform HRQoL estimates parameters in the model.

3.2.2.2. Critical appraisal of the design of the studies

The company reported a generally favourite risk of bias profile in relation to the IMpower010 trial, although noted that the trial was not blinded. The ERG considered that blinding was precluded by the fact that the comparator intervention was not a pharmaceutical intervention, since it was BSC. Blinding would have required a saline placebo to have been administered, although there are likely ethical issues about requiring patients with NSCLC to attend frequent study visits if they receive placebo. The complete quality assessment for IMpower010 is available in the CS (Section B.2.5, Table 8, p.39). The company used a modified version of the

Cochrane Risk of Bias tool, which the ERG considered broadly appropriate, although the modifications were not detailed in the CS.

3.2.3. Description and critique of the results of the studies

Baseline characteristics and efficacy data are presented for the PD-L1 ≥50% TC Stage II–IIIA population subgroup aligned with the anticipated licensed indication

3.2.3.1. Baseline characteristics

Baseline characteristics for participants included in the IMpower010 trial are reported in the CS Addendum (Table 1, p8) for the PD-L1 ≥50% TC Stage II–IIIA population ≥50 (9). This was not a pre-specified subgroup, although it forms the marketing authorisation. The ERG considered the demographics and baseline characterisics to be generally well balanced between the intervention and control arms, although there was a higher proportion of men in the atezoliumab arm. Clinical advice to the ERG indicated that the key baseline characteristic was disease stage as this is the key prognostic factor for outcomes in this population.

A summary of the baseline characteristics for the target population for the company's decision problem (PD-L1 ≥50% TC Stage II–IIIA) is presented below (9).

Table 9. Patient demographics and baseline characteristics for PD-L1 TC ≥50% Stage II–IIIA population, with PD-L1 TC ≥1% Stage II–IIIA population comparison

Characteristic, n (%)		PD-L1 TC ≥1% Stage II–IIIA[a]		PD-L1 TC ≥50% Stage II–IIIA[a]	
		Atezo (n=248)	BSC (n=228)	Atezo (n=115)	BSC (n=114)
Age	Median (range), y	61 (34-81)	62 (26-84)	[redacted]	[redacted]
	≥65 y	92 (37)	97 (43)	[redacted]	[redacted]
Sex	Male	171 (69)	147 (64)	89 (77)	78 (68)
Race[b]	White	162 (65)	166 (73)	[redacted]	[redacted]
	Asian	78 (31)	56 (25)	[redacted]	[redacted]
ECOG PS	0	146 (59)	133 (58)	[redacted]	[redacted]
	1	102 (41)	95 (42)	[redacted]	[redacted]
Histology	Squamous	96 (39)	85 (37)	47 (41)	45 (39)
	Non-squamous	152 (61)	143 (63)	68 (59)	69 (61)
Stage	II	131 (53)	113 (50)	62 (54)	57 (50)
	IIIA	117 (47)	115 (50)	53 (46)	57 (50)

Characteristic, n (%)		PD-L1 TC ≥1% Stage II–IIIA[a]		PD-L1 TC ≥50% Stage II–IIIA[a]	
Tobacco use history	Never	51 (21)	41 (18)	16 (14)	15 (13)
	Current/previous	197 (79)	187 (82)	99 (86)	99 (87)
***EGFR* mutation status[c]**	Positive	23 (9)	20 (9)	[redacted]	[redacted]
	Negative	123 (50)	125 (55)	[redacted]	[redacted]
	Unknown	102 (41)	83 (36)	[redacted]	[redacted]
***ALK* rearrangement status[c]**	Positive	12 (5)	11 (5)	[redacted]	[redacted]
	Negative	133 (54)	121 (53)	[redacted]	[redacted]
	Unknown	103 (42)	96 (42)	[redacted]	[redacted]

Abbreviations: ALK, anaplastic lymphoma kinase; Atezo, atezolizumab; BSC, best supportive care; ECOG PS, Eastern Cooperative Oncology Group; EGFR, epidermal growth factor receptor; PD-L1, programmed death-ligand 1; TC, tumour cell

Notes:

Some categories may add to >100% due to rounding

a23 patients in the Stage II–IIIA population had unknown PD-L1 status as assessed by SP263.

bPatients with other/unknown race are not shown.

cFor patients with non-squamous NSCLC, *EGFR/ALK* status was assessed locally or centrally.

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

Source: CS Addendum, Table 1, p.8.

3.2.3.2. Clinical effectiveness results

Data in the target population were presented for OS and DFS. The ERG considered the statistical analyses conducted in the IMpower010 trial to be broadly appropriate.

Overall survival

OS is the gold standard outcome measure for cancer trials; however, was only a secondary endpoint in the IMpower010 trial. The CS stated that OS was not formally tested, since the primary endpoint (DFS) was not statistically significant in the ITT population. However, the ERG noted that the ITT population was not the relevant population for this appraisal and the ERG noted a statistically and clinically significant difference in the DFS primary endpoint in favour of atezolizumab in both the PD-L1 ≥1% TC Stage II–IIIA and PD-L1 ≥50% TC Stage II–IIIA populations. Exploratory analysis of OS within the PD-L1 ≥50% TC Stage II–IIIA population suggested a trend in favour of atezolizumab, although statistical significance was not reached (unstratified HR 0.37 (95% CI: 0.18, 0.74)), which corresponds to a

[redacted]. The median OS [redacted], suggesting data immaturity.

The OS Kaplan-Meier (KM) curve for the PD-L1 ≥50% TC Stage II–IIIA population is shown below (Figure 2)

Figure 2. Kaplan-Meier plot of OS (PD-L1 ≥50% TC Stage II–IIIA population)

Clinical data cut-off date (CCOD): 21 Jan 2021
Clinical cut-off: 21 January 2021. Unstratified HRs are reported. CI, confidence intervals, mOS, median overall survival; NE, not evaluable.
Source: CS2 Addendum, Figure 5, p.14

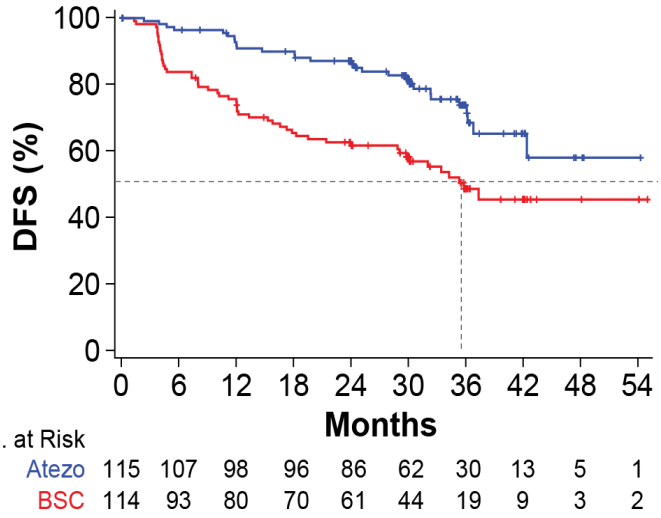
Disease-free survival

In the PD-L1 ≥50% TC Stage II–IIIA population, after a median follow-up of 34.2 months, there was a statistically and clinically significant improvement in the atezolizumab arm compared to the BSC arm. At the 21 January 2021 data cut, the proportion of patients in the atezolizumab arm who experienced disease recurrence or death was 24.3% compared to 45.6% in the BSC arm. The unstratified HR was 0.43 (95% CI: 0.27, 0.68; p = 0.0002), which corresponds to a 57% relative risk reduction of a DFS event with atezolizumab compared to BSC. Kaplan-Meier (KM)-specified median DFS was 35.7 months in the BSC arm but was not reached in the atezolizumab arm due to the low number of events. The data presented suggest that the DFS benefit for atezolizumab is greater in the PD-L1 ≥50% TC Stage II–IIIA population than in the PD-L1 ≥ 1% TC Stage II–IIIA population, for which the stratified HR was 0.66 (95% CI 0.50,

0.88, p=0.0039), representing a 34% relative risk reduction of a DFS event in the atezolizumab arm compared to BSC. However, the analytical inconsistency between the use of stratified and unstratified HR should be noted as a caveat, along with the fact that the analysis in the revised population is presented by the company as a secondary rather than primary endpoint.

The DFS KM curve for the PD-L1 ≥50% TC Stage II–IIIA population is shown below (Figure 3).

Figure 3. Kaplan-Meier plot of DFS (PD-L1 ≥50% TC Stage II–IIIA population)



Source: CS Addendum, Figure 3, p.12

The company conducted an exploratory, post-hoc analysis, in the PD-L1 TC ≥50% Stage II–IIIA population excluding EGFR/ALK positive participants (9 patients randomised to the intervention arm of IMpower010 and 11 patients randomised to the control arm). The analysis showed that whether EGFR/ALK positive patients were included or excluded, the DFS HR remained the same, with minor widening of the confidence intervals (HR 0.43, 95% CI 0.26, 0.71).[23]

Subgroup analyses

The company presented subgroup analyses from the IMpower-010 trial in the PD-L1 ≥50% TC Stage II–IIIA population, based on pre-defined subgroups by key baseline demographics, baseline clinical characteristics and biomarker status. The company reported that the effectiveness of atezolizumab was [redacted]. The clinical effectiveness in EGFR negative patients ([redacted]) than EGFR positive patients ([redacted]) shown in the PD-L1 ≥ 1% TC Stage II–IIIA population was not replicated in the PD-L1 ≥50% TC Stage II–IIIA population (EGFR positive

HR [redacted] vs EGFR negative [redacted] although there was greater uncertainty associated with the results for EGFR positive patients, with the 95% confidence interval crossing the line of no effect, potentially related to small sample size (n=14 for EGFR positive). In the PD-L1 ≥50% TC Stage II–IIIA population, the ERG considered the comparison based on ALK status to be not evaluable, given the reported [redacted] HR in the ALK positive subgroup, with the upper bound 95% CI being reported as [redacted]. In the revised target population, it is less clear to the ERG that EGFR and ALK positive patients do not benefit from atezolizumab compared to BSC.

The company claimed that the ADAURA trial[24] has "already established" osimertinib as the standard of care for EGFR and ALK positive patients. Expert clinical advice to the ERG suggested that osimertinib (approved for use through the Cancer Drugs Fund (CDF), in NICE TA761 will become standard of care for these patients, although the ERG noted that it is not available through routine commissioning. Clinical advice to the ERG noted that atezolizumab may not be used to treat EGFR+/ALK+ disease even in absence of osimertinib, owing to concerns that adjuvant immunotherapy would not be efficacious in the molecularly driven NSCLC subgroups. Therefore, since these EGFR and ALK positive patients were included in the trial and in the NICE scope and the company decision problem, the ERG considered on balance that the ERG base case analysis should, as per the company's base case, include the full PD-L1 ≥50% TC Stage II–IIIA population including EGFR and ALK positive patients.

Adverse effects

Adverse events (AEs) in the IMpower010 trial were reported in the CS Addendum (Section 1.5). These analyses were performed principally in the overall 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. However, the CS Addendum also provided certain AE data in the PD-L1 ≥50% TC Stage II–IIIA, which goes some way to resolving a potential uncertainty from the original CS regarding the relevance of the safety analyses for this appraisal. The company stated that the AE profile was comparable between the PD-L1 ≥50% TC Stage 2–3A and overall safety evaluable populations, with the most common atezolizumab-related Grade 3-4 AEs being [redacted] While data on treatment-related AEs are presented in the PD-L1 ≥50% TC Stage II–IIIA population in the CS Addendum (Table 6, pp19-20), no comparative analysis of AEs between the two arms was presented in this population.

Therefore, in comparing AEs between arms, the ERG had to rely on the overall safety evaluable population as presented in the original CS. In the overall safety evaluable population, AEs were common in both arms, but more participants encountered at least one AE in the atezolizumab arm than the BSC arm (92.7% vs 70.7%). The AEs with a 'notable difference' (≥5%) between arms were arthralgia ([redacted]), pyrexia ([redacted]), alanine aminotransferase (ALT) increased ([redacted]), aspartate aminotransferase (AST) increased ([redacted]), hypothyroidism ([redacted]), pruritus ([redacted]), rash([redacted]), diarrhoea ([redacted]) and hyperthyroidism ([redacted]), with AE rates in each case being higher in the atezolizumab arm.

3.3. Critique of trials identified and included in the indirect comparison and/or multiple treatment comparison

Following clinical effectiveness searches (see Section 3.1) and screening, the company included 50 publications reporting on 20 trials in the adjuvant setting (CS Appendix D, Table 6, pp.17-23) in its SLR, in addition to the CSR of the IMpower010 trial. The CS did not present a synthesis of these comparator trials since the company did not conduct an indirect treatment comparison (ITC).

3.4. Critique of the indirect comparison and/or multiple treatment comparison

No ITC was presented in the CS. No formal feasibility assessment for an ITC was presented. The rationale provided by the company was that the IMpower010 trial contained all relevant comparators. As discussed in Section 2.4, the ERG considered the company's exclusion of osimertinib as a comparator to be appropriate. Furthermore, osimertinib is not yet in routine commissioning in the UK for an indication relevant to this appraisal. The ERG considered that the provision of randomised head-to-head comparative evidence comparing atezolizumab and BSC was a good justification for not constructing an ITC, further noting the interpretative limitations of ITCs compared to direct comparisons. Furthermore, following NICE appraisal (TA761), osimertinib is not yet in routine commissioning in the UK and is only available through the Cancer Drugs Fund (CDF), for the adjuvant treatment of EGFR mutation-positive non-small-cell lung cancer after complete tumour resection

3.5. Additional work on clinical effectiveness undertaken by the ERG

None.

3.6. Conclusions of the clinical effectiveness section

The ERG considered that, despite identified limitations of the company's SLR e.g. a lack of clinical trial registry searches, it had identified key directly comparative evidence to inform decision making was identified. Among outcomes in the NICE final scope,[17] the ERG noted the non-collection of HRQoL data in the trial to be a limitation as no HRQoL data were available for the intervention or comparator in the target population from the trial. The ERG considered that generally the company's SLR and included trial were adequately described, although certain information was not described in sufficient detail.

There was one open-label randomised controlled trial comparing atezolizumab with BSC in people with PD-L1 ≥50% Stage II–IIIA NSCLC following resection and cisplatin-based adjuvant chemotherapy (IMpower010[15]). Atezolizumab was administered intravenously every three weeks with a dose of 1,200 mg. All other studies included in the company's SLR did not assess atezolizumab. The ERG was satisfied that the company's decision to not conduct an ITC was appropriate, given the existence of a suitable head-to-head comparative trial. Since a CDF recommendation is not a recommendation for routine use, the ERG concluded that osimertinib is not a relevant comparator for this appraisal

The ERG was satisfied that IMpower010 was generally a high-quality trial. The target population was PD-L1 ≥ 50% TC Stage II–IIIA was a subgroup of the trial population. Although this reflected a narrower population than that specified in the final scope the ERG noted that it was fully aligned with the marketing authorization. The ERG was satisfied that in the PD-L1 ≥50% TC Stage II–IIIA population there was evidence for a benefit for atezolizumab compared to BSC in terms of the trial primary endpoint DFS. The data also suggested a trend in favour of atezolizumab for OS, although statistical significance was not reached. OS was not formally tested since the primary endpoint (DFS) was not statistically significant in the ITT population. However, the ERG noted that the ITT population was not the relevant population for this appraisal and that as noted below, there was a statistically and clinically significant difference in the DFS primary endpoint in favour of atezolizumab in the relevant population for this appraisal, the PD-L1 ≥50% TC Stage II–IIIA population.

The ERG identified one key issue regarding the clinical effectiveness evidence:

- Immaturity of clinical effectiveness data in the key IMpower010 trial (see Key Issue 1)

4. COST-EFFECTIVENESS

4.1. ERG comment on company's review of cost-effectiveness evidence

The company performed systematic literature searches for (i) published cost-effectiveness studies of NSCLC with PD-L1 expression on ≥1% TC (Table 10); (ii) HRQoL studies (Table 11) and (iii) cost and resource use studies (Table 12).

Table 10. Summary of ERG's critique of the methods implemented by the company to identify cost-effectiveness evidence

Systematic review step	Section of CS in which methods are reported	ERG assessment of robustness of methods
Searches	Appendix J, Section J.2	The cost-effectiveness searches (CS, Appendix J, Section J.2) are comprehensive with a good selection of both keywords and indexed terms used (including for the drug names). A good range of sources is used. Economics search terms do not appear to have been taken from a tested search filter (such as those by CADTH[25] or SIGN[26]) and this may have affected the results.
Inclusion criteria	Appendix J (Table 20, page 335)	Broadly appropriate.[a] Broad criteria were applied. Full economic evaluations of interventions aimed at managing early-stage NSCLC receiving treatment in the adjuvant or neoadjuvant treatment settings published with no language restriction from data inception to Year 2021 were included. No restriction with regards to patient age or mutation status were applied. While not within NICE scope, studies considering people with Stage I–III disease were considered eligible during the screening process to assess the extent of evidence available.
Screening	Appendix J	Unclear. No details of methodology provided in Appendix J of CS. Study selection was documented in a PRISMA flow diagram (CS, Appendix J, Figure 11).
Data extraction	Appendix J	Unclear. No details of methodology provided in Appendix J of CS.

Systematic review step	Section of CS in which methods are reported	ERG assessment of robustness of methods
QA of included studies	Appendix J	Unclear. No details of methodology provided in Appendix J of CS.

Abbreviations: CS, Company Submission; ERG, Evidence Review Group; NICE, National Institute for Health and Care Excellence; NSCLC, non-small cell lung cancer; QA, quality assessment

Notes:

[a] A list of excluded studies was provided in Appendix J Table 21, p.340 of the CS together with reasons for exclusion

The ERG was broadly satisfied with the company's review of the cost-effectiveness literature but noted concerns regarding under-reporting of methods employed to ensure rigour, particularly screening and data extraction. The ERG was unable to evaluate if appropriate tools for trial quality assessment were chosen by the company as no detail was reported within the CS or Appendices.

The company identified full publications of 24 economic evaluations, but did not provide a summary table of these studies in the CS. The company reported that the majority of studies were cost-utility analyses reporting the cost per quality adjusted life year (QALY) gained for the interventions of interest (N=14). The company stated that the most commonly cited published sources of utility values across these studies were Doyle et al (2008) and Nafees et al (2008) but that, both of these studies report utilities for health states associated with advanced/metastatic stages of NSCLC.

The company reported that a total of 14 of the identified published economic evaluations reported use of a model but that a high level of variation was observed across the studies with regard to the selected disease states and pathways used in the models. A summary table of these studies was not provided in the CS. The company stated that the remaining 10 studies were trial-based analyses and did not report details of a model. A summary table of these studies was not provided in the CS.

Because of poor reporting, the ERG was unable to fully evaluate the company's statement that studies identified in the CS review indicated a lack of suitable utility values specifically for patients with early NSCLC for use in economic evaluations.

Table 11. Summary of ERG's critique of the methods implemented by the company to identify health related quality of life

Systematic review step	Section of CS in which methods are reported	ERG assessment of robustness of methods
Searches	Appendix K	The HRQoL searches (CS Appendix K) are comprehensive with a good selection of both keywords and indexed terms used (including for the drug names). A good range of sources is used. Utilities search terms do not appear to have been taken from a tested search filter (such as those by CADTH[25] or SIGN[26]) and this may have affected the results.
Inclusion criteria	Appendix K (Table 25, page.349)	Broadly appropriate.[a] Broad criteria were applied. Studies reporting HRQoL or utility values related to early-stage NSCLC (resectable; stage 0/I/II/III) receiving treatment in the adjuvant or neoadjuvant treatment settings. No restriction with regards to patient age or mutation status. No restriction with regards to publication date or language.
Screening	Appendix K	No detail provided. It was unclear to the ERG if screening was performed independently by two reviewers. Study selection was documented in a PRISMA flow diagram (CS, Appendix K, Figure 12).
Data extraction	Appendix K	No detail provided. The company summarised details for the identified studies (CS, Appendix K, Table 26, page 353).
QA of included studies	Appendix K	No detail provided. The company summarised details for the identified studies (CS, Appendix K, Table 26, page 353) on methods or assessment tool used.

Abbreviations: CS, Company Submission; ERG, Evidence Review Group; HRQoL, health-related quality of life; NSCLC, non-small cell lung cancer; QA, quality assessment

Notes:

[a] A list of excluded studies was provided in Appendix K Table 27, p.384 of the CS together with reasons for exclusion

The ERG was broadly satisfied with the company's review of the literature reporting health effects (health-related quality of life and utilities). The company identified 25 full publications, with utility data primarily derived from the US, Canada, and Europe (including Denmark,

Finland, France, Germany, Italy, the Netherlands, and the UK (Appendix K, Table 25, p.349). Fifteen studies reported intervention-specific utilities, but data were also reported for a range of different patient- and disease-related health states, including disease stage/status, time since diagnosis, and resectability status. The European Quality of Life-5 Dimensions (EQ-5D) was the most commonly used instrument for deriving utilities (3L version, N=11;[27-37] 5L version (N=4).[36,38-40] Utilities were derived directly from patients in all studies with the exception of Kim et al (2018)[41] which used proxy respondents; adult members of the Korean general public valued a series of vignette health states relating to patients with lung cancer.

The ERG agreed with the company's statement that only four studies met the stringent requirements of the NICE reference case (Grutters 2010,[28] Nalk 2017,[29] Sharples 2012,[30] and Khan 2016[36]) and are hence likely to be considered most appropriate for informing economic evaluations in the UK setting. In these four studies, utilities were derived directly from patients using the preferred EQ-5D-3L instrument and health states were valued using UK societal preferences elicited using the direct time trade off (TTO) method in accordance with NICE methods guidance.[42] While the ERG could not evaluate the method of quality assessment undertaken by the company due to absence of detail in the CS, the company reported that quality assessment of the included studies highlighted a number of limitations associated with the utility values reported. In particular, absence of information regarding the patient recruitment process, response rates to instruments, and missing data are likely to restrict the usefulness of the studies for informing economic evaluations.

Table 12. Summary of ERG's critique of the methods implemented by the company to identify healthcare resource use and costs

Systematic review step	Section of CS in which methods are reported	ERG assessment of robustness of methods
Searches	Appendix L	The searches (CS Appendix L) were well conducted with a good range of index and keyword terms used (including for the drug names) and a wide range of sources searched. The search filter does not appear to be a tested published filter (such as those by CADTH[25] or SIGN[26]); this may have affected the results.
Inclusion criteria	Appendix L (Table 32, p.393)	Appropriate [a.] Broad criteria were applied. The company included studies reporting healthcare costs and/or resource use for patients with early-

Systematic review step	Section of CS in which methods are reported	ERG assessment of robustness of methods
		stage NSCLC (resectable; stage 0/I/II/III) receiving treatment in the adjuvant or neoadjuvant treatment settings – no restriction with regard to patient age or mutation status. Studies published in English language from data inception to Year 2020 were included.
Screening	Appendix L	No detail provided. It was unclear to the ERG if screening was performed independently by two reviewers. Study selection was documented in a PRISMA flow diagram (CS, Appendix L, Figure 13).
Data extraction	Appendix L	No detail provided.
QA of included studies	Appendix L	No details of methods or assessment tool provided.

Abbreviations: CS, Company Submission; ERG, Evidence Review Group; NSCLC, non-small cell lung cancer; QA, quality assessment

Notes:

[a]Pre-defined PICOS selection criteria (CS, Appendix L, Table 32) were applied. A mapping of excluded studies together with reasons for exclusion were provided in a PRISMA flow diagram (CS, Appendix L, Figure 13). Excluded studies were summarised in Appendix L, Table 34, p.455.

The ERG was broadly satisfied with the company's review of the literature reporting healthcare resource use and costs. Overall, 102 publications which met the eligibility criteria of the review were identified for final inclusion (full publications, N=73). Given the volume of evidence identified, studies presented as full publications, with a sample size >200 patients, and reporting data for a priority country of interest (i8 countries [UK, France, Spain, Canada, Australia, Brazil, Germany and Italy], China, South Korea, Japan, and the US) were prioritised for data extraction and are the focus of the CS (N=40) (Appendix L, Table 33). The ERG was broadly in agreement with this approach.

The majority of studies reported direct medical cost data and the economic burden of early-stage NSCLC (N=32). The company identified only two studies which reported indirect cost data associated with patients with early NSCLC (Andreas 2018[43] and Zhang 2020[44]).

The company identified a total of 14 studies that reported resource use data associated with patients with early NSCLC.

While the ERG noted quality assessment methods were not described by the company, the company reported that they performed a quality assessment of the 40 studies identified in the literature review. They reported that studies generally had well defined objectives and presented results consistently with the methodologies adopted. However, very few studies conducted sensitivity analyses to test the robustness of major assumptions (N=3) and it was often unclear if costs were appropriately discounted.

The ERG noted that there was no discussion of the applicability of the identified study to the economic model within the CS.

4.2. Summary and critique of company's submitted economic evaluation by the ERG

4.2.1. NICE reference case checklist

Table 13. NICE reference case checklist

Attribute	Reference case	ERG comment on company's submission
Perspective on outcomes	All direct health effects, whether for patients or, when relevant, carers	✓ No comment
Perspective on costs	NHS and PSS	✓ No comment
Type of economic evaluation	Cost–utility analysis with fully incremental analysis	✓ No comment
Time horizon	Long enough to reflect all important differences in costs or outcomes between the technologies being compared	✓ A lifetime horizon is suitable for decision making in the context of a potentially life-extending therapy
Synthesis of evidence on health effects	Based on systematic review	✓ No comment
Measuring and valuing health effects	Health effects should be expressed in QALYs. The EQ-5D is the preferred measure of health-related quality of life in adults.	As no HRQoL data were collected in the pivotal IMpower010 study, the company sourced HRQoL data and utility estimates from their systematic review of the published literature. Most but not all of the patient utility estimates informing the company's base case are based on EQ-5D data, as documented in Section 4.2.7 of this report.
Source of data for measurement of health-related quality of life	Reported directly by patients and/or carers	Most but not all of the literature-sourced patient utility estimates

Attribute	Reference case	ERG comment on company's submission
		informing the company's base case are based on NSCLC-patient-reported HRQoL questionnaire data, as documented in Section 4.2.7 of this report.
Source of preference data for valuation of changes in health-related quality of life	Representative sample of the UK population	Only in the minority of studies informing the company's base case patient utility assumptions is it clear that the approach to valuation is based on preference data from a representative sample of the UK population, as documented in Section 4.2.7 of this report.
Equity considerations	An additional QALY has the same weight regardless of the other characteristics of the individuals receiving the health benefit	✓ No comment
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	✓ No comment
Discounting	The same annual rate for both costs and health effects (currently 3.5%)	✓ No comment

Key: EQ-5D, EuroQol 5 dimension; HRQoL: health-related quality of life; NHS, National Health Service; NSCLC, non-small cell lung cancer; PSS, Personal Social Services; QALY: quality-adjusted life year; TA: technology appraisal

4.2.2. Population

The company's 31 January 2022 submission of additional evidence focusses on the MHRA-approved use of atezolizumab as adjuvant treatment following complete resection for adult patients with Stage II to IIIA (per UICC/AJCC staging system 7th edition) non-small cell lung cancer (NSCLC) whose tumours have PD-L1 expression on ≥50% of tumour cells (TC) and whose disease has not progressed following platinum-based adjuvant chemotherapy.

Evaluation of DFS in the PD-L1 ≥50% TC Stage II–IIIA population was a secondary efficacy objective of IMpower010[15]. Patient baseline characteristics, treatment duration data and treatment effectiveness data from this subgroup are key input data for the company's January 2022 economic analysis.

The company's additional evidence submission (CS Addendum) presented post-hoc subgroup analysis of DFS in the PD-L1 ≥50% TC Stage II–IIIA population, excluding patients with confirmed EGFR+ or ALK+ disease (9 patients randomised to the intervention arm of IMpower010 and 11 patients randomised to the control arm). The additional evidence submission also presented a subgroup cost-effectiveness analysis using these data. Expert clinical advice to the ERG suggested that osimertinib (approved for use through the Cancer Drugs Fund (CDF), in NICE TA761 Osimertinib for adjuvant treatment of EGFR mutation-positive non-small-cell lung cancer after complete tumour resection, guidance published 19 January 2022)[11] will become standard of care for these patients. Further, clinical advice to the ERG noted that adjuvant atezolizumab may not be used to treat EGFR+/ALK+ disease even in absence of osimertinib, owing to concern that adjuvant immunotherapy may increase the risk of side effects from subsequent TKI treatment, though this is something the clinical community are not yet aligned on. Nevertheless, as a CDF recommendation is not a recommendation for routine use, the ERG concluded that osimertinib is not a relevant comparator for this appraisal.

On balance, given the decision problem and focus of the company's additional evidence submission, the ERG's review focuses on the company's evidence for the whole MHRA-approved population, including those patients with EGFR+/ALK+ disease.

4.2.3. Interventions and comparators

The intervention in the company's economic analysis is atezolizumab 1,200 mg every 21 days, for a maximum of sixteen 21-day cycles.

The analysis assumed with certainty that exactly one 1,200 mg vial of atezolizumab is administered at each visit. Independent advice to the ERG from one hospital pharmacist reassured the ERG that there are very few instances where a second atezolizumab vial is required in its currently approved indications, but such instances do occur. From June 2016 to the date of correspondence, 09 November 2021, the advising pharmacist's unit had recorded three uses of a second atezolizumab vial to remake a batch for a patient, in each case due to particles. This pharmacist reported making around 45 atezolizumab batches each year. Taking the period 01 June 2016 to 09 November 2021 inclusive, the time-period in question is 1,987 days, or 5.44 years (to 2 decimal places (2dp)). The estimated number of remakes per year, or per 45 batches, is three vials / 5.44 (2dp) years = 0.55 (2dp) vials, and the expected number of vials per administration is one vial + 0.55 (2dp) vials / 45 batches = 1.012 (to four significant figures (4sf)) vials.

In IMpower010[15] and in the company's analysis, not all patients who received atezolizumab adjuvant treatment completed all 16 cycles of atezolizumab, owing to "*AEs, relapse or other reasons*", according to the CS (p115). In the PD-L1 ≥50% TC Stage II–IIIA group, there were discontinuations [redacted], and by Cycle 16, [redacted] of those randomised to atezolizumab remained on-treatment. By contrast, the Kaplan-Meier estimate of DFS at this point is 95.5% (1dp). The company use the time-to-treatment-discontinuation data to inform treatment acquisition cost assumptions in the analysis, but otherwise assumed that when a patient discontinues treatment early, the patient is no different to a patient who completes the intended 16 cycles of treatment, in terms of their quality of life, disease management costs and long-term prognosis, unless a DFS event occurs. Independent clinical advice to the ERG is reassuring in that they do not see stopping early as predictive of worse long-term prognosis, from experience with immune-checkpoint inhibitors in non-adjuvant settings.

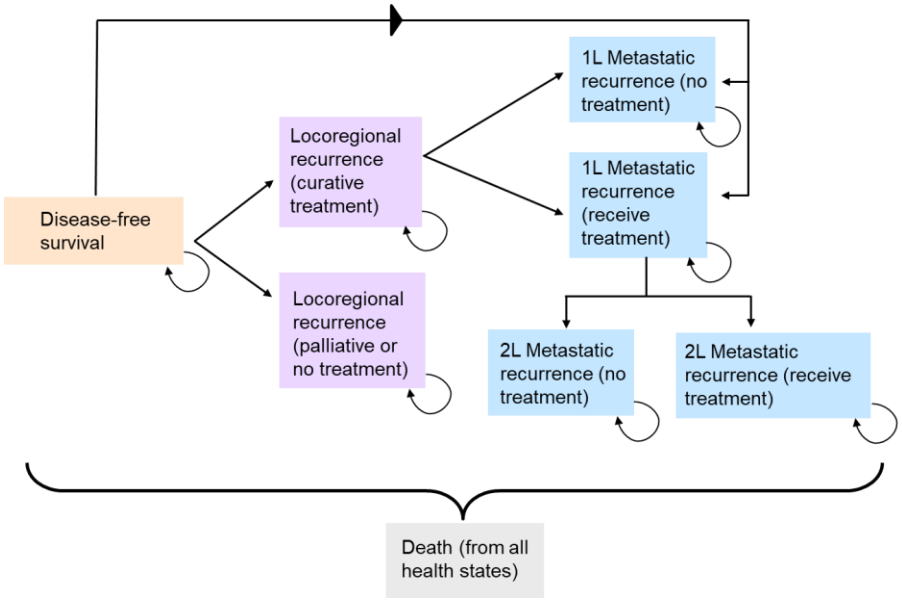
The comparator arm of the analysis, termed best supportive care (BSC) and described as active monitoring in the CS (p68), contains no active adjuvant treatment. Tumour assessment was carried out at baseline and every four months in Year 1, then every six months through Years 2-5, until disease recurrence, across both arms of IMpower010 (CS, p29). As such, no treatment acquisition or administration costs are included in the BSC arm in the adjuvant, disease-free stage of the analysis. Later in the disease pathway, active treatment assumptions differ by model arm and have important implications for the predicted cost-effectiveness of atezolizumab, as covered in the following sections of this report.

4.2.4. Model structure and logic

The company's economic analysis comprises a *de novo*, cohort-level, discrete-time model, which the company describe as a Markov model with five health states (CS Section B.3.2.2). Figure 4 replicates the model schematic the company use to characterise the model in the CS (CS Figure 9, Section B.3.2.2). Colour-coding is used in Figure 4 to differentiate between what the company describe as the five health states in the model: disease-free survival; locoregional recurrence; 1st metastatic recurrence; 2nd metastatic recurrence; and death. As visible from Figure 4, three of the company's health states; locoregional recurrence, 1st metastatic recurrence and 2nd metastatic recurrence; are partitioned by treatment pathway status. As described above though not visible in the company's diagram, the other alive health state in Figure 4; DFS; is partitioned by treatment status in the atezolizumab arm for costing purposes only. Importantly, and not indicated by Figure 4, some key transition probability parameters and assumptions around care and treatment received after leaving the DFS health state are

assumed to differ by model arm. Also not indicated by Figure 4, and described in more detail in Section 4.2.8 of this report, the company assumed a terminal care cost applies to some but not all patients upon entry to the death state, with a lower proportion of the cohort on the atezolizumab arm of the model incurring this cost.

Figure 4. Company's model schematic (CS Figure 9)



The cohort enters the model in the DFS state, in each model arm. Each model cycle is one month (1/12 of one year) long. The proportion of the cohort who remain in this state each model cycle varies with time, according to the company's chosen extrapolations of DFS Kaplan Meier data from PD-L1 ≥50% TC Stage II–IIIA patients in IMpower010, and post-hoc adjustments to these extrapolations, as described and critiqued in Section 4.2.6 of this report. For the proportion of the cohort leaving the disease-free survival state in each cycle, unless the age-dependent general population-equivalent probability of death is greater than that implied by model calculations, the sub-proportions moving to each of the possible locoregional recurrence, metastatic recurrence and death states is determined by (i) time-invariant estimates of the probability of death, for each arm, (with the time-variant remainder of DFS event probability each arm assumed to represent non-death DFS event probability), (ii) time-invariant estimates of the relative likelihood of locoregional versus metastatic recurrence, for each arm, (iii) time-invariant assumptions about the proportion of locoregional and metastatic recurrences that will receive active / curative treatment. This too is explained and critiqued in Section 4.2.6, but noted here to highlight a key characteristic of the company's chosen approach: all transitions between

health states bar a proportion of those from the disease-free survival state are assumed to be time-invariant.

Partly, though notably not for the probabilities described in the previous paragraph, the time-invariant nature of much of the company's analysis is related to the cohort-level approach chosen by the company. In cohort-level analyses such as the company's, it is burdensome to track time from any event that is not time-invariant with model start to any subsequent event. In the CS, the company justify their chosen model structure with reference to feedback from oncologists and health economists, in contrast to "the traditional three-state model", and cite its consistency with the model structure that informed the now completed osimertinib appraisal, TA761[12]. However, though comparable in terms of model health states, the model for TA761 allows locoregional and distant metastasis health state event risks to vary with time since health state entry, using tunnel states[12]. Therefore, the submitted model for this appraisal differs from, and relies on stronger assumptions than, the TA761 model.

The ERG requested further justification of the company's model type and structure in clarification question B1; in particular, the cohort-level, discrete-time nature of the company's cost-effectiveness model (and "traditional three-state models"), versus other available model types. In reply, the company recognised that an individual-level approach may have improved the accuracy of model results.

The flow of the model is generally progressive. Transitions are possible to worse alive states and death, with a logical exception that 2nd metastasis states can only be entered via 1st metastasis states. A less logical exception illustrated in Figure 4 is that the proportion of the cohort in the "locoregional recurrence (palliative or no treatment)" are assumed to be unable to experience metastatic recurrence. The ERG requested justification of this assumption. In reply, the company suggested that this assumption only implies that patients in the locoregional state cannot receive metastatic disease treatment, as the probability of death estimate they select (described and critiqued in Section 4.2.6.3) for this health state "*may have experienced metastasis before death*" (company response to clarification question B3). The ERG reiterated that the company assume that the proportion of the cohort in the "locoregional recurrence (palliative or no treatment)" can only (i) experience the health-related quality of life and costs associated with this state, or (ii) enter the death state. The assumption that these patients have zero probability of experiencing the health-related quality of life and costs associated with metastatic disease is a strong structural assumption chosen by the company.

4.2.5. Perspective, time horizon and discounting

The perspective of the company's analysis is that of the NHS and PSS on costs and that of patients on health effects, in line with the NICE reference case, though the perspective on health effects is not stated in the CS (Section B.3.2.7).

The analysis calculates results over a lifetime horizon, as is appropriate for a potentially life-extending treatment. Specifically, the time horizon of the company's base case analysis is set to 40 years. From a starting age of 61.2 years (the mean baseline age of the IMpower010 PD-L1 ≥50% TC Stage II–IIIA patient group), such an analysis would track the cohort to age 101.2 years. In the model, however, Markov trace calculations track the cohort for a maximum 473 cycles, or 39.42 years (2dp), taking the cohort to age 100.62 years (2dp). By this point in the company's base case analysis, >99.8% of the atezolizumab cohort and >99.9% of the BSC cohort have entered the death state.

The company discounted cost and health outcomes at 3.5% per annum, in line with the NICE reference case. We note that the company change the discount rate at the start of every year in the model, as opposed to every cycle (month). The company apply the 3.5% per annum discount rate to total life year (LY) calculations reported in the CS, as well as total QALY calculations. This is noted as LY predictions, unlike QALY predictions, are seldom thought of as implicitly discounted for time preferences: for this reason, total LY results presented in the CS are not analogous to the company's life expectancy estimates for patients with or without atezolizumab adjuvant treatment.

The company applied a half-cycle correction to predicted health state membership over time, "to mitigate bias and [assume] transitions across health states occur mid-cycle on average" (CS, Section B.3.2.4). Though not stated in the CS, half-cycle correction is not applied to treatment cost calculations in the disease-free survival state. Whether a half-cycle correction is appropriate for these treatment calculations is not straightforward, as the treatment cycle length (21 days) is misaligned with the company's chosen cycle length (30.44 days (2dp)). Nevertheless, with the company's application of discount rates every year rather than every cycle, no discounting is applied to costs in the first 12 model cycles, by which point the 48-week atezolizumab treatment schedule is complete.

4.2.6. Treatment effectiveness and extrapolation

4.2.6.1. Overall approach

The company stated that the primary data source for the economic model are data from the IMpower010 trial (CCOD: 21 January 2021) (CS, Document B, Section B.3.3.1). More specifically, patient baseline characteristics, duration of treatment data and DFS data from the target Stage II–IIIA, PD-L1 TC ≥50% subgroup of IMpower010 are used, and DFS data and assumptions are a key driver of cost-effectiveness results in the company's model.

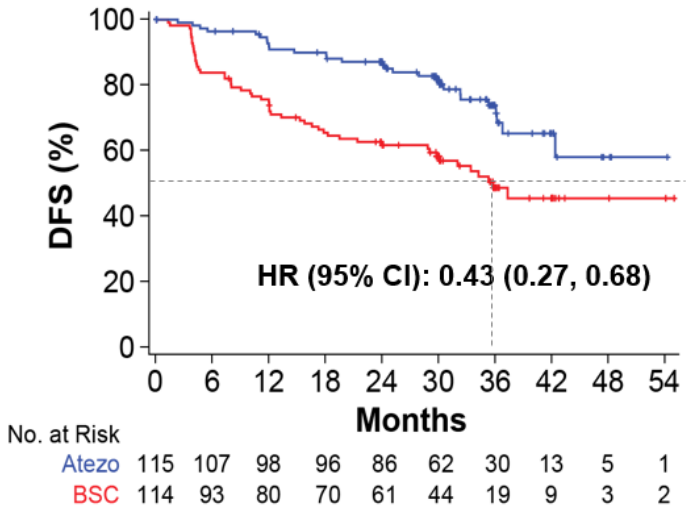
Importantly, and as described across Sections 4.2.6.2, 4.2.6.3 and 4.2.6.4 below, in some instances in their preferred analysis, the company opted not to use available data from IMpower010. As a result, other external data sources and assumptions comprise important data sources for the company's model, alongside IMpower010 DFS data.

4.2.6.2. Disease-free survival

The company's approach to modelling lifetime DFS across model arms is important for the company's cost-effectiveness results. As shown in Section 5.1, the company's base case results predict that adjuvant atezolizumab treatment will provide a mean patient benefit of [redacted] incremental QALYs (discounted, reported to 2dp). This is based on an estimated [redacted] incremental QALY gain in the DFS model state, offset partially by an estimated [redacted] QALY loss in post-DFS model states (all estimates discounted, and reported to 2dp).

Figure 5, reproduced from Figure 4 of the company's additional evidence submission, shows the IMpower010 DFS KM data for the patient group in question. The company took what they summarised as a five-step approach to analyse, adjust and validate these data, before using the resulting projections to inform health state membership over time in the cost-effectiveness analysis. The company summarise this approach in a box, reproduced as Figure 6 below. As per the company's own description, the first step – parametric survival analysis – cited NICE DSU guidance.[45] The remaining four steps do not, and Steps 3 and 4 are notably nonstandard. This subsection next describes and critiques the company's approach to capture long-term DFS projections in the cost-effectiveness model, starting from analysis of the KM data in Figure 5.

Figure 5. (CAES Figure 4): Kaplan-Meier plot of DFS (PD-L1 ≥50% TC Stage II–IIIA subgroup)



PD-L1 TC ≥ 50% Stage II-IIIA		
	Atezo (n=115)	BSC (n=114)
mDFS,	NE	35.7
DFS HR (95% CI)	0.43 (0.27, 0.68)	

Abbreviations: Atezo, atezolizumab; BSC, best supportive care; CI, confidence interval; CAES, company additional evidence submission; DFS, disease-free survival; HR, hazard ratio; NE, not evaluable; PD-L1, programmed cell death ligand 1; TC, tumour cells

[a] Per SP263 assay. [b] Stratified log-rank. [c] Crossed the significance boundary for DFS.

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

Figure 6. CS (Document B, Section B.3.3.4) summary of approach to (analyse), adjust and validate Figure 5 DFS KM data

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**
4. **Introduced a ramping-up period to address the unrealistic "kink" in the DFS curve**
5. **Validated cure assumption survival outputs with identified literature and UK clinical expert opinion**

Abbreviations: DFS, disease-free survival; KM, Kaplan-Meier; NICE, National Institute for Health and Care Excellence

Implementation and interpretation of parametric survival analysis

The company assessed the validity of a proportional hazards (PH) assumption for the DFS KM data in the original submission (the PD-L1 ≥1% TC Stage II–IIIA subgroup equivalent of Figure 5) using visual interpretation of a log-cumulative hazard plot (CS, Figure 10), concluding that a PH assumption could not be safely assumed to hold. Based on this, the company fitted seven parametric models to data from each treatment arm separately. The seven models chosen comprise the six that NICE DSU Technical Support Document (TSD) 14 advises should be considered[45](exponential, Weibull, Gompertz, log-logistic, log-normal and generalised gamma) and the gamma model.

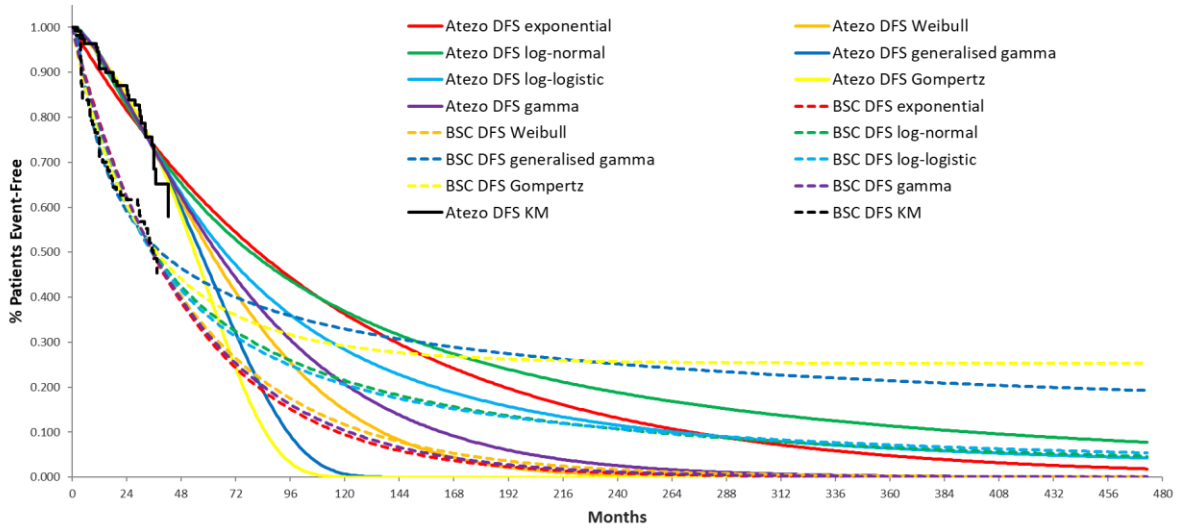
In the January 2022 additional evidence submission, the company took an equivalent approach to analyse PD-L1 ≥50% TC Stage II–IIIA subgroup DFS data, providing corresponding cumulative hazards and Q-Q plots as appendix data, without interpretation. The company implicitly assume that structural assumptions assumed for PD-L1 ≥1% TC Stage II–IIIA DFS projections in the November 2021 CS hold for the MHRA-approved PD-L1 ≥50% TC Stage II–IIIA patient group.

The PD-L1 ≥50% TC Stage II–IIIA subgroup DFS KM data and parametric model fits are shown, across the analysis time horizon of ~40 years, in Figure 7. In Figure 7, BSC arm data are indicated with dashed plot lines, while atezolizumab arm data are shown with continuous plot lines, and KM data and parametric model types are colour-coded. The ERG created Figure 7 from data in the company's economic model.

As an aside, the ERG notes that the company did not consider an accelerated failure time (AFT) model incorporating a treatment effect, but we accept that TSD14 does not offer strong guidance to do so.[45] The ERG noted that nowhere in the company's original submission dossier were parametric model fits to KM data from both arms of IMpower010 shown on the same axes.

Across each parametric model function, visual fit to the observed KM data is fairly good, and long-term extrapolations converge across treatment arms over time. For generalised gamma and Gompertz models, convergence is most rapid, with the BSC projection crossing the respective atezolizumab projection within five years of time zero in each case. As Figure 7 shows, the generalised gamma and Gompertz fits to BSC KM data have more favourable long-term projections than any atezolizumab model tested.

Figure 7. Parametric model fits to IMpower010 DFS KM data (PD-L1 ≥50% TC Stage II–IIIA subgroup)



Abbreviations: Atezo, atezolizumab; BSC, best supportive care; DFS, disease-free survival; KM, Kaplan-Meier; PD-L1, programmed cell death ligand 1; TC, tumour cells

The company assessed the goodness of fit of each model to the observed PD-L1 ≥1% TC Stage II–IIIA subgroup data visually and using Akaike and Bayesian Information Criteria statistics, concluding that for the observed period, "*there was no clearly best fitting distribution*" (CS, p71). The ERG noted the immaturity of the submitted (21 January 2021 database lock) IMpower010 DFS data. In the company's January 2022 additional evidence submission, the company implicitly assume the approach taken and inference drawn for PD-L1 ≥1% TC Stage II–IIIA subgroup data holds true in the smaller PD-L1 ≥50% TC Stage II–IIIA subgroup.

For interpretation of plausible extrapolations, the company referred to the literature. On page 73 of the CS (Document B), the company write both "*these parametric curves […] underestimated DFS as observed in the literature*" and "*There is a paucity of literature available reporting DFS in patients with early NSCLC*". The ERG struggled to follow the company's logic here: if there is insufficient published data on DFS in early NSCLC to draw conclusions, how can the company conclude that their own DFS results are drawn into question by the published data?

The process by which the company obtained studies for DFS extrapolation through "*focussed literature searching*" (CS, Section B.3.3.3.5) was not clear to the ERG; the company's

identification and selection strategy was not documented. It was not clear whether any searches were carried out for registry data or cohort studies.

The company cited only one study that reports DFS data in patients with resected NSCLC, albeit a review of large trials; a 2008 publication from Pignon et al[46] evaluating postoperative cisplatin-based chemotherapy in patients with NSCLC. The stated aim of the study was to "identify treatment options associated with a higher benefit for groups of patients who particularly benefit from postoperative chemotherapy", through a pooled analysis of published trial data.[46] The company report that the authors provide five-year DFS and OS estimates of approximately 40% and 55%, respectively, presumably from Pignon et al's Figure 2, although this is not stated in the CS. The company did not note that 38% of the Pignon et al chemotherapy group sample (856 of 2,281 patients) had Stage IA or IB NSCLC at baseline,[46] omitting a prognostic comparison between patients in the relevant arms of the component studies of Pignon et al and relevant patients from IMpower010.

With reference to Pignon et al[46] and other studies that report OS data but no DFS data, the company concluded that the literature supported a five-year DFS for the BSC arm of around 40–50%. The ERG found this conclusion to be optimistic, given the evidence the company present; in particular, given the presence of Stage IA and IB patients in Pignon et al, and importance of disease staging as a prognostic factor. The KM estimate of BSC DFS at the end of the observed PD-L1 ≥50% TC Stage II–IIIA IMpower010 data is 45.2%, at 37.29 months. The company's parametric survival extrapolations of the IMpower010 BSC data shown in Figure 7 project five-year DFS estimates of between 30.8% (exponential) and 42.8% (generalised gamma). The ERG observe that the company report identifying one study providing DFS evidence in post-operative NSCLC, and that this somewhat dated study predicts five-year DFS of around 40%, with a sample in which 38% of patients had Stage IA or IB NSCLC at baseline.

Overall, the ERG concluded that the company had identified limited published data for validating DFS projections, but that the evidence from Pignon et al[46] is broadly consistent with the five-year estimates from BSC parametric survival models tested, bar the generalised gamma projection. That is, active monitoring only for post-operative, post-chemotherapy Stage II–IIIA NSCLC is predictive of five-year DFS below 42.8%, but probably greater than 30.8%.

***Post-hoc adjustments to parametric survival* extrapolations**

Imposition of a cure assumption

The company cited Sonoda et al. (2019)[47] which they used to inform a stated assumption that 91.5% of patients who are estimated to remain in the DFS state after five years can be considered cured. The company do not state how they identified Sonoda et al. (2019), nor do the company state any of the sample characteristics or study design of Sonoda et al. (2019). The company's description of Sonoda et al. (2019)[47] is limited to the following passage:

"*Sonoda et al. 2019(97) showed that approximately 6% of recurrences occurred after five years [...] The study also reported that an additional 2.5% [of] patients developed a recurrence after 10 years ("ultra-late recurrences"). This suggests that the cure probability is approximately 91.5%*" (CS, Document B, p75).

The ERG observed that Sonoda et al. (2019) aimed to analyse "the features of ultra-late recurrence in cases with NSCLC who had undergone curative resection",[47] using data from 1,458 consecutive cases treated in one hospital in Tokyo, Japan, between January 1990 and December 2006, inclusive. The ERG noted that the median follow-up across the Sonoda et al. (2019) sample was 10.1 years post-resection.[47] Other prognostic sample characteristic differences and clinical setting differences between the Sonoda et al. (2019)[47] sample setting and contemporary NHS England practice notwithstanding, the ERG are particularly concerned that 53% of the Sonoda et al. (2019) sample (768 patients) are reported as having Stage I disease.[47] Overall, the ERG concluded that the company has not provided sufficiently considered justification for the assumption that 91.5% of patients who remain disease-free for five years post-resection and post-adjuvant chemotherapy are no longer at risk of disease recurrence or disease-related mortality.

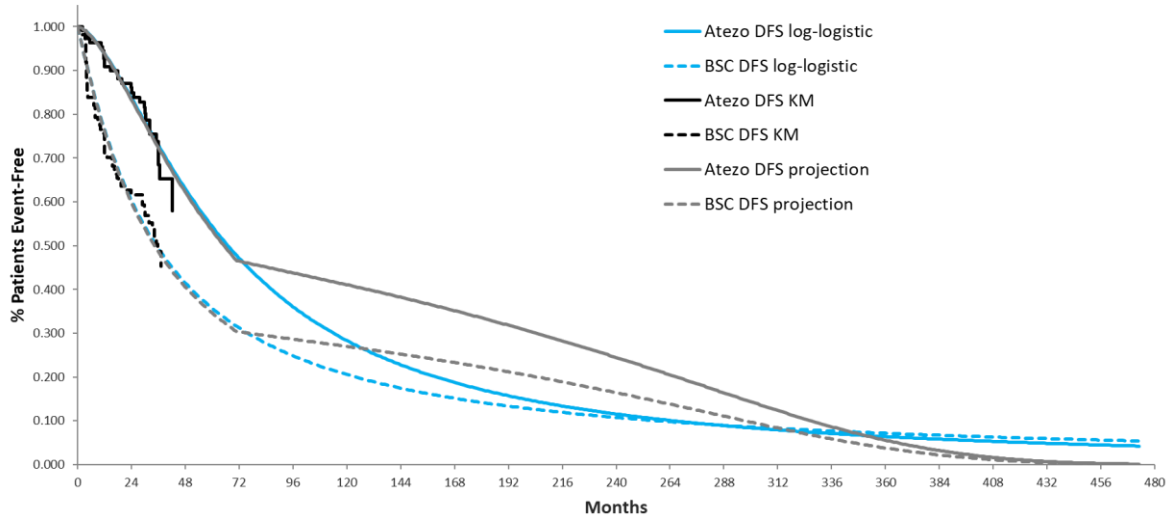
Use of general population-equivalent survival data

The company applied mortality adjustments to limit the minimum cycle probability of death to that of the age-equivalent cycle probability of death, using 2017–2019 Office for National Statistics life table data.[48] The company also used these data to inform the cycle probability of death for the proportion of the cohort in the DFS state they assume to be cured. The company apply a standardised mortality ratio (SMR) adjustment of 1.25 to general population mortality estimates when applied to cycle survival probabilities in the DFS state, based on a 2012 study of patients with Stage I-III disease.[49] Notably, the company did not apply this adjustment when

using the ONS general population data to limit the minimum cycle probability of death in post-DFS health states, so the minimum possible probability of death in each model cycle was lower (more favourable) in post-DFS health states than in the DFS state. The ERG queried this in clarification question B29. In reply, the company acknowledged the inconsistency, and noted that applying the adjustment to all minimum cycle death probability limits had a minimal impact on the (company's) ICER. In the company's January 2022 additional evidence submission base case, shown in Section 5 of this report, the inconsistency is corrected.

After application of the cure assumption and general-population-equivalent mortality caps described above, the DFS projections for atezolizumab and BSC arms are substantially altered from those shown in Figure 7. The company used log-logistic model fits to the DFS data as a starting point in their base case; the KM data and log-logistic extrapolations shown in Figure 7 are reproduced (by the ERG) in Figure 8 alongside the equivalent projections with the company's cure assumption and general population mortality caps applied. As Figure 8 shows, the company's base case analysis assumes 91.5% of the DFS state are "cured" at six years, not five years (as stated in the CS). The ERG assumed this was a modelling error, and that the company intended to assume 91.5% of the DFS state are cured five years from baseline. This is referred to as ERG correction to the company base case #1 in Section 6.1 of this report.

Figure 8. Cure assumption-adjusted log-logistic DFS projections alongside unadjusted log-logistic DFS extrapolations from Figure 7

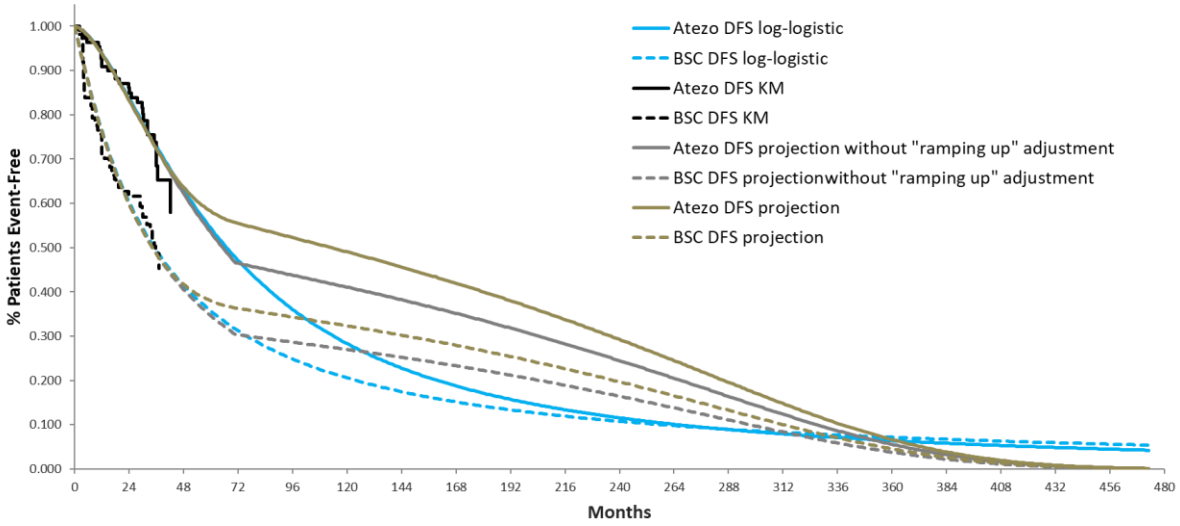


Abbreviations: Atezo, atezolizumab; BSC, best supportive care; DFS, disease-free survival; KM, Kaplan-Meier

"Ramping up" adjustment

The company next inflated DFS, starting three years before assumed cure point, a post-hoc adjustment described as a "Ramping up" adjustment "to address the unrealistic "kink" in the DFS curve" (CS, Document B, p68, p76-77). Specifically, the company linearly increased the proportion of the DFS sub-cohort assumed to be cured from 0% at Cycle 36 (the 37th cycle / month of the model) to 91.5% at Cycle 72. The effect and its implications for lifetime DFS projections across model arms are substantial and not limited to the period between Cycles 36 and 72, as illustrated in Figure 9. The ERG found no justification for this inflation of lifetime DFS projections across model arms and noted that the visual implications of the company's "ramping up" adjustment were not presented in isolation anywhere in the CS.

Figure 9. Implications of the company's "ramping up" adjustment to Figure 8 DFS projections



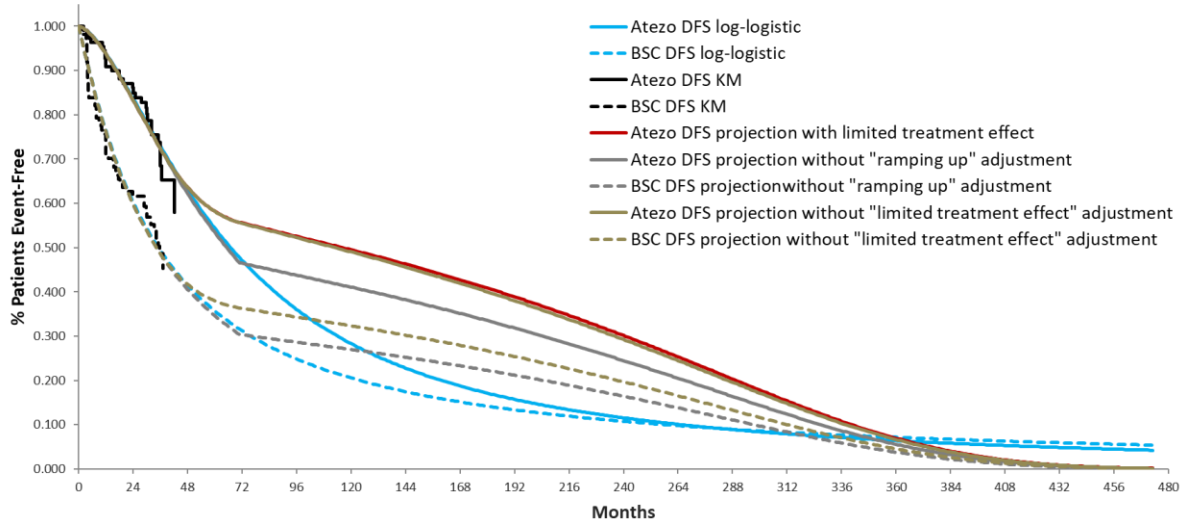
Abbreviations: Atezo, atezolizumab; BSC, best supportive care; DFS, disease-free survival; KM, Kaplan-Meier

Treatment effect duration adjustment

The company's final post-hoc adjustment to DFS projections informing the analysis is, , to "*allow[…] the treatment effect of atezolizumab to decrease over time*" (CS, p77). In application, the company set the cycle probability of a DFS event on the atezolizumab arm equal to the estimated cycle probability of a DFS event on the BSC arm, from Cycle 60 onwards. The company justify this adjustment as aligned with assumptions in previous appraisals in NSCLC (CS, p77). Figure 10 contains its implications for the atezolizumab DFS projection: the lifetime DFS projection is slightly inflated, indicated by slight red upper shading to the gold DFS

projection without the treatment effect adjustment. This is contra to the expected implication of a treatment-effect-limiting adjustment: it enhances the projected lifetime treatment effect, rather than reducing it. The reason for this is in the observed KM data and parametric model fits to these data; the KM data initially separate across arms before this trend starts to reverse. As noted above in interpretation of all Figure 7 extrapolations, long-term log-logistic extrapolations converge across treatment arms over time. This trend results in the cycle probability of a DFS event becoming lower on the BSC arm model arm than the atezolizumab model arm, from model Cycle 58 onwards: two cycles before the treatment effect adjustment is applied. As such, the company's treatment effect duration adjustment slightly improves the estimated DFS projection for atezolizumab, for every cycle in which it is imposed in the company's base case. Overall, the ERG found the company's presentation of their chosen treatment effect adjustment misleading.

Figure 10. Implications of the company's "limited treatment effect" adjustment to Figure 9 DFS projections



Abbreviations: Atezo, atezolizumab; BSC, best supportive care; DFS, disease-free survival; KM, Kaplan-Meier

Final curve selections

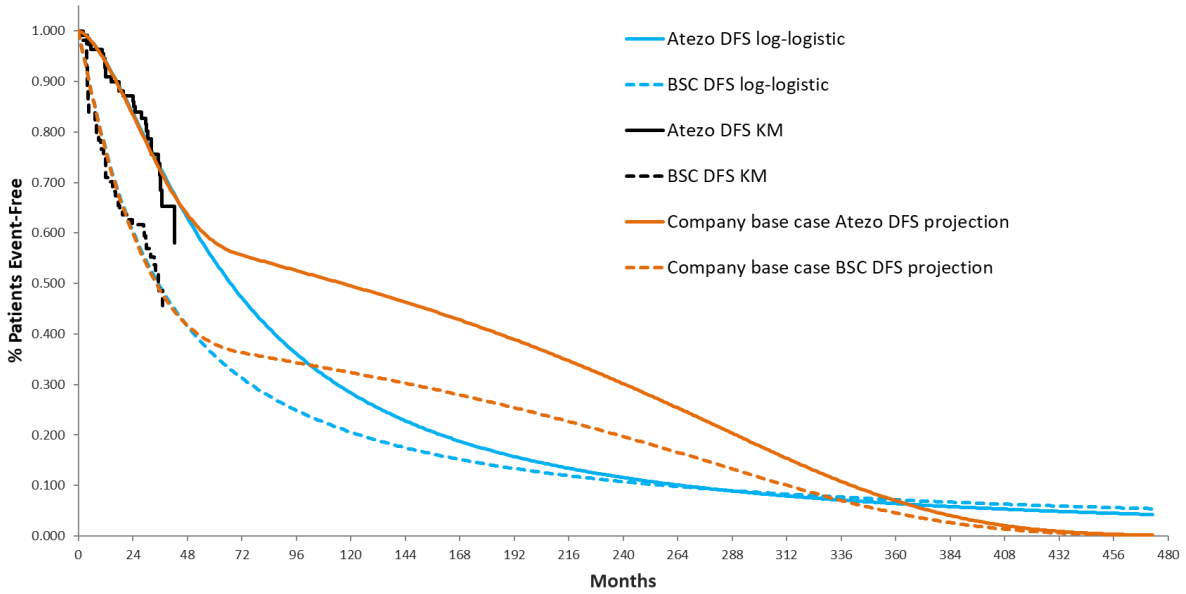
The company's January 2022 additional evidence submission (CS Addendum) curve selection logic was unchanged from that applied to the PD-L1 ≥1% TC Stage II–IIIA data in the CS. Based on the company's interpretation of expected survival for the affected patient group in absence of adjuvant atezolizumab treatment, the company dismissed the generalised gamma and Gompertz models as overly optimistic and dismiss the exponential, Weibull and gamma models as overly pessimistic, selecting the log-logistic extrapolations shown in blue in Figure 10

as one of two “clinically plausible options” (CS, Document B, p85). Yet, from this point, as discussed and illustrated above, the company diverged from standard log-logistic extrapolations through various weakly justified post-hoc adjustments that improve the absolute and relative DFS projection for atezolizumab. The ERG was not convinced by the company’s step-by-step divergence from standard parametric extrapolations, and do not find the company’s interpretation of the highly limited published data identified to be reasonable.

In the CS, the company reported seeking clinical oncologist advice on survival expectations but did not report any details of how this advice was elicited. In response to clarification question B23, the company provided presentation slides and meeting reports for various engagement meetings held with clinical and health economic experts from April 2021 to August 2021. Expert selection and elicitation processes for these meetings remained unclear, and importantly, it was not clear whether the invited experts reviewed and approved meeting reports after each meeting. However, despite these limitations, the details provided are useful.

Overall, the ERG found the company’s post-hoc adjustments to NICE DSU TSD-recommended parametric survival modelling and choice of final DFS projection to be poorly justified, and note that each post-hoc adjustment - bar the standard practice of limiting survival chances to be no better than the age-equivalent general population - inflates the absolute and relative lifetime DFS projection for the atezolizumab arm of the model. The company’s January 2022 base case DFS projections are shown in orange in Figure 11 alongside the PD-L1 ≥50% TC Stage II–IIIA DFS KM data and standard log-logistic fits to those data.

Figure 11. Company base case DFS assumptions, alongside associated KM data and unadulterated log-logistic fits to those data



Abbreviations: Atezo, atezolizumab; BSC, best supportive care; DFS, disease-free survival; KM, Kaplan-Meier

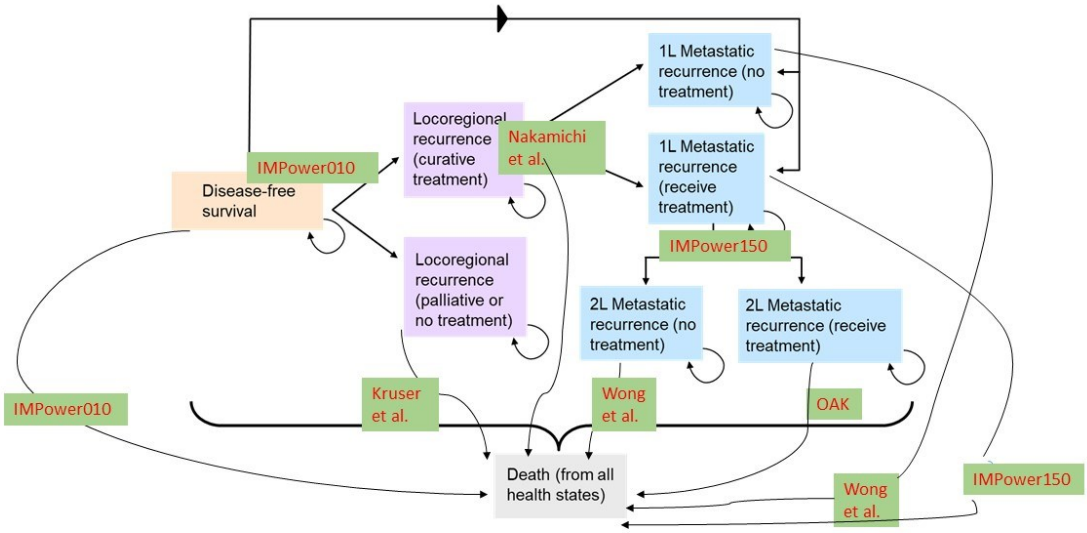
4.2.6.3. Post-DFS events

Post-DFS events and related health states comprise much of the logic in the company's model, as indicated by CS Figure 9, reproduced as Figure 4 in Section 4.2.4 of this report. As noted previously, the company's base case analysis predicts a post-DFS incremental loss of [redacted] (discounted) QALYs associated with atezolizumab versus BSC. The direction of this result is explained by the treatment pathway implications of introducing atezolizumab in the adjuvant setting: the company assume that rechallenge with (immune-checkpoint-inhibitor) immunotherapy will not be reimbursed by NHS England (CS, p92). This assumption is aligned with the expectation of the independent NHS Consultant Oncologist advising the ERG. This same Consultant Oncologist expressed uncertainty over whether adjuvant atezolizumab treatment will provide any OS benefit, given the pathway implications and limited OS data from IMpower010, though they stressed that the published IMpower010 results are encouraging. Given this feedback, in estimating a DFS QALY benefit of adjuvant immunotherapy ([redacted] discounted QALYs) that is more than [redacted] greater than the post-DFS QALY benefit of immunotherapy (in the comparator arm; [redacted] discounted QALYs), the ERG was concerned that the company's approach may be underestimating the post-adjuvant relative benefit of available immune-check-inhibitor treatments, including atezolizumab, and in doing so, bias results in favour of adjuvant atezolizumab.

Post-DFS model assumptions are perhaps most important for cost-effectiveness results in their implications for expected cost implications across model arms: the company's base case analysis predicts post-DFS costs to be [redacted] higher on the BSC arm of the model, [redacted] the [redacted] incremental DFS costs the company predicts for introducing atezolizumab in the adjuvant setting (all estimates time-preference discounted, reported to 0 dp and inclusive of a confidential price discount for atezolizumab but not for other treatments used later in the pathway). While the company's post-adjuvant treatment choice, treatment duration and treatment cost assumptions are described and critiqued in Section 4.2.8 of this report, their importance is noted here as the post-DFS health state transition assumptions employed by the company interplay with them.

The remainder of this sub-section describes and critiques the company's approach to post-DFS health state transition assumptions. Figure 12 is an ERG-edited version of CS Figure 9, in which single-term references to the external data sources used to inform (time-invariant) post-DFS transition probability assumptions are noted in green boxes. The IMpower150[50] and OAK[51] studies are, like IMpower010[15] Roche-led studies. Kruser et al[52] Nakamichi et al[53] and Wong et al[54] are single studies from which the company sourced PFS (Nakamichi et al[53]) and OS (Kruser et al[52] Wong et al[54]) KM plots. The company reported a structured review of real-world evidence in Appendix M of the CS. In the Document B (p87), the company cited this review as a source of post-DFS transition probability data. Appendix M partially reported search strategy and data selection, but no PRISMA diagram is reported, and the company did not report explicit inclusion criteria for study selection, in either Appendix M or Document B. In response to clarification question B32, the company provided the rationale behind the final study choices (Kruser et al[52] Nakamichi et al[53] and Wong et al[54]. The ERG noted the absence of predefined inclusion criteria}) but the ERG noted that it remained unclear whether a priori study selection criteria were applied. Overall, the ERG was not confident that the most appropriate data sources were selected by the company to inform post-DFS health state transition assumptions.

Figure 12. Edited reproduction of CS Figure 9, with added arrows denoting transitions to the "Death" state and green boxes describing non-IMpower010 sources employed by the company to inform transition probability assumptions



Source: IMpower010,[15] IMpower150,[50] Kruser 2014,[52] Nakamichi 2017,[53] OAK,[51] Wong 2016[54]

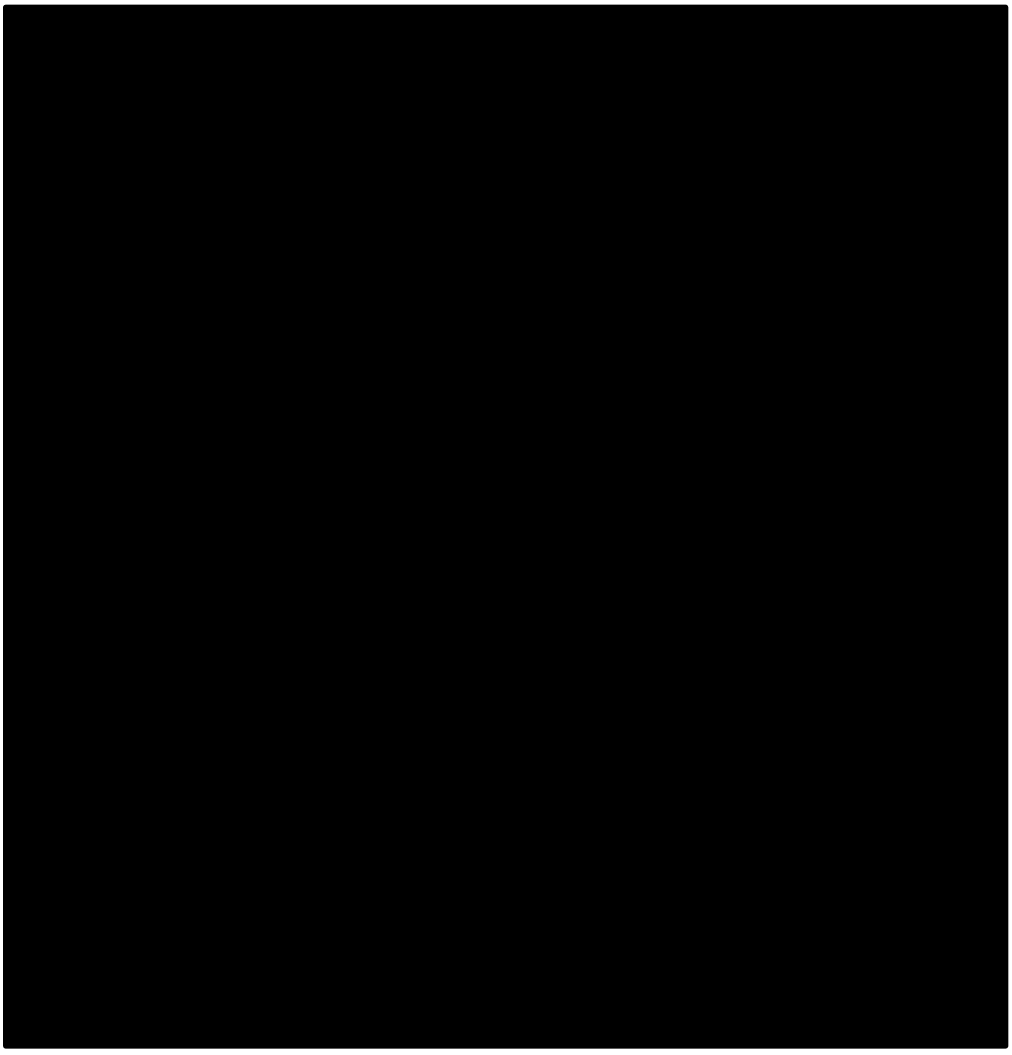
In the cases of Kruser et al[52] Nakamichi et al[53] and Wong et al[54] the company report digitising published KM plots to generate pseudo-patient-level data. In the cases of IMpower010, IMpower150 and the OAK study, patient level data (PLD) were available to the company.

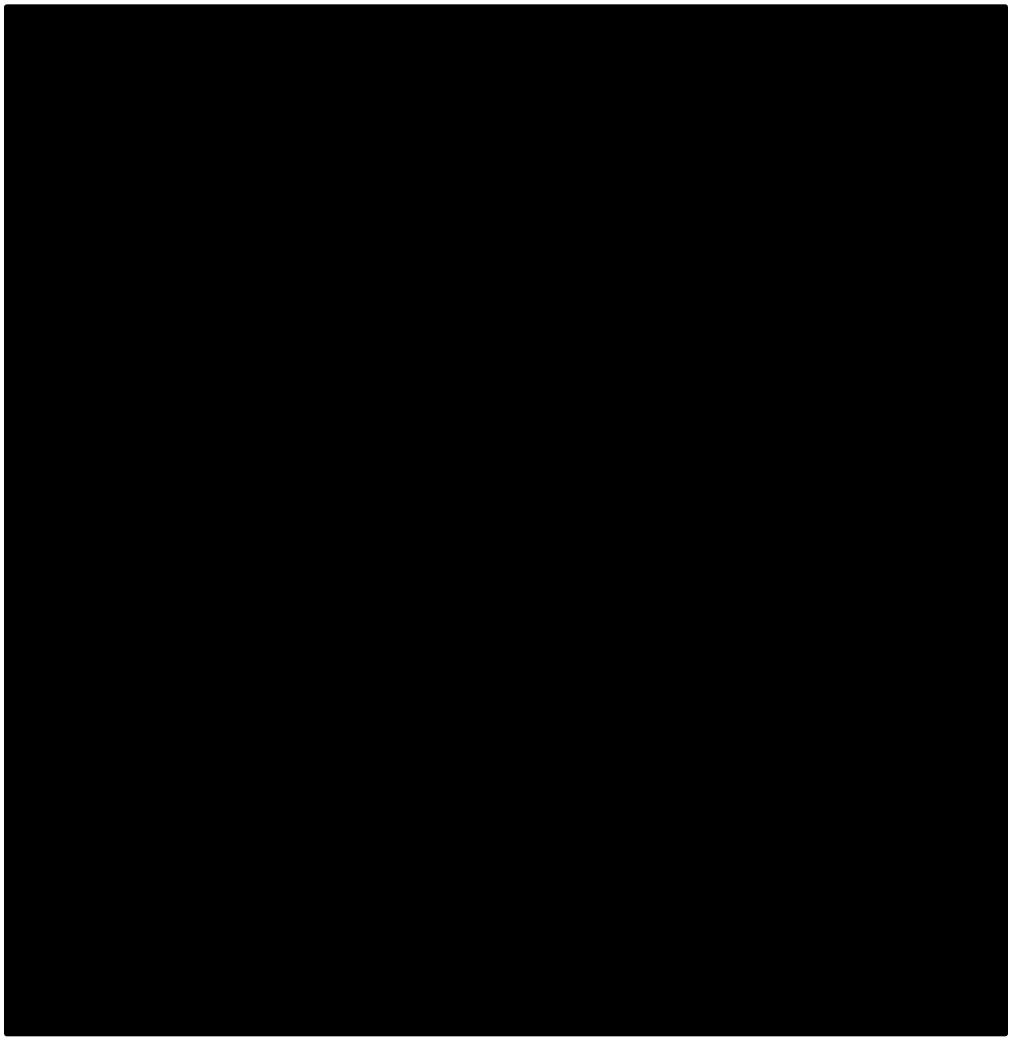
Despite this data availability, the company's analysis of these data was limited to fitting exponential survival models. No exploration of the appropriateness of the exponential model for fitting to external data was presented in the CS, and no survival models other than exponential were fitted. In each case, the company commented in a footnote that "*This was a simplifying assumption as using a different parametric distribution would make it time varying"* (CS, Document B, Section B.3.3.6). The ERG reiterate that it was the company's choice to specify a cohort-level, discrete-time approach to modelling using spreadsheet logic (refer also to Section 4.2.4).

To understand the validity of the company's exponential assumption for Kruser et al[52] Nakamichi et al[53] Wong et al[54] IMPOWER150[50] and OAK study[51] KM data, the ERG produced a log-survivor plot for each dataset, shown in Figure 13. The company model contained KM

survival estimates for OAK and IMPOWER150, and this was used to produce the plots in Figure 13 (top). To produce the plots in Figure 13 (bottom), the KM plots presented in the CS were digitised by the ERG at random points (a sufficient number to describe the curve) using the software Graph Grabber v2.0.2 (Quintessa Ltd.). In these log-survivor plots, a straight line indicates that an exponential survival model is appropriate. The ERG's visual interpretation of these graphs is that the exponential distribution assumption may be appropriate for the OAK[51] and IMPower150 arm B [50] data used in the analysis, but not for the IMPower150 arm C, Kruser et al[52] Nakamichi et al[53] or Wong et al[54] data used in the analysis.

Figure 13. ERG-generated log-survivor plots, from data used to inform post-DFS transition probability assumptions in the CS.





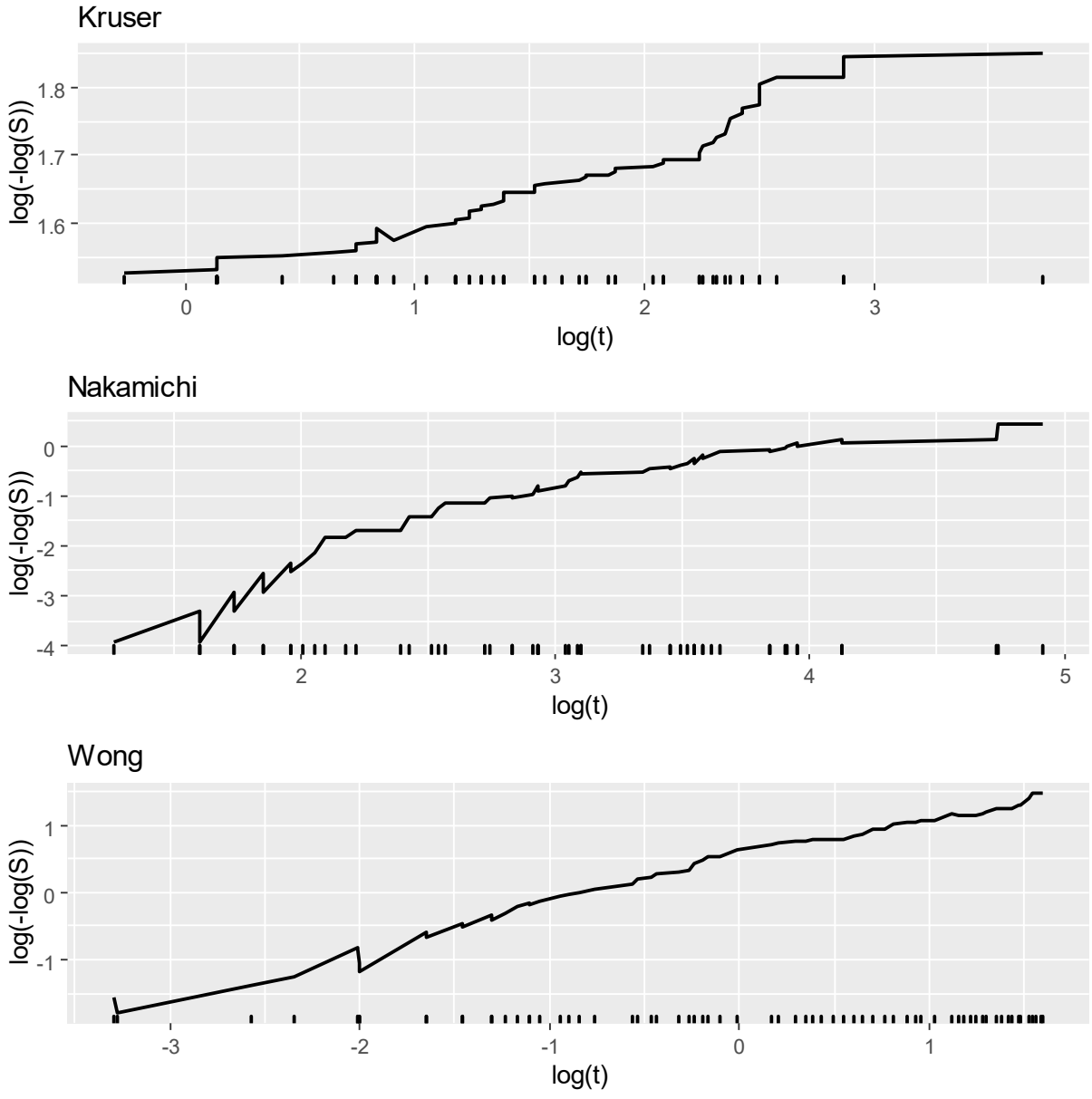
Abbreviations: CS, company submission; DFS, disease free survival; ERG, Evidence Review Group

Note: Top: using trial Kaplan-Meier data (OAK and IMPower150) supplied in the company model. Bottom: using trial data from digitisation of Kaplan-Meier plots in CS Doc B. Tick marks indicate times of points selected during digitisation. Flattening at later times reflects low numbers at risk in the corresponding Kaplan-Meier plots.

Source: OAK[51], IMPower150[50], Kruser 2014,[52] Nakamichi 2017,[53] and Wong 2016[54]

The ERG further explored the recreated Kruser et al[52] Nakamichi et al[53] and Wong et al[54] data by means of log-cumulative hazard plots for a visual assessment of the appropriateness of a Weibull model. Figure 14 shows these log-cumulative hazard plots. A straight line would indicate that a Weibull distribution is appropriate (with the exponential model being a special case of the Weibull distribution with gradient=1). The ERG visual interpretation is that, of these, a Weibull distribution may be appropriate for the Wong et al. data,[54] but not for the Kruser et al[52] or Nakamichi et al[53] data.

Figure 14. ERG-generated log-cumulative hazard plots, from data used to inform post-DFS transition probability assumptions in the CS. Tick marks indicate times of points selected during digitisation of the original Kaplan-Meier plots.



Abbreviations: CS, company submission; DFS, disease free survival; ERG, Evidence Review Group

Note: Tick marks indicate times of points selected during digitisation of the original Kaplan-Meier plots.

Source: Kruser 2014,[52] Nakamichi 2017,[53] and Wong 2016[54]

The company included two approaches to calculate transition probability estimates from the noted published sources, assuming an exponential distribution. The simplest of the two used the

median OS (or PFS) estimate only, while the second approach fitted an exponential model to digitised KM data. The company chose to use the simpler approach in their base case analysis, without good justification. Further, the company applied the simpler approach erroneously in their model, calculating the hazard from the median estimate and applying the hazard as the cycle probability. In Section 6 of this report, correction of this error is referred to as ERG correction to the company base case #2.

Not fully indicated in Figure 12, the company's post-DFS modelling approach is also reliant on assumptions about the proportion of patients partitioned to different non-Death health states upon state transition. Specifically, the company employed assumptions around (i) the relative proportion of patients experiencing non-death DFS events who transition to locoregional vs metastatic recurrence, (ii) the proportions of patients with recurrent disease (locoregional, 1st metastases, 2nd metastases) who are given active or curative-intent treatment vs palliative or no treatment; (iii) the proportion of patients experiencing a PFS event in the locoregional recurrence (curative treatment) state (using PFS data from Nakamichi et al[53]) whose event is disease recurrence vs death. These assumptions and the data sources used are summarised in Table 14.

Notably, while other assumptions in Table 14 are not assumed to differ across model arms, the company assume that the proportion of non-death DFS events that are locoregional recurrence events as opposed to metastatic recurrence events is different across arms, based on observed incidence data from IMpower010, analysed post-hoc. The ERG requested clarification on the company's justification for this assumption; specifically, analysis of whether type of DFS event was significantly associated with treatment arm; in clarification question B11. In response, the company provided analysis of differences in time to metastatic events (as first DFS event) across arms, but not analysis of the association of treatment arm with type of DFS event, as requested. In the company's January 2022 additional evidence submission, the proportion of non-death DFS events assumed to be locoregional recurrence events as opposed to metastatic recurrence events was updated using PD-L1 ≥50% TC Stage II–IIIA subgroup data, as reflected in Table 14. However, the validity of these estimates is unclear to the ERG, from reporting across Tables 7, 34 and 35 of the company's submission of additional evidence. Overall, the ERG feels there is insufficient evidence to assume a treatment effect upon *type* of DFS event, on top of capturing a treatment effect upon DFS.

Table 14. Additional post-DFS (constant) transition partitioning assumptions and sources employed in the CS, beyond those indicated in Figure 12

From	To	Atezolizumab	BSC	CS source; cited source
Disease-free survival	Locoregional recurrence (if not Death)	[redacted]	[redacted]	CAES Table 7; IMpower010[15] PD-L1 ≥50% TC Stage II–IIIA subgroup
	1st metastatic recurrence (if not Death)	[redacted]	[redacted]	
Locoregional recurrence entry	Curative treatment	80.00%	80.00%	CS p87; Sonoda et al 2020 *
	Palliative / no treatment	20.00%	20.00%	
Locoregional curative treatment	1st metastatic recurrence	81.00%	81.00%	CS p89; PACIFIC trial[53]
	Death	19.00%	19.00%	
1st metastatic recurrence	Treatment	[redacted]	[redacted]	CS p91 and p95; Expert opinion
	No treatment	[redacted]	[redacted]	
2nd metastatic recurrence	Treatment	[redacted]	[redacted]	
	No treatment	[redacted]	[redacted]	

Abbreviations: BSC, best supportive care; CAES, company's additional evidence submission; CS, company submission; DFS, disease-free survival; TC, tumour cells

* corrected reference (following clarification question A5; was supplied as Sonoda et al. [2019][47] in CS)

To summarise the ERG's perspective on the company's post-DFS health state transition assumptions, the ERG are concerned that the company's approaches to data identification, selection and analysis and other modelling assumptions fall short of the standards set out in the NICE Guide to the Methods of Technology Appraisal.[42]

4.2.6.4. Overall survival

The OS projections in the company's base case analysis are implied by the company's approach to model DFS and post-DFS health state transitions, as described across Section 4.2.6.2 and Section 4.2.6.3.

OS (in the ITT population) was a prespecified secondary outcome in IMpower010, and the company reported OS KM data for the relevant IMpower010 subgroup in both the CS (PD-L1 ≥1% TC Stage II–IIIA patients) and the company's January 2022 additional evidence submission (PD-L1 ≥50% TC Stage II–IIIA patients). The PD-L1 ≥50% TC Stage II–IIIA OS KM data are reproduced in Figure 15, below.

Figure 15. (CAES Figure 5): Kaplan-Meier plot of OS (PD-L1 ≥50% TC Stage II–IIIA population)

Abbreviations: CAES, company's additional evidence submission; CI, confidence interval; HR, hazard ratio; NE, not evaluable; OS, overall survival; PD-L1, programmed cell death ligand 1; TC, tumour cell

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

The company's base case OS projections are shown in Figure 16, alongside the OS KM data shown in the ERG-generated Figure 15. Figure 16 illustrates how the company's approach to capture post-DFS events produces OS projections that are markedly below the observed KM data on both treatment arms, and implying a sizeable relative lifetime OS benefit, far beyond the observed data.

Figure 17 shows the company base case DFS projections and corresponding DFS KM data as documented in Section 4.2.6.2, alongside the OS KM data and projections shown in Figure 16. Figure 17 is useful in illustrating the importance of DFS assumptions for OS projections in the company base case. As described in Section 4.2.6.2, the company base case assumed a proportion of patients yet to experience a DFS event face general population-weighted mortality risks, increasingly linearly from 0% at 36 months to 91.5% at 72 months. This is reflected in the visual shape and scale of the DFS and OS projections in Figure 17.

Figure 16. Company base case OS projections, alongside OS KM plots for the IMpower010 PD-L1 ≥50% TC Stage II–IIIA population

Abbreviations: Atezo, atezolizumab; BSC, best supportive care; KM, Kaplan-Meier; OS, overall survival; PD-L1, programmed cell death ligand 1; TC, tumour cell

Figure 17. Company base case OS and DFS projections, alongside OS and DFS KM plots for the IMpower010 PD-L1 ≥50% TC Stage II–IIIA population

Abbreviations: Atezo, atezolizumab; BSC, best supportive care; DFS, disease free survival; KM, Kaplan-Meier; OS, overall survival; PD-L1, programmed cell death ligand 1; TC, tumour cell

Concerned that the company's analysis was a poor reflection of the observed OS data, the ERG asked the company to provide a cost-effectiveness scenario in which DFS and OS projections

across model arms are driven by the relevant IMpower010 KM data (clarification question B10). In response, the company incorporated a model scenario in which standard parametric fits to observed OS data were used, with DFS projections affected primarily through existing model logic.

Figure 18 illustrates the OS and DFS model projections when the company's "OS Survival Analysis" approach is taken. While the OS projection fit to the observed KM data is improved relative to the company's base case analysis, the DFS projection fit to the observed DFS KM data is worsened, and projections beyond KM data are wildly different to those of the company's base case analysis. Notably, the atezolizumab and BSC OS projections cross after eight years and four months (DFS curves also cross, though later), with the scenario projecting a lifetime survival benefit for BSC. A similar affect is observed across other standard two-parameter survival models, owing to the shape of the atezolizumab OS KM data.

Figure 18. Company's "OS Survival Analysis" scenario DFS and OS projections, alongside OS and DFS KM plots for the IMpower010 PD-L1 ≥50% TC Stage II–IIIA population

Abbreviations: Atezo, atezolizumab; BSC, best supportive care; DFS, disease-free survival; KM, Kaplan-Meier; OS, overall survival; PD-L1, programmed cell death ligand 1; TC, tumour cells

The ERG found the company's "OS Survival Analysis" scenario to be unhelpful in characterising the likely cost-effectiveness of adjuvant atezolizumab for lung cancer patients, beyond illustrating the substantial uncertainty surrounding the anticipated lifetime patient benefit and overall cost-effectiveness of atezolizumab in this setting.

4.2.7. Health-related quality of life

The IMpower010 trial[15] did not collect patient-reported-outcome data. As a result, the company identified sources of health state utility values from the published literature and other company trials. The company performed a systematic literature review to identify sources with relevant utility values, as reported in Section 4.1 of this report.

From the CS, the ERG was unable to fully verify the appropriateness of the literature values identified, as the company did not provide all the summary details as recommended in the NICE STA User Guide.[55] These details were provided by the company in response to clarification question B24, allowing the ERG to verify the sources satisfactorily. In addition, the company referenced Nafees et al. 2008[56] and Chouaid et al. 2013[57] but did not state how these studies were identified. In response to clarification question B25 the company explained that the studies were identified when looking at accepted NICE HTA submissions in NSCLC.

In total, the company identified 25 relevant full publications in its systematic literature review (Section 4.1). These publications were examined for suitability, five of which were deemed appropriate by the company to be used as sources for utility values for DFS (Manser et al. 2006,[58] Grutters et al. 2010,[28] Jang et al. 2010,[37] Black, Keeler and Soneji 2014,[59] Yang et al. 2014[34]). Reasons provided for study exclusion included the study sample comprising: a combination of NSCLC and small cell lung cancer (SCLC) patients; a combination of disease stages; patients who did not receive surgery. A summary of the selected utility values with the company's justification is provided in Table 15. The company's base case disutility value for disease-free survival used a weighted average of Stage II and Stage III disutility values, derived from results of a study of 172 NSCLC patients attending a Canadian cancer centre and completing EQ-5D(-3L) and European Organization for Research and Treatment of Cancer Quality of Life Core 30 questionnaires,[37] weighted by the relative proportion of IMpower010 ITT sample patients with Stage II and III disease at baseline. The study used a US tariff to estimate EQ-5D utility from EQ-5D questionnaire responses.[37]

No studies containing utility values for locoregional recurrence were identified. Therefore, the company used an estimated utility value for a patient with non-Stage IV 1st line progressive disease, from a multivariate regression analysis of prospectively collected EQ-5D(-3L, UK tariff) data from 319 Dutch patients with locally advanced and metastatic NSCLC,[57] as proxy for locoregional recurrence utility. This analysis also provided possible utility values for 1st- and 2nd-line metastatic recurrence. In addition, utility data from the Roche-led IMpower150[50] and

IMpower110[60] trials and van den Hout et al. (2006) were considered[61] for both metastatic health states. The van den Hout et al (2006)[61] study was identified through a supplementary search of previous NSCLC appraisals; in van den Hout et al patient-reported EQ-5D(-3L) data were collected from Dutch patients receiving radiotherapy for inoperable Stage III-IV NSCLC. The EQ-5D valuation tariff used was not reported. Possible utility values for 2nd-line metastatic recurrence also included those from Nafees et al (2008),[56] Nafees et al. aimed to generate UK HTA-relevant utility values for metastatic NSCLC health states, using expert oncologists to first refine health states description, before estimating utility values for health states through a standard gamble exercise with an n=100 general population sample.[56]

Table 15. (adapted from CS Table 41) - Company base case utility values with justification

Health state	Population	Utility value: mean (SE)	Disutility value	Source	Company justification
Disease-free survival	Stage II	0.78 (0.06)	0.02	Jang et al. 2010[37]	Below general population utility and above utility for locoregional recurrence
	Stage III	0.73 (0.04)	0.07		
	Weighted average		0.03		
Locoregional recurrence	Curative treatment	0.77 (0.03)	0.08	Chouaid et al. 2013[57]	Only data source identified for locoregional recurrence
	Palliative treatment	0.62 (0.03)	0.17	Van den Hout et al. 2006[61]	Utility values for patients treated with palliative intent
	No treatment	0.62 (0.03)	0.17		
Metastatic recurrence (1L)	Treatment	0.71 (0.01)	0.11	IMpower150[50]	The trial population aligns with the population of interest and is most conservative. Accepted in NICE TA584.
	No treatment	0.62 (0.03)	0.17	Van den Hout et al. 2006[61]	As above
Metastatic recurrence (2L)	Treatment	0.69 (0.02)	0.13	IMpower150[50]	The trial population aligns with the population of interest and is most conservative. Accepted in NICE TA584.
	No treatment	0.62 (0.03)	0.17	Van den Hout et al. 2006[61]	As above

Abbreviations: CS, company submission; SE, standard error; TA, technology appraisal

The ERG observed that while worse health states are generally associated with lower utility values in Table 15, for patients with disease recurrence receiving no active treatment, the company's approach implies that patient utility is not affected by recurrence type (locoregional,

1st metastasis, 2nd metastasis). The company did not explain or attempt to justify this implicit assumption.

In application in the company's base case analysis, the company adjust the values in Table 15 to account for the expected effect of ageing upon patient utility. In this, the company assume that the utility of the target NSCLC patient group changes with age in line with observed effects of ageing upon general population utility, from an analysis of Health Survey for England data.[62] The utility value from each source is subtracted from the comparable general population utility, creating an estimate for the disutility in each health state. The disutility estimates were then subtracted from the general population utility value appropriate for the population in the selected health state. This ensures the utility values remain below those of the age-equivalent general population estimates. The original utility values and the calculated disutility values are shown in Table 15.

The ERG identified an error in the application of utility assumptions in the company's model. If the user selected a specific literature source for DFS utility, the value attributed to a different study would be selected. The root of this error was inconsistent within-range ordering across ranges referenced in the company's logic, which uses Excel's MATCH function. As a result, when the company selected their preferred source, Jang et al[37] a source from a different study, Manser et al(2006)[58] was selected. The company also spotted this error after submission, noting it in the clarification response, and factoring correction of this error into the January 2022 company base case results shown in Section 5 of this report.

The company omitted additional disutility effects associated with AEs to avoid double counting, as impact on utilities from AEs may have already been accounted for in the identified utility sources (CS, Document B, p.100). Yet, the ERG noted that the company provided no case-by-case justification of this assumption, with reference to data collection in the selected studies.

Mindful of the patient HRQL implications of introducing an active treatment into the adjuvant setting, the ERG asked the company to revise their approach to adverse event utility assumptions in clarification question B15. In response, the company identified two sources of disutility to use as alternatives for an approximation of AE disutility and incorporated them into alternative scenario analyses using simplifying assumptions. The first value was the disutility value Nafees et al. estimated for febrile neutropenia in their 2008 study, described above:[56] 0.09002 (reported as 0.09 in the company response to B15). The second value was taken from the ERG report from NICE TA578 Durvalumab for treating locally advanced unresectable

NSCLC after platinum-based chemoradiation[63]: a disutility value of 0.11, assumed for hypertension and hypokalaemia in TA578. A source for this disutility value is provided within TA578: the same Nafees et al study reporting the 0.09002 disutility estimate for febrile neutropenia.[56] However, there is no 0.11 value reported in Nafees et al. (2008)[56] the provenance of this estimate remains unclear to this ERG.

Overall, the ERG was generally satisfied with the health-related quality of life assumptions in the submission, given the lack of EQ-5D data in IMpower010. However, the ERG considered applying an AE disutility estimate to be appropriate for all on-treatment health states.

4.2.8. Resources and costs

The company report a systematic review to identify healthcare resource use data, and though the analysis is from the cost perspective of the NHS and PSS, the cost and resource use assumptions employed by the company across health states are numerous and not always justified. As described in Section 4.2.6.3, cost and resource use assumptions in post-DFS health states are particularly important for cost-effectiveness results.

The company sourced drug acquisition cost estimates from (i) the electronic market information tool (eMIT) and (ii) the 2021 British National Formulary (BNF)[64]. In the company's additional evidence submission, the company note an error in their original submission: the dose size for docetaxel was taken to be 160 mg/m^2, when the appropriate dose size is 75 mg/m^2. The company correct for this in their January 2022 base case analysis. The ERG had independently cross-checked the company's submitted cost and dose estimates with reported sources. In this, the ERG sought to identify any unintended mistakes and verify that the cheapest cost had been assumed, in instances where different eMIT and BNF cost estimates were available for the same product. There were three notable findings from this exercise beyond the error the company identified, the first two of which the ERG correct for in the ERG-corrected company base case in Section 6:

- The ERG identified lower BNF costs for bevacizumab than those used by the company: £810.10 for a 400 ml vial and £205.55 for a 100 mg vial, versus £924.40 and £242.66, respectively. The use of these lower cost estimates is ERG correction to the company base case #3, as referenced in Section 6 of this report. The ERG noted that the lower cost estimates are for concentrate for solution for infusion as opposed to solution for infusion.

- The ERG identified erroneous costing and dosing assumptions for the oral treatment nintedanib, the corrections for which comprise ERG Correction to the company base case #4, as referenced in Section 6 of this report:
  - the company assumed the cost of 120 x 100 mg tablets (one pack) for one 100 mg tablet and the cost of 60 x 150 mg tablets (one pack) for one 150 mg tablet
  - the company assume two 150 mg nintedanib doses every three weeks, whereas the BNF lists its use as: "200 mg twice daily on Days 2–21 of a standard 21-day docetaxel cycle..." within its 2nd-line metastatic or locally recurrent adenocarcinoma NSCLC indication
- Unlike the company, the ERG could not identify a 50 mg composition of pembrolizumab on the BNF

The remainder of this section describes and critiques the company's approach to capture the costs of treatment acquisition and administration, disease management and adverse event management, with reference to independent clinical advice received by the ERG. The subsections of this section broadly align with the different disease states under consideration, as defined by the company's chosen model structure. The section closes with a description and critique of the company's approach to capture terminal care costs.

4.2.8.1. Disease-free survival

Treatment acquisition and administration

As described in Section 4.2.3 of this report, adjuvant atezolizumab treatment is assumed to comprise exactly one 1,200mg vial of atezolizumab every 21 days, for a maximum of sixteen 21-day cycles. The company's analysis assumes a confidential Patient Access Scheme (PAS) discount of [redacted] to the list price of atezolizumab.

As atezolizumab is being proposed to be used in the adjuvant setting in PD-L1≥50% (Stage II–IIIA) patients only, the PD-L1 status of patients would need to be known at this stage in the pathway. The ERG's independent (NHS Consultant Oncologist) clinical adviser confirmed that the approval of atezolizumab at this early stage would bring forward PD-L1 testing, in their centre and others. The company did not consider the NHS cost implications of earlier PD-L1 testing in the CS. While the ERG was mindful that this omission biases the company's results in their favour, it was reassured by its independent adviser that for those patients who experience

metastatic recurrence, the introduction of a PD-L1 test at the adjuvant stage would be an earlier test but not an additional test. Clinical advice indicated that an estimated one-third of patients are PD-L1 ≥50% (and therefore the cost per PD-L1 ≥50% patient identified is not a high multiple of the cost of the test). Finally, the cost of a PD-L1 test is not high: a figure of £40.50 has been used in previous NSCLC appraisals.[65] Overall, the ERG was reassured that company's omission of PD-L1 testing implication is unlikely to have introduced substantial bias to the results.

As also described in Section 4.2.3 of this report, and in Section B.3.5.2 of the CS, "time to off treatment" data from IMpower010 were used by the company to limit the assumed mean treatment acquisition cost of adjuvant atezolizumab; the company assumed the cost would apply only to those remaining on-treatment at equivalent cycles in IMpower010. In their January 2022 additional evidence submission, the company updated these data to those from the Stage II-IIA PD-L1 ≥50% IMpower010 subgroup; these data are reflected in the company base case results presented in Section 5 of this report.

Atezolizumab is administered intravenously (IV). The company assumed that the administration cost associated with atezolizumab administration is equal to the NHS Reference Cost (2019-2020) for delivery of simple parenteral chemotherapy at first attendance (Code SB12Z). The ERG's independent adviser felt the NHS Reference Cost Code SB12Z description was reasonable, but noted that before each atezolizumab administration, a patient is expected to have clinical review, through either a doctor-led or nurse-led clinic, to ensure the patient can continue to tolerate treatment and has not developed any side effects or symptoms that suggest a recurrence. The ERG's clinical advisor estimated that each visit would involve a blood test, to ensure the patient is safe to proceed; the patient would then attend as a day case in a separate visit, to receive the treatment. The ERG asked the company to amend the assumed administration cost of adjuvant atezolizumab in line with this independent advice (clarification question B13). In response, the company provided a scenario which incorporated costs for (i) clinical review to ensure a patient can continue treatment (£192.90; NHS Reference costs 2019/2020 Code 370 Outpatient visit) and (ii) a complete blood count (£2.58; NHS Reference costs 2019/2020 Code DAPS05) were included for the average number of cycles in the trial, which the company report to be 13 cycles. The ERG noted that when a pre-treatment check leads to discontinuation, this check is unlikely to be captured as an "on-treatment" event; as such, even factoring in additional costs appropriately for "on-treatment" administrations is likely to slightly underestimate overall per-patient administration costs.

As described in Section 4.2.3 of this report, the comparator arm of the analysis, termed BSC by the company and described as active monitoring in the CS (p68), contained no active adjuvant treatment. As such, the company assume no treatment acquisition or administration cost for BSC in the DFS health state.

Disease management and care

The company assumed that the disease-free health state is associated with a constant cost associated with NHS disease management, for the first five years post-resection and post-chemotherapy. The same cycle cost was assumed across treatment arms, but as patients on the atezolizumab arm of the model are projected to spend a greater proportion of projected life expectancy in the DFS health state, a lower DFS health state cost improves the predicted cost-effectiveness of adjuvant atezolizumab, *ceteris paribus*.

The company assume "disease-free" patient management and care comprises chest radiography scans (1.4 per year), outpatient visits (1.4 per year), community nurse visits (1.18 per year), clinical specialist nurse visits (1.7 per year) and general practitioner (GP) visits (2.8 per year), as described in CS Table 48, leading to a total assumed model cycle (monthly) cost of £53.19.

As noted in Section 4.2.3 of this report, and described in the CS (p29), in IMpower010, tumour assessment was carried out at baseline and every four months in Year 1, then every six months through Years 2 to 5, until disease recurrence, across both arms of IMpower010. The ERG's independent clinical adviser described typical follow-up as three to four monthly for the first two years, then six monthly for a year, then annually. The ERG's clinical advisor additionally noted that while the protocol for follow-up may differ dependent on the local set-up, it could include surgical follow up, oncology follow-up (if treated with chemotherapy), clinical nurse specialist (CNS) led follow-up or respiratory follow-up. Overall, the ERG had some concerns that the company assumptions may underestimate the NHS disease management cost for NSCLC in the DFS setting: by not accounting for the specialist-led nature of follow-up as described by the ERG's adviser, and by underestimating the frequency of follow up, overall and particularly in the short term. On the other hand, the ERG's adviser notes that while chest X-rays are usual for in-person follow-up visits, since the beginning of the COVID-19 pandemic, more reviews have been conducted over telephone, and as a result, chest radiography scans have been less frequent.

The company assumed that there is no NHS cost associated with patient care for those estimated to remain disease-free for five years post-resection and -consolidating chemotherapy. The ERG's clinical adviser confirms that follow-up is usually for five years only after surgery, assuming the patient remains disease-free. The ERG remained mindful that the assumption of no NHS health care cost for those remaining disease-free for five years in the model is a strong assumption. If there is any cost associated with this state, the predicted cost-effectiveness of adjuvant atezolizumab would worsen, as the company's analysis predicted a greater proportion of patients to achieve disease-free survival to five years on the atezolizumab arm versus the BSC arm, as illustrated in Section 4.2.6.2 of this report.

Adverse event management

The company assumed no adverse event costs for adjuvant treatment with atezolizumab as the proportion of patients experiencing treatment-related AEs/SAEs of Grade 3 and above were all [redacted] (CS, Document B, B.3.3.7.1).

The ERG's independent clinical adviser anticipated that patients and the healthcare system would bear an additional adverse event burden with the introduction of atezolizumab to the adjuvant setting, from their experience using immunotherapy in adjuvant and metastatic settings. It is anticipated that all Grade 2 and above events will require NHS resources, even if this comprises only regular clinical visits for a Grade 2 event. For example, patients may be put on steroids, which will then raise questions about bone health; other clinicians may then be involved. In clarification question B14, the ERG asked the company to amend adverse event management cost assumptions, to incorporate a relevant cost for all observed treatment-related Grade 2+ adverse events in the relevant IMpower010 patient group. In response, the company provided a pragmatic scenario analysis in which a cost estimate of £7,508 is assumed for any adjuvant AE management; an inflation-adjusted cost for febrile neutropenia sourced from NICE TA531 ("Pembrolizumab for untreated PD-L1-positive metastatic non-small-cell lung cancer"), used to inform adverse event assumptions for treatment of metastatic recurrence in the company's base case analysis. In this scenario, the company assume a 40.71% (2dp) probability this cost will occur for adjuvant atezolizumab patients, based on IMpower010 event rates in the Stage II–IIIA PD-L1 ≥50% subgroup. However, from reporting in the company-amended economic model, it appeared that these are Grade 2 event rates (the data appear under "IMpower010 Grade 2 events" headings, in sheet "AE ERG scenario"), as opposed to

Grade 2+ event rates, and the ERG was concerned that this approach may have omitted Grade 3+ events, though the company have since confirmed that these are Grade 2+ event rates.

4.2.8.2. Locoregional recurrence

Treatment selection, acquisition and administration

As noted in Section 4.2.6.3 of this report, the company assume that 80% of patients experiencing locoregional recurrence will receive active treatment with curative intent, with the remaining 20% receiving palliative care only. Specifically, the company assume that patients receiving active treatment at this stage receive chemoradiation therapy, with chemotherapy comprising four 21-day cycles of treatment with cisplatin and vinorelbine. The ERG's independent clinical adviser felt the company's 80/20 split assumption was reasonable, if difficult to estimate, and noted that other chemotherapy regimens (carboplatin and paclitaxel; cisplatin and etoposide) are available may be used instead of cisplatin and vinorelbine, depending on clinician preference.

Cisplatin and vinorelbine are both administered IV, and the company assume the same NHS Reference Cost (2019-2020) code (SB12Z; for delivery of simple parenteral chemotherapy at first attendance) for these treatments as for atezolizumab. However, the company assumed this cost applies to each drug element of combined treatment (for locoregional recurrence and metastatic recurrence), implying that cisplatin + vinorelbine administration is twice as expensive as atezolizumab administration. Independent clinical advice to the ERG suggests one tariff for day case attendance is appropriate, irrespective of the complexity of treatment.

Disease management and care

The company assumed that the locoregional recurrence health state is associated with a constant cost associated with NHS disease management. This cycle cost is assumed to comprise computed tomography (CT) chest scans (four per year with active treatment versus 0 with palliative or no treatment), chest radiography scans (1.20 per year), outpatient visits (4.76 per year), community nurse visits (1.96 per year), clinical specialist nurse visits (8.50 per year) and general practitioner (GP) visits (4.30 per year), as described in the CS (Document B, Table 51), leading to a total assumed model cycle (monthly) cost of £201.24 associated with disease management for patients receiving active treatment with curative intent, and of £161.57 associated with patients receiving palliative or no treatment. The ERG's independent clinical adviser's approach to care broadly aligns with the company's assumptions here.

Adverse event management

The company assumed a constant cost associated with adverse event management for active locoregional recurrence treatment. The company state "*AEs in the locoregional recurrence health state were informed by the TA578 durvalumab cost effectiveness analysis*" (CS, p126), but do not explain or justify this choice. TA578 appraised durvalumab for treating locally advanced unresectable non-small-cell lung cancer after platinum-based chemoradiation.[66] The company state that they used standard of care arm of TA578, but provide no justification. The resultant monthly adverse event management cost assumed to be associated with chemoradiation for locoregional recurrence is £14.05.

4.2.8.3. Metastatic recurrence

***Treatment* selection, acquisition and administration**

1st metastatic recurrence

The company assumed [redacted] of patients experiencing a 1st metastatic recurrence will receive active treatment, based on expert advice. The ERG's clinical adviser felt this was probably a reasonable estimate although open to uncertainty.

If treated, the company reported that they had assumed the following treatment distributions, across model arms:

- Atezolizumab:
  - 100% pemetrexed + carboplatin
- BSC:
  - 28% pembrolizumab + pemetrexed
  - 23% pemetrexed + carboplatin
  - 33% pembrolizumab
  - 16% pembrolizumab + carboplatin

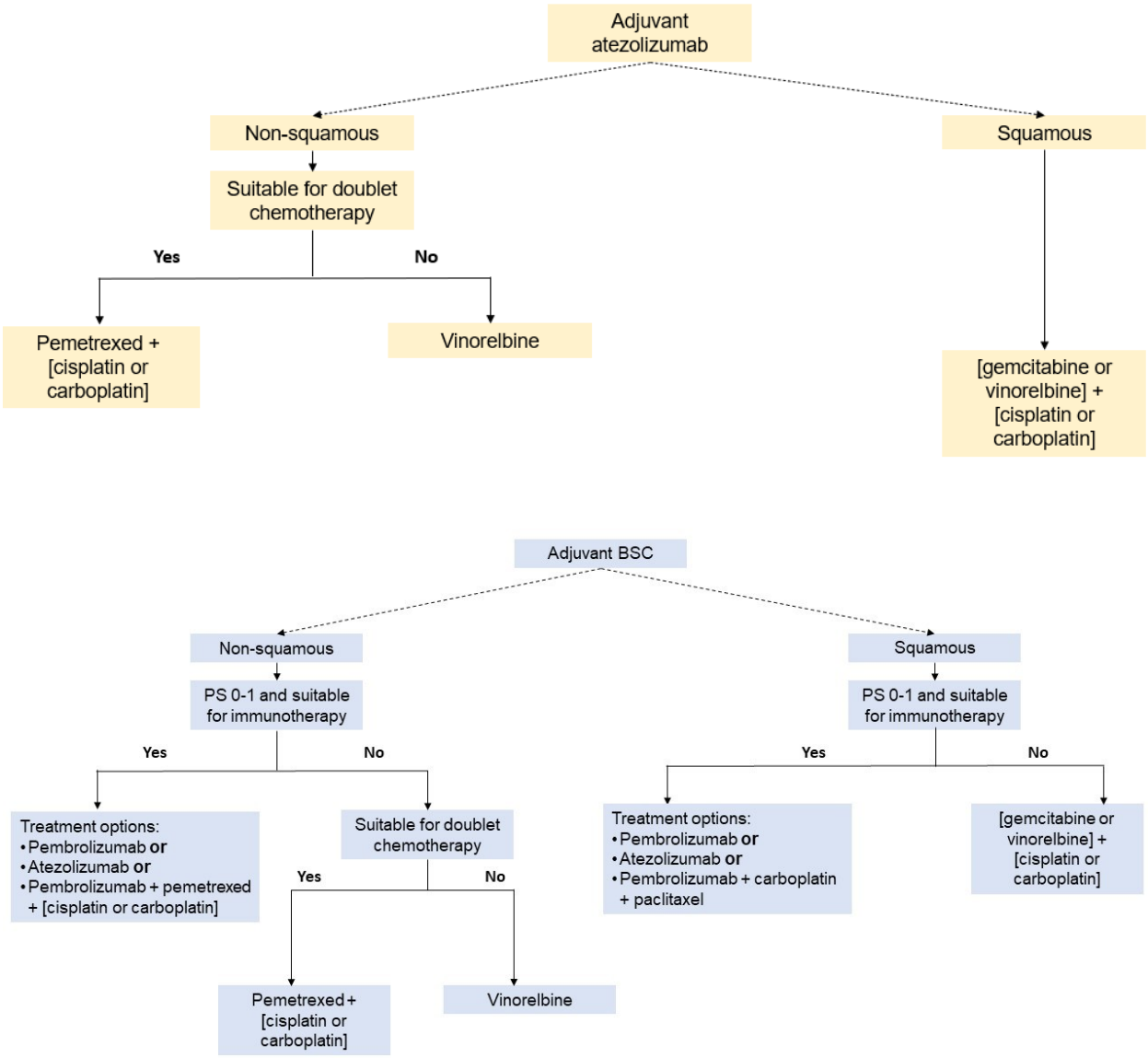
The company stated that they used expert opinion to determine treatment categories, and to inform the assumed distribution of treatments across categories, though it is not clear if this input came from the same group of experts.

Implicit in the company's stated pathway assumption is the assumption that patients will only receive one course of PD-L1/PD-1 targeting immunotherapeutic agent (atezolizumab, pembrolizumab). So, adjuvant atezolizumab precludes atezolizumab or pembrolizumab to treat metastatic recurrence. The ERG's independent adviser expects this assumption will align with permitted use of immunotherapeutic agents in NHS England practice, if adjuvant atezolizumab is approved.

Despite the company's stated assumption, the company's analysis erroneously assumes that patients who experience metastatic recurrence >12 months after treatment initiation with adjuvant atezolizumab can be treated with immunotherapies in the metastatic setting. In application, this assigns comparator arm metastatic treatment assumptions to patients who enter the 1st metastatic treatment state after >12 months (cycles). This erroneous setting was highlighted by the company at the allotted stage for review of ERG factual accuracy, and correction of this company error is referred to as ERG Correction #5 in section 6.1 of this report.

The ERG's clinical adviser noted that treatment decisions at first metastatic recurrence are driven by disease mutation status and whether patients have squamous or non-squamous carcinoma. The company make no mention of these nuances in the CS, and do not refer to the histology or mutation status of disease in the IMpower010 sample in question when describing their treatment decision assumptions. With an assumed focus on non-mutation-driven disease, the ERG's clinical adviser described the following treatment options at this stage of the pathway, with reference to a published NHS algorithm (Figure 19) [67]

Figure 19. Treatment options at 1st metastatic recurrence, with reference to a published NHS algorithm



Abbreviations: BSC, best supportive care; NHS, National Health Service; PS, performance status

Source: Royal Surrey NHS Foundation Trust, 2021[67]

With reference to the latest available Royal College of Physicians National Lung Audit,[9] but acknowledging uncertainty in the estimate, the ERG's clinical adviser expects around 80% of patients presenting with metastatic recurrence and fit to receive active treatment will be performance status 0-1 and otherwise suitable for immunotherapy.

Based on feedback from the ERG's clinical adviser, the ERG makes further necessary assumptions. Among patients who present with metastatic recurrence are suitable for immunotherapy, the ERG expects that around 70% will have stable disease, and therefore be likely to receive pembrolizumab or atezolizumab as monotherapy, with a roughly even split between these treatments. The ERG expects the remaining 30% would have more rapidly progressive disease that would prompt combination immuno-chemotherapy. Of those not eligible for immunotherapy but fit for chemotherapy, the ERG expects that nearly all would be treated with doublet chemotherapy.

For patients with squamous NSCLC, the ERG expects that most patients treated with doublet chemotherapy will receive gemcitabine plus a platinum (generally carboplatin), noting vinorelbine + cisplatin is typically used earlier in the treatment pathway, in the adjuvant setting. The ERG's clinical adviser advised that carboplatin is increasingly becoming the platinum therapy of choice, over cisplatin, given patient experience benefits and the removal of access barriers which previously prompted cisplatin use in this space.

In the IMpower010 Stage II–IIIA PD-L1 ≥50% sample, 59.1% of patients randomised to atezolizumab and 60.5% of patients randomised to the control arm had disease with non-squamous histology (company's additional evidence submission, Table 1). With reference to a published analysis of PD-L1 status across the samples of three NSCLC studies in the KEYNOTE trial programme,[68] the ERG expects that 70–80% of patients have non-squamous carcinoma.

In the company's 31 January 2022 additional evidence submission (CS Addendum), the company reported a further 1:1 call with a UK clinical expert in December 2021 and provided a file containing comments on the metastatic treatment pathway. Despite the contents of this file and the NHS treatment algorithm, the only change to 1st metastatic recurrence treatment assumptions made by the company between the November 2021 CS and January 2022 evidence submission (CS Addendum) was to assume 23% of patients previously treated with adjuvant atezolizumab, and 100% of patients who received no active adjuvant treatment, would be treated with pemetrexed + carboplatin, as opposed to pemetrexed + cisplatin.

Overall, the ERG was concerned that the company's 1st metastatic recurrence treatment choice assumptions are insensitive to the nuances of the NHS treatment pathway and inaccuracies in these assumptions may be important for cost-effectiveness results: the company's assumed

cycle (monthly) cost of treatment acquisition and administration for active 1st metastasis treatment is £2,114.19 in the atezolizumab arm of the model, and £7,225.59 in the BSC arm.

The ERG was also concerned by the company's treatment duration assumptions at 1st line metastasis. Whereas in the DFS state, the assumed cost of atezolizumab is limited to the estimated proportion of patients who remained on treatment in each cycle in IMpower010 (as described in Section 4.2.8.1 of this report), the only treatment duration-limiting assumption the company employ in the 1st line metastasis state is to assume pembrolizumab treatment will stop after two years. The ERG noted that the atezolizumab cohort spend 3.504 months (2.917 time-discounted months) in the "1st metastasis, on treatment" health state in the company base case, while the BSC cohort spend 5.757 months (5.118 time-discounted months) in this state; as such, the implications of the company's assumptions in this area are time-limited. Nevertheless, the ERG was concerned that the company's 1st metastasis treatment choice and duration assumptions may not adequately reflect practice, an available published algorithm or available evidence. In this, the ERG was concerned that the company's approach to 1st metastatic treatment assumptions biases cost-effectiveness results in favour of atezolizumab adjuvant therapy.

2nd metastatic recurrence

The company assume [redacted] of patients experiencing second metastatic recurrence will receive active treatment, again based on expert advice. The ERG's independent adviser aligned with this estimate, with reference to published post-hoc analysis of KEYNOTE-024 clinical trial data.[69]

In the CS, the company assumed [redacted] of BSC patients would receive atezolizumab monotherapy at this stage, implying a far higher mean expected 2nd metastatic recurrence treatment cost in the comparator arm of the model. However, following December 2021 engagement with the ERG and NICE, and a 1:1 call with a UK clinical expert referenced above, the company revised their approach in the January 2022 additional evidence submission, to assume the following treatment distributions, across model arms:

- [redacted] nintedanib + docetaxel
- [redacted] pemetrexed + carboplatin
- [redacted] docetaxel

- [redacted] gemcitabine + carboplatin

Advice from the ERG's clinical expert highlighted an issue with these revised assumptions, given the company's 1st metastatic recurrence treatment assumptions. For instance, the company assume 100% of patients treated for 1st metastatic recurrence on the atezolizumab arm will receive pemetrexed + carboplatin, and then assume [redacted] of the patients from this group who relapse and are later treated for 2nd metastatic recurrence will again be treated with pemetrexed + cisplatin. Considering pemetrexed + platinum therapy to be a 1st line treatment option, the company's revised assumptions are otherwise broadly consistent with the ERG's clinical expert's advice and cited NHS treatment algorithm. The result of the company's treatment assumptions at this stage are a monthly treatment cost of £3,707.22 across model arms. Importantly, patients are assumed to accrue these treatment (and disease and adverse event management) costs until death. As for 1st metastasis treatment assumptions, the ERG view the company's assumption of zero treatment discontinuations for 2nd metastatic treatment as contra to expectations and a cause of bias in favour of atezolizumab. As for 1st metastatic treatment assumptions, the ERG note that the effect of any inaccuracies was limited by the estimated time spent in the 2nd metastatic treatment state: 1.401 months (1.125 time-discounted months) in the atezolizumab model arm, 2.238 months (1.909 time-discounted months) in the BSC arm.

Disease management and care

The company assumed that the metastatic recurrence health states are each associated with a constant cost associated with NHS disease management. The company's total assumed model cycle (monthly) cost of metastatic disease management and care is £352.11 for 1st metastasis without active treatment, £391.78 with, and £608.34 for 2nd metastatic disease, with or without active treatment. By comparison, the assumed monthly disease management costs for disease-free survival and locoregional recurrence, described above, were £53.19 and £161.57-£201.24, respectively. The monthly metastatic disease management NHS resource burden is assumed to comprise CT chest scans (4 per year with active 1st metastasis treatment (1L treatment) versus 0 with 2nd metastasis treatment (2L treatment) or no treatment), chest radiography scans (6.79 per year 1L treatment vs 6.50 per year 2L treatment), electrocardiogram (1.04 per year 1L treatment vs 0.88 per year 2L treatment), outpatient visits (9.61 per year 1L treatment vs 7.91 per year 2L treatment), community nurse visits (8.70 per year), clinical specialist nurse visits (12 per year), general practitioner (GP) visits (12 per year 1L treatment only), GP home visits (26.09

per year 2L treatment only) and Therapist visits (26.09 per year 2L treatment only), as described in CS Table 58.

The ERG's independent clinical expert advised that as patients progress through treatment lines, response rates fall and patients are more likely to progress more quickly. As such, patients may not have as many CT scans and other hospital-based treatment and will be more likely to be referred for community-based care under GPs and palliative care providers. The ERG infer that the company may be overestimating the disease management cost of metastatic disease particularly for 2nd metastasis, and increasingly with time from 2nd metastatic event, while noting the total time spent across on- and off-treatment 2nd metastatic health states: 1.815 months (1.467 time-discounted months) in the atezolizumab model arm, 2.899 months (2.490 time-discounted months) in the BSC arm.

Adverse event management

The company assumed a constant cost associated with AE management for active metastatic recurrence treatment, differing by 1st and 2nd metastatic treatment, and by whether immunotherapy or chemotherapy is the assumed treatment option. The company based its assumptions on assumptions from two atezolizumab models submitted to NICE, TA584 (IMpower150 trial)[…] and TA520 (OAK trial) (CS, p127). The company provide no further justification; the result of their approach is an assumed monthly AE management cost of £87.07 in the atezolizumab arm and £93.45 in the BSC arm for first-line metastatic treatment, and £308.41 across model arms for second-line metastatic treatment.

4.2.8.4. End of life care

The company included a terminal care cost of £4,598.01 in their model, citing one previous NICE appraisal (TA705)[70] as precedent, but not providing the original source for the estimate, in either Document B or the cost-effectiveness model. While there is precedent across numerous oncology appraisals for including a terminal care cost, in this case the company assume this cost applies only to *some* patients. Specifically, the company assume the cost applies only to patients assumed to have disease-related cause of death, and this proportion is assumed to be higher on the BSC arm of the model (65%) than on the atezolizumab arm (51%). The data underpinning these estimates were not described in the CS. In response to clarification question B16 requesting documented analysis of the association between cause of death and treatment arm in the Stage II–IIIA, PD-L1 ≥1% IMpower010 sample, the data provided do not

align with the estimates used in the CS. In the company's additional evidence submission (Appendix G), the company provided the same post-hoc analysis of the association between cause of death and treatment arm, for the Stage II–IIIA, PD-L1 ≥50% IMpower010 sample. In this sample, 11 patients on the intervention arm and 26 patients on the comparator arm had died. Though there appears to have been correlation between cause of death and treatment arm from this post-hoc analysis, the sample size is small, and any causal effect is not clear. Further, the ERG are not convinced by the company's unjustified assumption that the NHS and PSS cost of terminal care is zero for lung cancer patients who are recorded as experiencing "all cause" death, as opposed to £4,598.01 for lung cancer patients recorded as experiencing disease-related death.

Overall, the ERG was neither clear on the basis for the company's submitted cause-of death assumptions, nor convinced that there is a causal association between atezolizumab adjuvant treatment and *cause of* death. Further, the ERG did not believe there is sufficient justification for assuming terminal care is associated with a substantial NHS and PSS costs for some lung cancer patients but not cost for others, in a manner that implies a lower per-patient terminal care cost for the atezolizumab arm than the BSC arm.

5. COST-EFFECTIVENESS RESULTS

5.1. Company's cost-effectiveness results

The results reported by the company in their January 2022 additional evidence submission (CS Addendum) are shown in Table 16. The deterministic and probabilistic results for Stage II–IIIA patients following resection and platinum–based chemotherapy with NSCLC whose tumours have PD-L1 expression on ≥50% TC, including the PAS price for atezolizumab (discount from list price of [redacted]

[redacted]

Table 16. Company base case results

	Discounted costs	Discounted QALYs	Incremental discounted costs	Incremental discounted QALYs	Cost per QALY gained
Company deterministic base case					
Atezolizumab	[redacted]	[redacted]	[redacted]	[redacted]	-
BSC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Company probabilistic base case					
Atezolizumab	[redacted]	[redacted]	[redacted]	[redacted]	-
BSC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: BSC, best supportive care; QALYs, quality adjusted life year

The company also presented base case ICERs assuming the list price for atezolizumab: £18,627 and £19,334 for the deterministic and probabilistic analyses, respectively (Tables 16 and 18, company's January 2022 additional evidence submission), and note how the PAS analysis results in reduced costs for atezolizumab and the same costs for BSC owing to the company assumption of no atezolizumab being used in metastatic states in those initially receiving BSC.

The company noted that their analysis does not include the confidential discounts for therapies other than atezolizumab used in the treatment pathway, notably pembrolizumab for first-line metastatic NSCLC and nintedanib for second-line metastatic NSCLC.

5.2. Company's sensitivity analyses

5.2.1. Deterministic sensitivity analysis

With the exception of (time-preference) discount rates, which were evaluated at 1.5% and 5%, the lower and higher values chosen for each parameter assessed were varied in the CS using 20% and 80% points on the assumed confidence interval of each parameter tested. The ERG are unclear why these points were used instead of the lower and upper limits of a 95% confidence interval, and requested further clarification and justification from the company, noting how the range of values tested was smaller than might typically be expected. In response to clarification questions the company revised their approach and presented a deterministic sensitivity analysis using the upper and lower limits of the 95% confidence intervals from the PSA ouput. This approach is also used in the results submitted by the company in the January 2022 addendum.

The ERG also noted that the initial model submitted incorporated the FIXED function into the formulae to run the DSA, thus limiting the values used to two decimal points. The ERG were unclear why the company imposed this restriction and requested clarification on this point (clarification question B20), noting that this approach underestimates the assumed uncertainty around the input parameters. In response, the company explained this function was incorporated to limit the run time of the model, though removed it in model updates including the updated model submitted in January 2022.

The company report the range of values assessed for parameters in their January 2022 anaylsis in Table 20 of the company additional evidence submission. According to the company's analyses, the most influential parameters assuming the PAS price for atezolizumab were the proportion of patients in the 1st line metastatic state who receive treatment, the proportion of patients who have metastatic recurrence (in both treatment arms) and the market share for pemetrexed and carboplatin for those patients in the BSC arm who are treated for a 1st line metastatic recurrence. The ERG noted that the DSA ICERS were not tabulated in the CS or January 2022 addendum, though the company note in their summary of sensitivity analysis results that the lowest and highest ICERs produced were [redacted] and [redacted] respectively, and that these were derived from the upper and lower values assumed for the proportion of patients on 1st line metastatic treatment in the 1st-line metastatic health state (0.79 and 0.56 respectively).

5.2.2. Probabilistic sensitivity analysis

The company undertook probabilistic sensitivity analysis (PSA) to explore parameter uncertainty by assigning various distributions to input parameters and running the model for 1000 iterations "*to ensure results had converged*" (CS B.3.8.1 p142). The ERG note that the convergence plots presented in the model (sheet "Results Chart") suggest that the ICER is not stable after 1000 iterations, thus that convergence is not achieved as stated by the company. The ERG requested that the company re-run their PSA using at least 5,000 iterations (clarification question B19) and report the updated mean costs, QALYs and ICER accordingly. In response, the company updated their PSA to use 5,000 model iterations. Moreover, the ERG had further concerns with the company approach and implementation of the PSA in the model. In particular, the ERG felt that a number of potentially important and uncertain variables were held fixed in the company model, and were unclear of the companies rationale for this. The ERG requested further clarification and improvements on these points (ERG priority question B18), and in response the company updated their model, resolving the ERG concerns.

The company presented the results of the updated PSA in Section 2.5.1 of the company's additional evidence submission, both at discounted and list price for atezolizumab. The company's probabilistic analysis comprised comparing mean summary PSA results to summary deterministic results, presenting probabilistic results on PSA scatterplot, and presenting a cost-effectiveness acceptibility curve informed by PSA results. The company state that the probabilistic and deterministic results are similar, indicating no signs of non-linearity in the model. However, the ERG note that mean predicted cost savings and QALY benefits are both lower in the probabilistic analysis than the deterministic analysis, and note the negative correlation and broad dispersion of PSA scatterplot points in Figures 6 and 7 of the company's additional evidence submissionb.

At the PAS price, the company report how atezolizumab was dominant in 57.8% of simulations. At a willingness-to-pay threshold of £20,000 per QALY gained, the company estimate a 98% probability that atezolizumab is cost-effective.

5.2.3. Scenario analyses

The company provide a series of deterministic scenario analyses to assess uncertainty around remaining inputs and structural assumptions in the model (CS, p148). Section 2.5.3 of the company's additional evidence submission summarises the scenarios evaluated under the following headings: model settings; clinical inputs; health state utilities; costs and resource use;

and additional scenarios from the clarification questions. The company present the results of the analyses in Table 21 (PAS price) and Table 22 (list price) of their additional evidence report; and note that in all scenarios evaluated, atezolizumab remains cost effective and is dominant at the PAS price for most scenarios evaluated. The most sensitive scenarios related to those assessing the distribution selection for the DFS extraplolation and when using OS extrapolated data. However, the ICERs were all [redacted]. The company advise that while the model is sensitive to distributional choice, all options explored were considered conservative by the UK clinical experts that were involved in the validation of the model. The ERG note how the Net Monetary Benefit (NMB) of atezolizumab falls when the trial data to inform recurrence type is pooled across arms and also falls if the treatment effect in maintained over the full time horizon of the model; a counterintuitive result discussed in Section 4.2.6.2 of this report.

5.2.4. Subgroup analyses

The company provide a subgroup analysis in a subset of the population which excludes EGFR+/ALK+ patients. Results are reported in Section 2.6 of the January 2022 Company additional evidence submission. The with-PAS results in this subgroup indicate that atezolizumab is dominant in both the deterministic and probabilistic analyses (company additional evidence submission Tables 24 and 26); more so than in the licensed population as a whole, with predicted per-patient health benefits of [redacted] QALYs and cost savings of [redacted], in the deterministic analysis.

5.3. Model validation and face validity check

In Appendix N of the CS, the company reported a limited comparison of median DFS between the model arms and IMpower010 observed data. Concerned that the company's analysis lacked concordance with observed IMpower010 Stage II–IIIA PD-L1>=1% DFS and OS over time, the ERG requested further exploration of model-trial fidelity across these endpoints. In response to clarification questions B6 and B9, the company provided a comparison of their model OS predictions with the corresponding OS KM data, for the first time. As illustrated in Section 4.2.6.4 of this report, the company's responses highlighted the manner in which their submitted model underpredicted KM OS for the Stage II–IIIA PD-L1≥1% group. Notably for interpretation of uncertainty in lifetime model projections, the company response to clarification question B6 noted that in interpretation of OS data, "*after Month 36, there is high uncertainty given the small number of patients at risk and the small number of events occurring after then*".

Clarification question B17 sought understanding of the concordance of locoregional recurrence and metastatic recurrence health state membership, across the company's model and the relevant trial population, at (32-month) median trial follow-up. In response, the company did not provide this information, stating that it was not possible to do so as tumour assessment was not planned after first recurrence in IMpower010.

Throughout the CS, including in the company's decsription of their approach to validation, the company referenced discussions with experts that informed or validated assumptions in the company's approach, but provided no details or documentation from these discussions beyond footnote descriptions such as four oncologists were consulted in April 2021. Clarification question B23 requested details of and documentation from these meetings; in response, the company provided slide decks and reports from each meeting referenced in the CS. As noted in Section 4.2.6.2 of this report, expert selection and elicitation processes for these meetings remain unclear, and it remains unclear whether the invited experts reviewed and approved meeting reports after each meeting. However, despite these limitations, the details provided were useful in helping the ERG better understand the company's approach.

The CS reported that an independent validation of the model conducted prior to submission included a technical cell-by-cell verification of formulas, functions and coding.

6. EVIDENCE REVIEW GROUP'S ADDITIONAL ANALYSES

The ERG performed a technical review of the company's cost-effectiveness analysis upon receipt of the original CS dossier. When the company submitted updated versions of their cost-effectiveness model; first in response to clarification questions, then as part of the addendum submission on 31 January 2022, then during the ERG Report factual accuracy check stage on 11 April 2022; the ERG was successful in verifying the company's reported changes to deterministic analyses by recreating deterministic results from the previously submitted model version.

This section is organised as follows. Section 6.1 details the impact of errors identified in the ERG's validation of the executable model. Section 6.2 details a series of scenario analyses exploring the robustness of the cost-effectiveness results to specific assumptions and additional uncertainties identified by the ERG. These analyses were conducted using the ERG-corrected company base-case analysis as a baseline.

The scenario analyses presented in Section 6.2 focus on exploring the following issues and uncertainties:

- Company's choice of DFS parametric survival model (Exploratory Analysis (EA) #1 and EA #2)
- Company's approach to post-hoc inflation of DFS projections (EAs #3 and #4)
- Timing of company-assumed cure point (EA #5)
- Company assumption that treatment arm influences DFS event type (EA #6)
- Company assumption of no cost or HRQL consequences of adjuvant atezolizumab treatment (EA #7)
- Company assumption that exactly one 1200mg vial of atezolizumab is administered at each adjuvant atezolizumab administration visit (EA #8)
- Company assumption that atezolizumab administration NHS resource burden is equal to the NHS Reference Cost for delivery of simple parenteral chemotherapy at first attendance (EA #9)

- Company's approach to estimate post-DFS transition probability values, from published sources (EA #10)
- Company's approach to apply terminal care costs to some patients only (EA #11)
- Company's metastatic recurrence treatment assumptions (EA #12)
- Company assumption of separate administration cost for each pharmacological element of combination intravenous therapy (EA #13)
- Company assumption that only a predefined stopping rule would cause treatment discontinuation, within metastatic recurrence health states (EA #14)

In Section 6.3, the ERG base-case is presented, based on a combination of some of the exploratory analyses presented in Section 6.2.

6.1. ERG corrections and adjustments to the company's base case model

The January 2022 company base case results presented in Section 5 include three company-implemented corrections to the November 2021 CS base case, beyond changes made to adapt the analysis to the restricted PD-L1 ≥50% TC Stage II–IIIA population. These corrections were partly informed by clarification questions, and affect assumed risk of death, patient utility projections and metastatic recurrence treatment costs, as described across Sections 4.2.6, 4.2.7 and 4.2.8. respectively.

Beyond these corrections, the ERG has made four further corrections to the January 2022 company base case results presented in Section 5. These four corrections are described as ERG Correction #1 to #4, throughout Section 4.

- ERG Correction #1, described in Section 4.2.6.2, corrects the company's base case analysis to assume 91.5% of the DFS state are "cured" at 5 years (as stated in the CS), rather than 6 years (as implemented in the company's analysis).
- ERG Correction #2, described in Section 4.2.6.3, corrects the company's approach to calculate transition probability estimates from the published median OS or PFS estimates. The company's approach was not described or justified by the company, either in the CS, or in response to ERG Question B32. Further, the company's approach does not align with a publicly available survival parameter conversion tool,[71] which describes the following

relationship between event probability and median survival time, for an exponential distribution:

$$Probability\ of\ event(t) = 1 - e^{-ht}$$

$$h = \frac{\ln(2)}{median\ event\ time(t)}$$

Where h is hazard rate and t is time period. ERG Correction #2 uses the relationship above to calculate event probabilities from company-identified median survival estimates, in post-DFS model health states.

- ERG Correction #3, described in Section 4.2.8, applies a lower cost for bevacizumab than those used by the company: £810.10 for a 400ml vial and £205.55 for a 100mg vial, versus £924.40 and £242.66, respectively.[64] The ERG note that the lower cost estimates are for concentrate for solution for infusion as opposed to solution for infusion.

- ERG Correction #4, also described in Section 4.2.8, corrects for erroneous costing and dosing assumptions for the oral treatment nintedanib. In the company's analysis, cost of 120 100mg tablets (one pack) is assumed for one 100mg tablet and the cost of 60 150mg tablets (one pack) is assumed for one 150mg tablet. Further, the company assume two 150mg nintedanib doses every three weeks, whereas the BNF lists its use as "200 mg twice daily on days 2–21 of a standard 21 day docetaxel cycle.." within its 2nd-line metastatic or locally recurrent adenocarcinoma NSCLC indication.[64]

- ERG Correction #5, also described in Section 4.2.8, corrects the company assumption that adjuvant atezolizumab patients can be rechallenged with immunotherapy >12 months after adjuvant atezolizumab initiation, in line with the stated company assumption and ERG expert expectation that adjuvant atezolizumab would preclude atezolizumab- or pembrolizumab-containing strategies as metastatic recurrence treatment options.

Table 17 shows summary deterministic and mean probabilistic (5,000 PSA iterations) results from the ERG-corrected January 2022 company base case analysis. Collectively, ERG Corrections #1-5 reduce the total expected costs and increase the total expected QALYs on each model arm, in comparison to the company base case results presented in Table 16. In isolation, the ERG Correction with most consequence for cost-effectiveness results is ERG Correction #5, which substantially reduces the anticipated 1st metastatic recurrence treatment

costs in the adjuvant atezolizumab model arm, implying lifetime per-patient cost savings if adjuvant atezolizumab is approved. To a greater extent than the results in Table 16, with ERG corrections, the company's preferred analysis predicts the introduction of atezolizumab adjuvant therapy will offer an expected QALY benefit at a reduced cost to the NHS and PSS. As in Table 16, the ERG-corrected mean probabilistic results predict less favourable incremental cost and QALYs estimates than corresponding deterministic results, for atezolizumab vs BSC.

Table 17. ERG-corrected company base case results

	Discounted costs	Discounted QALYs	Incremental discounted costs	Incremental discounted QALYs	Cost per QALY gained
ERG corrected company deterministic base case					
Atezolizumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
BSC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ERG corrected company probabilistic base case					
Atezolizumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
BSC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: BSC, best supportive care; ERG, evidence review group; QALYs, quality adjusted life years

6.2. Exploratory and sensitivity analyses undertaken by the ERG

This section explains and interprets results from each ERG EA in turn. Each EA explored a deterministic univariate deviation from the ERG-corrected deterministic company base case analysis. Results from every EA are tabulated in Table 19 (Section 6.2.16), in terms of incremental cost, QALY and ICER implied for adjuvant atezolizumab in each case, and in terms of the deviation from ERG-corrected company base case results each EA produces.

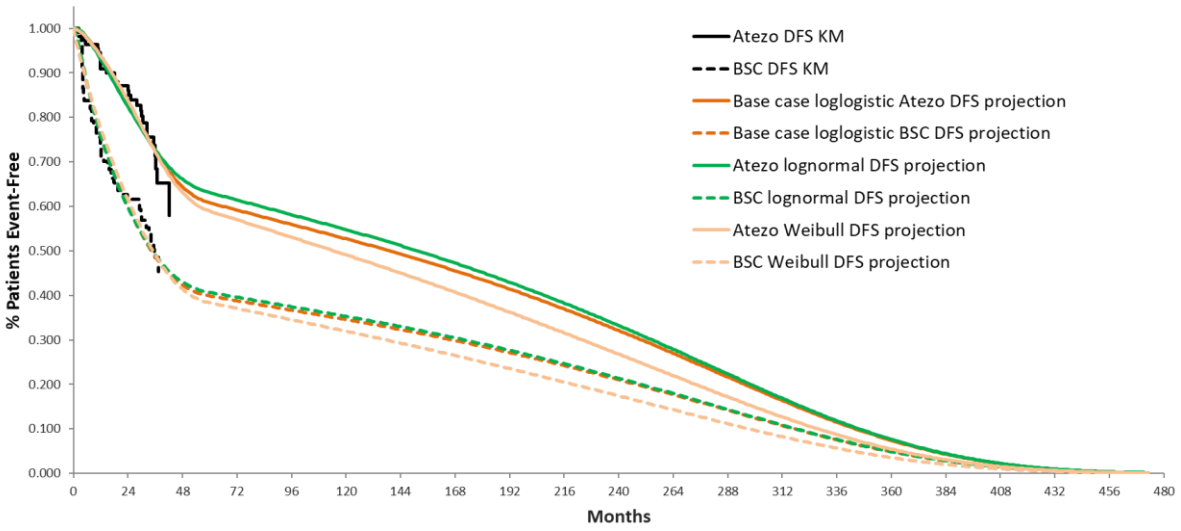
6.2.1. Exploration of DFS alternative parametric survival model – log-normal – EA #1

Section 4.2.6.2 noted the limited justification for one parametric survival model choice over another, as a suitable fit to and extrapolation of IMpower010 PD-L1 ≥50% TC Stage II–IIIA DFS data. The company chose a log-logistic model fit to the DFS KM data in their base case, though as described in Section 4.2.6.2, the company have not justified this selection with reference to the IMpower010 PD-L1 ≥50% TC Stage II–IIIA subgroup data. Further, the CS lacked justification for the log-logistic model over alternatives as a fit to even the IMpower010 PD-L1 ≥ 1% TC Stage II–IIIA DFS data. As explained by Figure 7 (Section 4.2.6.2), the difficulty in choosing one parametric model over another is that the different standard parametric models

produce very different lifetime projections, with notable implications for projected cost-effectiveness estimates. The published evidence on long-term DFS prospects for the patients who would stand to benefit from atezolizumab's introduction as an adjuvant treatment is scarce, and what evidence does exist is not specific to the Stage II-IIA PD-L1 ≥50% patient group affected by this appraisal. With the company's (ERG-corrected) 5-year cure assumption and other post-hoc adjustments, the variation in DFS projections across model types is lessened but the proportion projected to be event-free still differs across different models, particularly on the adjuvant atezolizumab arm.

Figure 20 illustrates the different DFS projections implied by two alternative parametric model choices for DFS, holding everything else in the ERG-corrected company base case constant. Log-normal and Weibull models are chosen to illustrate the implications of no less evidence-based but more optimistic (log-normal) and more pessimistic (Weibull) alternatives to base case log-logistic projections.

Figure 20. Company base case DFS projections alongside alternative projections based (initially) on other standard parametric models



Abbreviations: Atezo, atezolizumab; BSC, best supportive care; DFS, disease free survival; KM, Kaplan-Meier

Deviating from the ERG-corrected company base case analysis by using the log-normal projections in EA #1 improves the predicted lifetime cost savings and QALY benefits of adjuvant atezolizumab, relative to the ERG- corrected company base case. Similar to the ERG-corrected company base case, EA #1 predicts adjuvant atezolizumab to dominate BSC.

6.2.2. Exploration of DFS alternative parametric survival model – Weibull – EA #2

Using the less optimistic Weibull DFS projections shown in Figure 20, the predicted incremental lifetime QALY gain associated with adjuvant atezolizumab decreases relative to the ERG-corrected company base case, though the predicted lifetime cost savings associated with adjuvant atezolizumab also decrease. Similar to the ERG-corrected company base case and EA #1, EA #2 predicts adjuvant atezolizumab to dominate BSC.

6.2.3. Removal of DFS "Ramping up" adjustment – EA #3

As discussed in Section 4.2.6.2, the company's post-hoc "Ramping up" adjustment is unjustified and inflates DFS projections above parametric model predictions, biasing incremental QALY projections in favour of adjuvant atezolizumab. Removal of this ""Ramping up" adjustment in EA #3 illustrates the magnitude of bias, with the predicted QALY gain associated with adjuvant atezolizumab decreasing by [redacted] relative to the ERG-corrected base case. EA #3 also causes the predicted cost-savings associated with adjuvant atezolizumab to increase, and like the ERG-corrected company base case and EAs #1 and #2, predicts adjuvant atezolizumab to dominate BSC.

6.2.4. Removal of DFS "treatment effect waning" adjustment – EA #4

As explained and discussed in Section 4.2.6.2, application of the company's "treatment effect waning" adjustment counterintuitively inflates the atezolizumab DFS projection. Removing the adjustment reduces the predicted QALY gain associated with adjuvant atezolizumab by [redacted] and reduces the predicted cost-savings associated with adjuvant atezolizumab by [redacted]. Adjuvant atezolizumab remains dominant in EA #4.

6.2.5. Exploration of alternative cure assumption – EA #5

As discussed in Section 4.2.6.2, the company's intended cure assumption; that 91.5% of patients who remain DFS at five years can be considered no longer at risk of recurrence; lacks evidence. There are no PD-L1 ≥50% TC Stage II–IIIA subgroup DFS events beyond 40 months in the latest available (21 January 2021) data cut of IMpower010, and there is no indication of a plateau in the DFS KM data. The company did not attempt to fit mixture-cure models, noting that: "*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*." (CS, p166) Yet there is no guarantee or even indication in the data that

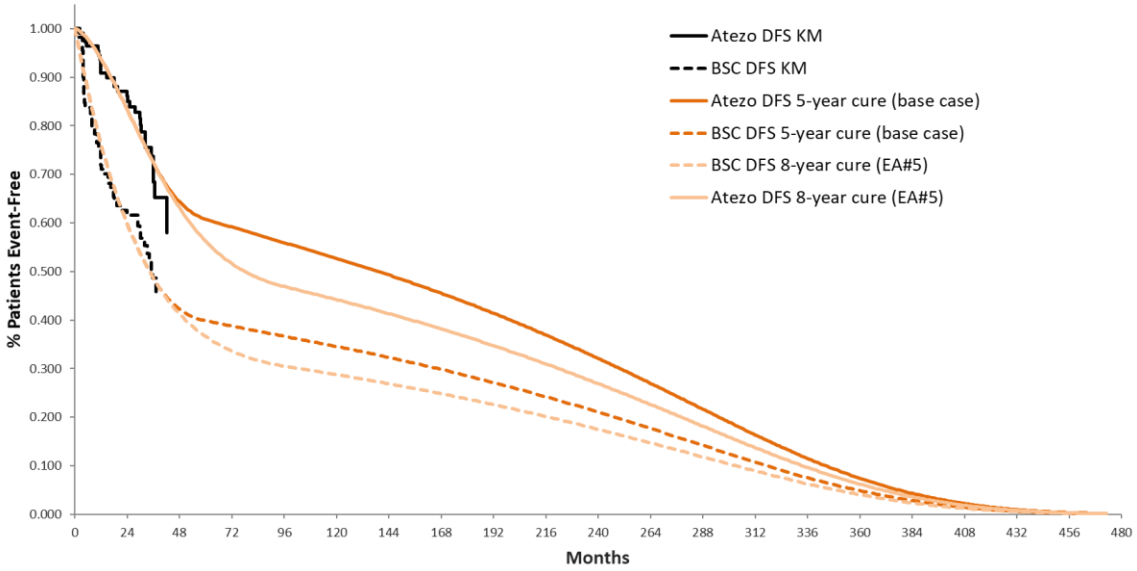
a cure effect will emerge with longer follow-up. Further, the company's cure assumptions are based on a limited reference to a single study of patients in a Japanese hospital, 53% of whom had Stage I disease.[47] Overall, the company provide very little justification for their base case cure assumptions.

Nevertheless, the ERG's clinical adviser notes that long-term disease remission is expected for a group of patients who are treated with adjuvant resection and platinum-based therapy under current care, though notes disease Stage as a prognostic factor and advises that it is difficult to state an expected proportion for Stage II–IIIA patients specifically.

In TA671 (Osimertinib for adjuvant treatment of EGFR mutation-positive non-small-cell lung cancer after complete tumour resection)[11], cure assumptions informed committee decision-making. The TA761 ERG specified two preferred analyses, differed in the timing of the cure assumption.[11] The TA761 ERG's "optimistic" preferred analysis made curative assumptions at five years, consistent with the company submission, while their "pessimistic" preferred analysis delayed onset of curative assumptions to eight years post-baseline in the intervention arm only, to account for three-years of osimertinib treatment in the dataset. The different treatment mechanisms of osimertinib and atezolizumab and 48-week maximum treatment duration of adjuvant atezolizumab muddy translation of assumptions across appraisals, but the lack of evidence and uncertainty around cure assumptions in TA671 and in this appraisal are similar.

In EA #5, the company's cure assumption is delayed to eight years on both model arms. Figure 21 shows the lifetime DFS implications of an eight-year cure assumption in comparison to an ERG-corrected company base-case five-year assumption. Total lifetime DFS is reduced on both model arms, to a marginally greater extent on the adjuvant atezolizumab arm. The projected lifetime QALY gain associated adjuvant atezolizumab remains substantial, at [redacted] incremental discounted QALYs, while the predicted cost-savings associated with atezolizumab increase to [redacted], meaning adjuvant atezolizumab remains dominant.

Figure 21. 8-year cure DFS projections alongside base case five-year DFS projections



Abbreviations: Atezo, atezolizumab; BSC, best supportive care; DFS, disease free survival; EA, exploratory analysis; KM, Kaplan-Meier

6.2.6. Removal of company assumption that adjuvant atezolizumab influences DFS event type – EA #6

As described in Section 4.2.6.3, the company assumed a greater proportion of DFS events are metastatic recurrence events rather than locoregional recurrence events on the BSC arm, versus the atezolizumab arm. The company base this assumption on post-hoc observations of IMpower010 data, without theoretical rationale, or explanation of why they looked for such an association. In response to clarification question B11, in which the ERG requested analysis of whether type of DFS event was significantly associated with treatment arm in the IMpower010 sample in question, the company provided analysis of differences in time to metastatic events (as first DFS event) across arms, but no analysis of the association of treatment arm with type of DFS event.

Overall, the ERG viewed the evidence informing the company assumption that adjuvant atezolizumab influences DFS event type as very uncertain. Relaxing the assumption reduces the expected cost saving associated with adjuvant atezolizumab by [redacted] and reduces the expected QALY gain by [redacted] QALYs. Nevertheless, adjuvant atezolizumab remains dominant in EA #6.

6.2.7. Exploration of cost and HRQL consequences for adverse events of adjuvant atezolizumab treatment – EA #7

As documented in Sections 4.2.7 and 4.2.8.1, the ERG consider it appropriate to apply AE disutility and cost consequences to all on-treatment health states, and requested company scenarios accounting for these considerations at the ERG Clarification stage of this appraisal. In response to clarification question B14, in which the ERG requested a relevant cost for adjuvant atezolizumab AEs to be incorporated, the company took a pragmatic approach in identifying the highest AE cost from three previous NSCLC appraisals (ranging from £921.00 to £7,507.93), each of which could be conservatively assumed to apply to any AE. In response to clarification question B15, in which the ERG requested a relevant patient utility adjustment for adjuvant atezolizumab AEs to be incorporated, the company took a similarly pragmatic approach and identified two disutility values; 0.09002 and 0.11. As reported in Section 4.2.8.1, while the ERG could source the former value to a published estimate of disutility for febrile neutropenia [56], the provenance of the latter value remains unclear to the ERG.

In EA #7, the ERG assume the monthly 1L metastatic AE cost the company use for the BSC arm (£93.45) also applies to the adjuvant atezolizumab stage of the intervention arm. The ERG take this approach as a less extreme and more internally consistent, yet practical, alternative to the company's scenario analyses. The 1st line metastatic recurrence state of the BSC arm is chosen as in current practice patients at this stage will be given PD-L1/PD-1-targeting immunotherapy if suitable. To adjust for anticipated AE HRQL effects of adjuvant atezolizumab treatment, the lower disutility value identified by the company is used. In EA#7, the expected cost saving associated with adjuvant atezolizumab falls by [redacted] and the expected QALY gain falls by [redacted] QALYs. Adjuvant atezolizumab remains dominant in EA #7.

6.2.8. Exploration of implications of batch remake occurrences – EA #8

As described in Section 4.2.3, the company assume with certainty that exactly one 1200mg vial of atezolizumab is administered at each adjuvant atezolizumab treatment visit. Independent advice to the ERG from one hospital pharmacist has highlighted that rarely, pharmacy batch remakes are required, with the cost incurred by the NHS. Data from this pharmacist suggests the mean number of 1200mg atezolizumab vials per patient administration is 1.012 vials (4sf). Assuming 1.012 vials (4sf) per adjuvant atezolizumab administration and assuming no wastage, the expected lifetime cost saving associated with adjuvant atezolizumab falls by [redacted]. Adjuvant atezolizumab remains dominant.

6.2.9. Capturing adjuvant atezolizumab administration resource use expectations – EA #9

Following clinical advice, the ERG consider it appropriate to include costs for clinical review and blood test in addition to the IV cost for the administration of adjuvant atezolizumab, as summarised in Section 4.2.8.1. Following clarification question B13, which requested these additional costs be incorporated, the company included a cost for clinical review and blood tests as part of the administration costs for atezolizumab. EA #9 incorporates these expected costs into the intervention arm of the analysis, causing the expected lifetime cost saving associated with adjuvant atezolizumab to fall by [redacted]. Adjuvant atezolizumab remains dominant.

6.2.10. Exploration of company's alternative approach to estimate exponential post-DFS model transition probability values – EA #10

The company included two approaches to calculate transition probability estimates from the noted published sources, assuming an exponential distribution. The simplest of the two used the median OS (or PFS) estimate only, while the second approach fitted an exponential model to digitised KM data. The company chose to use the simpler approach in their base case analysis, without good justification. Further, the company applied the simpler approach erroneously in their model, calculating the hazard from the median estimate and applying the hazard as the cycle probability. In Section 6 of this report, correction of this error is referred to as ERG Correction to the company base case #2. Using exponential model fits to digitised KM data has little effect upon cost-effectiveness results, as expected. The expected cost saving associated with adjuvant atezolizumab falls by [redacted] and the expected QALY gain falls by [redacted] QALYs. Adjuvant atezolizumab remains dominant.

6.2.11. Removal of company assumption that only some patients incur terminal care costs – EA #11

The ERG did not believe there was sufficient justification for the assumption that the terminal care cost associated with "all cause" death is zero, as explained in Section 4.2.8.4. As documented in Section 4.2.8.4, the company assume a terminal care cost of terminal care cost of £4,598.01 applies to some patients, but not others, in a manner that implies higher terminal care costs on the comparator arm of the analysis. The ERG was not convinced that the company's post-hoc analysis of cause of death data from IMpower010 justification for this favourable assumption, and demonstrate the effect of relaxing this assumption; instead assuming all patients incur a £4,598.01 terminal care cost; in this EA. In EA #11, the expected

lifetime cost saving associated with adjuvant atezolizumab falls by [redacted]. Adjuvant atezolizumab remains dominant.

6.2.12. Exploration of metastatic recurrence treatment assumptions – EA #12

At 1st metastatic recurrence, the company's assumptions are not representative of the expected NHS treatment pathway, as discussed in Section 4.2.8.3. EA #12 captures ERG adviser- and NHS algorithm-consistent treatment and administration costs at 1st metastatic recurrence, with the following assumed about patients *at 1st metastatic recurrence*, based on advice noted in Section 4.2.8.3.

- 80% of patients fit for treatment are assumed to have performance status 0 or 1 and otherwise be immunotherapy-suitable.
- 70% of immunotherapy-suitable patients are assumed to have stable disease, and therefore receive atezolizumab or pembrolizumab monotherapy, as opposed to pembrolizumab + pemetrexed + platinum.
- 50% of those receiving atezolizumab or pembrolizumab monotherapy are assumed to receive atezolizumab, as opposed to pembrolizumab.

More generally, and also based on advice noted in Section 4.2.8.3, the following assumptions are made:

- 75% of patients are assumed to have non-squamous NSCLC.
- 90% of platinum therapy use is assumed to be carboplatin, as opposed to cisplatin.
- 90% of doublet chemotherapy is assumed to be gemcitabine + platinum, as opposed to vinorelbine + platinum.

Consistent with the CS, in line with advice from the ERG's clinical expert, where eligible the ERG assume a patient will only receive one course of PD-L1/PD-1 targeting immunotherapeutic agent (atezolizumab, pembrolizumab); adjuvant atezolizumab would preclude atezolizumab or pembrolizumab to treat metastatic recurrence.

In the probabilistic analysis of the ERG's preferred base case in Section 6.3, parameter uncertainty around the above probability estimates were assumed to follow beta distributions, with 100 total successes (alpha parameter) or failures (beta parameter) in each case. For

example, parameter uncertainty around the proportion of platinum therapy use assumed to be carboplatin was captured using a beta distribution with alpha = 90 and beta = 10.

Table 18 summarises the implied 1st metastatic treatment options, expected uptake of each option given stated assumptions, and implied deterministic monthly treatment administration cost associated with each treatment option. The treatment options are those described by the ERG's adviser based on the cited NHS treatment algorithm,[67] as described in Section 4.2.8.3. To inform monthly treatment cost estimates, SmPC descriptions of dosage, administration frequency and any stopping rules for each pharmaceutical in Table 18 were consulted[72-76] to verify company assumptions if the drug was already incorporated in the model, or otherwise inform dosing and administration frequency assumptions from first principles. To verify and source treatment costs, latest NHS eMIT and BNF databases were consulted, with the lowest cost estimate used when different estimates were available across the two databases. The approach to monthly treatment cost calculation in Table 18 assumes no wastage, for simplicity. The administration cost assumed for IV therapy is that used by the company (NHS Reference Cost (2019-20) Code SB12Z), as described in Section 4.2.8.1. Consistent with ERG adviser guidance noted in Section 4.2.8.1 and as explored at all treatment lines in EA #13, the approach to monthly treatment cost calculation in Table 18 assumes the administration cost of IV combination therapy is no greater than the administration cost of IV monotherapy. Consistent with results presented elsewhere in Sections 5 and 6, Table 18 cost estimates use the cPAS-discounted price for atezolizumab, but otherwise represent list prices.

Table 18. EA #12 1st metastatic recurrence treatment options, uptake and cost summary

Model Arm	Disease Histology	Treatment Regimen	Monthly Treatment and Admin Cost	Expected Uptake	Uptake-adjusted Monthly Cost
Atezolizumab	Non-squamous carcinoma	Pemetrexed & Cisplatin	£2,444.48	6.75%	£165.00
		Pemetrexed & Carboplatin	£2,470.60	60.75%	£1,500.89
		Vinorelbine	£2,216.63	7.50%	£166.25
	Squamous carcinoma	Gemcitabine & Cisplatin	£1,590.56	2.25%	£35.79
		Gemcitabine & Carboplatin	£1,616.69	20.25%	£327.38
		Vinorelbine & Cisplatin	£2,236.59	0.25%	£5.59
		Vinorelbine & Carboplatin	£2,246.00	2.25%	£50.53
BSC	Non-squamous carcinoma	Pembrolizumab	£8,341.45	21.00%	£1,751.71
		Atezolizumab	[redacted]	21.00%	[redacted]
		Pembrolizumab & Pemetrexed & Cisplatin	£10,068.35	1.80%	£181.23
		Pembrolizumab & Pemetrexed & Carboplatin	£10,094.47	16.20%	£1,635.30
		Pemetrexed & Cisplatin	£2,444.48	1.35%	£33.00
		Pemetrexed & Carboplatin	£2,470.60	12.15%	£300.18
		Vinorelbine	£2,216.63	1.50%	£33.25
	Squamous carcinoma	Pembrolizumab	£8,341.45	7.00%	£583.90
		Atezolizumab	[redacted]	7.00%	[redacted]
		Pembrolizumab & Carboplatin & Paclitaxel	£8,410.42	6.00%	£504.63
		Gemcitabine & Cisplatin	£1,590.56	0.45%	£7.16
		Gemcitabine & Carboplatin	£1,616.69	4.05%	£65.48
		Vinorelbine & Cisplatin	£2,236.59	0.05%	£1.12
		Vinorelbine & Carboplatin	£2,260.72	0.45%	£10.17

Abbreviations: BSC, best supportive care; EA, exploratory analysis

The implied expected monthly treatment and acquisition cost of 1st metastatic recurrence treatment acquisition and administration from Table 18 is £2,251.43 for patients on the adjuvant atezolizumab arm of the analysis, and [redacted] for patients on the BSC arm. In comparison to company base case assumptions (£2,114.19 and £7,225.59 respectively, as described in Section 4.2.8.3), expected 1st metastatic recurrence costs are reduced on both arms, with the notable reduction on the BSC arm explained in part by the lower expected use of pembrolizumab, relative to company assumptions.

At 2nd metastatic recurrence, the only warranted amendment to the company's January 2022 assumptions is removal of pemetrexed + carboplatin as treatment option, based on advice and algorithm indication, documented in Section 4.2.8.3, that this is a 1st metastatic recurrence treatment option only. In EA #12, assumed uptake of pemetrexed + carboplatin at 2nd metastatic recurrence is reduced from [redacted] to 0%, across treatment arms. This [redacted] market share is assumed to be distributed across other treatment options, so that the relative split across these options remains consistent with company base case assumptions. This implies that of those patients assumed to receive active 2nd metastatic recurrence treatment, 60.27% receive nintedanib + docetaxel, 31.51% receive docetaxel monotherapy, and 8.22% receive gemcitabine + carboplatin. The implied monthly 2nd metastatic recurrence treatment and administration cost is £1,164.36 across model arms; a lower estimate than the £1,420.82 implied by the company's revised treatment assumptions.

The expected lifetime cost associated with adjuvant atezolizumab [redacted] in EA #12, by [redacted] Adjuvant atezolizumab remains dominant, but far less so than in the ERG-corrected company base case. Importantly, EA #12 does not relax the company assumption of no metastatic recurrence treatment discontinuation, addressed separately in EA #14.

6.2.13. Removal of company assumption of separate administration cost for each pharmacological element of combination intravenous therapy – EA #13

As discussed in Section 4.2.8.2, for combination therapy with multiple IV components, the company assumes the same (NHS Reference Cost (2019-2020) code (SB12Z)) cost applies to each drug element of combined treatment (for locoregional recurrence and metastatic recurrence). This implies, for example, that cisplatin + vinorelbine administration is twice as expensive as atezolizumab administration. Independent clinical advice to the ERG suggests one tariff for day case attendance is appropriate, irrespective of the complexity of treatment. When

the same (SB12Z) cost is assumed for every IV visit, as opposed to every IV drug element of every administration visit, the expected per-patient cost associated with the introduction of adjuvant atezolizumab [redacted] by [redacted] Adjuvant atezolizumab remains dominant.

6.2.14. Relaxation of company assumption of no treatment discontinuation within metastatic recurrence health states – EA #14

As explained in Section 4.2.8.3, the company assume no treatment discontinuation among those assumed to be eligible for active treatment, until they experience another event (that is, 2nd metastasis or death). The only exception to this is the imposition of a two-year stopping rule for pembrolizumab, within the 1st metastatic recurrence health state.

While the effect of the assumption is limited by the estimated time spent in these states in the company's analysis, as noted in Section 4.2.8.3, this assumption is inconsistent with the approach used for adjuvant atezolizumab in the company's analysis (whereby treatment discontinuation data from IMpower010 are used to limit expected atezolizumab costs), and contra to decision-making assumptions in metastatic NSCLC NICE appraisals including TA705 (Atezolizumab monotherapy for untreated advanced non-small-cell lung cancer[70]).

The effect of the company approach is to skew cost effectiveness results in favour of adjuvant atezolizumab, primarily as patients on the BSC arm of the analysis face higher expected 1st metastatic recurrence costs (as described in Sections 4.2.8.3 and 6.2.12).

Accurately correcting for the bias is not possible without treatment discontinuation data for metastatic treatments (some of which are owned by the company). Even with good data, accounting for per-cycle discontinuations within the company's chosen model structure would be cumbersome and time-consuming. As a practical illustration, EA #14 assumes that those eligible for metastatic treatment spend half their time in metastatic recurrence health states actively receiving treatment, by applying a multiplier of 0.5 to the monthly estimated costs of metastatic recurrence treatment. Applying this adjustment increases the expected per-patient cost associated with atezolizumab by [redacted], in isolation causing the model to predict adjuvant atezolizumab to be associated with a lifetime incremental cost burden, with an associated ICER of [redacted] gained.

6.2.15. Relaxation of the assumption of no retreatment with PD-L1 or PD-1 targeting immunotherapeutic treatments at metastatic recurrence – EA #15

It is the assumption of the ERG's clinical adviser and the company that adjuvant atezolizumab, if recommended, will preclude use of atezolizumab or pembrolizumab where recommended later in the treatment pathway. Nevertheless, for illustrative purposes the ERG provide an exploratory analysis indicating the implications of relaxing this assumption for cost-effectiveness results, subject to the assumptions of the company's model.

In EA #15, 1st metastatic treatment cost and effectiveness assumptions are aligned across model arms. That is, assumptions on the adjuvant atezolizumab arm of the model are set equal to assumptions on the BSC arm. For effectiveness, this means 77% of patients receiving active treatment for 1st metastatic treatment are assumed to receive atezolizumab- or pembrolizumab-containing therapy and face a 0.052 (3dp) cycle probability of an event (recurrence or death), and the remaining 23% of patients are assumed to face a 0.108 (3dp) cycle probability of an event. The ERG note that imposing this assumption within the company's model leads to an error flag in sheet "Efficacy Inputs" cell "H:161". This appears to be due a rounding error, that the ERG do not see as meaningful for results.

For costs, EA #15 assumes the clinical adviser- and NHS algorithm-informed treatment uptake described in EA #12 (Section 6.2.12) for BSC patients applies across treatment arms. That is, an expected monthly treatment and administration cost of [redacted] The ERG note that the clinical adviser- and NHS algorithm-informed assumptions described in Sections 4.2.8.3 and 6.2.12 imply 80% of 1st metastatic recurrence patients suitable for treatment receiving atezolizumab- or pembrolizumab-containing therapy.

EA #15 leads to a [redacted] increase in the expected per-patient cost of atezolizumab, and a [redacted] QALY (2dp) increase in expected QALYs gained associated with the introduction of adjuvant atezolizumab, implying an ICER of [redacted] per QALY gained associated with adjuvant atezolizumab. As discussed in Section 6.4, the effect of EA #15 upon model results illustrates how in the company's model, PD-L1 or PD-1 targeting immunotherapeutic treatments are not predicted to be cost-effective. Though this analysis does not include the cost implications of any confidential discount agreements for pembrolizumab, this appears to highlight the company's model's inconsistency with NICE recommendations for atezolizumab-

and pembrolizumab-containing therapies as cost-effective at 1st metastatic recurrence (TAs 683, 705 and 531).

The ERG do not view the company's model to be a robust guide to the likely cost-effectiveness of PD-L1 or PD-1 targeting immunotherapeutic treatments for metastatic recurrence after adjuvant atezolizumab. This is partly owing to a lack of evidence on the effectiveness of atezolizumab- or pembrolizumab-containing therapy for metastatic recurrence after previous treatment with atezolizumab, but also owing to the company's approach to model post-DFS patient outcome and cost assumptions, which we highlight under ERG Key Issues 3 and 5. This is partly owing to a lack of evidence on the effectiveness of atezolizumab- or pembrolizumab-containing therapy for metastatic recurrence after previous treatment with atezolizumab, and also owing to the company's approach to model post-DFS patient outcome and cost assumptions, which is highlighted under ERG Key Issues 3 and 5.

6.2.16. Impact on the ICER of additional clinical and economic analyses undertaken by the ERG

The ERG made each change described in Sections 6.2.1 to 6.2.14 individually. The effect of each change upon the ERG-corrected company base case is provided in Table 19. Generally, the effect of isolated EA changes upon the company-preferred ICER is [redacted]. Further, none of the EAs [redacted]. However, it is important to consider that results in this report do not include confidential discounts to treatments other than atezolizumab, which given pathway implications, reduce the predicted cost-effectiveness of adjuvant atezolizumab. In addition, as many of the EAs in Table 19 interplay, the effect of these exploratory changes in combination are more consequential. This is illustrated in the ERG's preferred analyses, in Section 6.3.

Two of the three EAs with the greatest impact upon results of those tested in Table 19, EAs #12 and #14, address imprecision and bias in the company's metastatic recurrence treatment pathway and in treatment duration assumptions. Relaxing the assumption that adjuvant atezolizumab precludes later treatment with atezolizumab or pembrolizumab (EA #15) is the most impactful EA. The fourth most consequential EA, #9, partially addresses underestimation of the financial treatment administration burden associated with the introduction of adjuvant atezolizumab in the company's analysis. Each of the EAs tested predict a health benefit of

adjuvant atezolizumab of at least [redacted] QALYs. As such, each is reliant on an assumption that short-term DFS benefit in IMpower010 will translate to greater-than-proportionate lifetime DFS and OS benefit in NHS practice.

Table 19. ERG's exploratory analyses

Exploratory assumption	Section in ERG report	Incremental costs	Incremental QALYs	ICER £/QALY	+/- company base case
ERG-corrected company base-case	6.1	[redacted]	[redacted]	[redacted]	
EA #1: Lognormal DFS	6.2.1	[redacted]	[redacted]	[redacted]	[redacted]
EA #2: Weibull DFS	6.2.2	[redacted]	[redacted]	[redacted]	[redacted]
EA #3: Remove "ramping up" adjustment	6.2.3	[redacted]	[redacted]	[redacted]	[redacted]
EA #4: Remove "treatment effect waning" adjustment	6.2.4	[redacted]	[redacted]	[redacted]	[redacted]
EA #5: Cure assumption delayed to 8 years	6.2.5	[redacted]	[redacted]	[redacted]	[redacted]
EA #6: DFS event type not affected by treatment arm	6.2.6	[redacted]	[redacted]	[redacted]	[redacted]
EA #7: Apply AE cost and HRQL effects for all active treatments	6.2.7	[redacted]	[redacted]	[redacted]	[redacted]
EA #8: Assume some atezolizumab batch remakes	6.2.8	[redacted]	[redacted]	[redacted]	[redacted]
EA #9: Capture adjuvant atezolizumab administration burden expectations	6.2.9	[redacted]	[redacted]	[redacted]	[redacted]
EA #10: Company's alternative "digitised approach" to exponential post-DFS transition probability estimation	6.2.10	[redacted]	[redacted]	[redacted]	[redacted]
EA #11: Terminal care costs for all patients	6.2.11	[redacted]	[redacted]	[redacted]	[redacted]
EA #12: Capture expected metastatic treatment pathway	6.2.12	[redacted]	[redacted]	[redacted]	[redacted]
EA #13: Assume one administration cost for combination IV therapy	6.2.13	[redacted]	[redacted]	[redacted]	[redacted]
EA #14: Relax assumption of no treatment discontinuation within metastatic recurrence health states	6.2.14	[redacted]	[redacted]	[redacted]	[redacted]
EA #15: Relax assumption of no PD-1/PD-L1 targeting immunotherapy at 1st metastatic recurrence after adjuvant atezolizumab	6.2.15	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: AE, adverse event; DFS, disease free survival; EA, exploratory analysis; ERG, Evidence Review Group; HRQL, health related quality of life; ICER, incremental cost-effectiveness ratio; IV, intravenous; QALY, quality adjusted life year

6.3. ERG's preferred assumptions

The ERG's preferred adaptations to the ERG-corrected company-preferred base case draw on most but not all of the EAs described and presented in the previous section. Table 20 demonstrates the step-by-step impact of ERG-preferred changes to the company's preferred settings, towards ERG-preferred analyses.

The ERG specified two preferred analyses: an "optimistic" ERG-preferred base case and an alternative, less-optimistic ERG-preferred base case. The estimated mean probabilistic ICER (all probabilistic results presented are based on 5,000 PSA iterations) is [redacted] using optimistic assumptions and [redacted] using less optimistic assumptions, as shown in Table 20.

The differences between the ERG-corrected company base case and the ERG's "optimistic" settings are adjustments the ERG view as necessary within the scope of the ERG's role, to address bias and inaccuracies in the company's preferred approach.

The differences between the ERG's optimistic and alternative preferred analyses are differences in assumptions around DFS parametric model selection and timing of cure assumption. These are aspects of the model for which there is little or no evidence from the company's evidence submissions to justify one choice over another, but aspects for which choices are consequential for cost-effectiveness predictions. To an extent, this is a feature of cost-effectiveness analysis of technologies in adjuvant settings. In this situation, the ERG feel it is appropriate to specify two preferred base case analyses, to illustrate the importance of key unevidenced uncertainties for decision-making, rather than tend uncertainly towards one set of assumptions.

We note that we do not see our optimistic and alternative approaches as maximum and minimum estimates of the cost-effectiveness of adjuvant atezolizumab. In particular, the ERG notes that some structural and other uncertainties in the company's analysis, discussed in Section 6.4, have not been fully addressed by ERG amendments to the company's model. Given the uncertainty around lifetime projections of survival and morbidity risk, we stress that the cost-effectiveness of adjuvant atezolizumab is inherently uncertain.

Table 20. ERG's preferred model assumptions

Description	Section in ERG report	Cumulative ICER £/QALY
Company base-case (det)	*5.1*	[redacted]
ERG-corrected company base case (det)	*6.1*	[redacted]
ERG-corrected company base case (det) + EA #3 = A *EA #3: Remove "ramping up" adjustment*	*6.2.3*	[redacted]
A + EA #4 = B *EA #4: Remove "treatment effect waning" adjustment*	*6.2.4*	[redacted]
B + EA #6 = C *EA #6: DFS event type not affected by treatment arm*	*6.2.6*	[redacted]
C + EA #7 = D *EA #7: Apply AE cost and HRQL effects for all active treatments*	*6.2.7*	[redacted]
D + EA #8 = E *EA #8: Assume some atezolizumab batch remakes*	*6.2.8*	[redacted]
E + EA #9 = F *EA #9: Capture adjuvant atezolizumab administration burden expectations*	*6.2.9*	[redacted]
F + EA #11 = G *EA #11: Terminal care costs for all patients*	*6.2.11*	[redacted]
G + EA #12 = H *EA #12: Capture expected metastatic treatment pathway*	*6.2.12*	[redacted]
H + EA #13 = I *EA #13: Assume one administration cost for combination IV therapy*	*6.2.13*	[redacted]
I + EA #14 = J = ERG-preferred optimistic base case (det) *EA #14: Relax assumption of no treatment discontinuation within metastatic recurrence health states*	*6.2.14*	[redacted]
ERG-preferred optimistic base case (mean prob)		[redacted]
J + EA #2 = K *EA #2: Assume Weibull distribution for DFS*	*6.2.2*	[redacted]
K + EA #5 = L = ERG-preferred pessimistic base case (det) *EA #5: Delay cure assumption to 8 years*	*6.2.5*	[redacted]
ERG-preferred alternative base case (mean prob)		[redacted]

Abbreviations: AE, adverse event; DFS, disease free survival; det, deterministic; EA, exploratory analysis; ERG, Evidence Review Group; HRQL, health-related quality of life; ICER, incremental cost-effectiveness ratio; IV, intravenous; prob, probabilistic; QALY, quality adjusted life year

Note: negative ICERs indicate adjuvant atezolizumab as less costly and more effective than BSC (dominant)

Table 21 and Table 22 summarise probabilistic mean and deterministic summary results, for ERG-preferred optimistic and alternative analyses, respectively. Figure 22 and Figure 23 (adapted by the ERG from figures in the company's model) show PSA scatterplots from the probabilistic analyses summarised respectively in Table 21 and Table 22. The differences between mean probabilistic and deterministic ICERs are explained by the asymmetrical distributions of the PSA iterations in Figure 22 and Figure 23. These figures illustrate the

substantial parameter uncertainty in the expected incremental QALYs associated with adjuvant atezolizumab.

Table 21. Probabilistic and deterministic results summary, ERG-preferred optimistic base case

	Discounted costs	Discounted QALYs	Incremental discounted costs	Incremental discounted QALYs	Cost per QALY gained
Deterministic base case, ERG-preferred optimistic analysis					
Atezolizumab	[redacted]	[redacted]			
BSC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Probabilistic base case, ERG-preferred optimistic analysis					
Atezolizumab	[redacted]	[redacted]			
BSC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: BSC, best supportive care; ERG, Evidence Review Group; QALY, quality-adjusted life-year.

Figure 22. PSA Scatterplot, ERG-preferred optimistic base case

Abbreviations: ATZ, atezolizumab; BSC, best supportive care; ERG, Evidence Review Group; ICER, incremental cost-effectiveness ratio; Inc, Incremental; PSA, probabilistic sensitivity analysis; QALY, quality-adjusted life-year.

Table 22. Probabilistic and deterministic results summary, ERG-preferred alternative base case

	Discounted costs	Discounted QALYs	Incremental discounted costs	Incremental discounted QALYs	Cost per QALY gained
Deterministic base case, ERG-preferred pessimistic analysis					
Atezolizumab	[redacted]	[redacted]			
BSC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Probabilistic base case, ERG-preferred pessimistic analysis					
Atezolizumab	[redacted]	[redacted]			
BSC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: BSC, best supportive care; ERG, Evidence Review Group; QALY, quality-adjusted life-year.

Figure 23. PSA Scatterplot, ERG-preferred alternative base case

Abbreviations: ATZ, atezolizumab; BSC, best supportive care; ERG, Evidence Review Group; ICER, incremental cost-effectiveness ratio; Inc, Incremental; PSA, probabilistic sensitivity analysis; QALY, quality-adjusted life-year.

6.4. Conclusions of the cost-effectiveness section

The ERG was broadly satisfied that the cost-effectiveness evidence submitted by the company addresses the decision problem at hand. That is, the company's cost-effectiveness model estimates the lifetime cost-effectiveness implications of introducing adjuvant atezolizumab to

NHS England practice for the health service from a cost perspective, and for the affected PD-L1 ≥50% TC Stage II–IIIA NSCLC patient group, from a health effects perspective.

The ERG was not satisfied that the company's cost-effectiveness results provide an unbiased estimate of the likely cost-effectiveness of adjuvant atezolizumab. The company's economic analysis is in large part driven by DFS KM data from the PD-L1 ≥50% TC Stage II–IIIA subgroup of IMpower010. Use of these data is appropriate, though for inference the ERG note that while assessing DFS in the PD-L1 ≥50% TC Stage II–IIIA population was a secondary efficacy objective in IMpower010, this sample comprises n=115 patients on the atezolizumab arm and n=114 on the BSC arm. The ERG also noted the 21 January 2021 data cut-off date of the submitted dataset, 2 years and 5 days after the last patient was randomised into IMpower010. From these data, the company projected atezolizumab to offer an extension in DFS of over 4 years (undiscounted, translating to a [redacted] incremental discounted DFS QALY gain), through a series of post-hoc adjustments to the company's selected (log-logistic) parametric survival model extrapolations. Most important among these adjustments is the imposition of a cure assumption: specifically, that 91.5% of patients who remain disease-free at 5 years are no longer at risk of disease recurrence, with lifetime survival, HRQL and NHS/PSS cost consequences. As discussed in Section 4.2.6, all aspects of the company's cure assumptions are almost completely unjustified by relevant data, though the ERG's clinical adviser notes that follow-up is usually for 5 years only after surgery, if the patient remains disease-free. Further, decision-making in the recently completed TA761[11] appraisal of osimertinib in EGFR mutation-positive post-resection NSCLC patients was based on broadly similar cure assumptions.

The company's approach to post-DFS modelling is a source of concern for the ERG. From an expected prognosis and survival perspective, the company intended to assume adjuvant atezolizumab will preclude subsequent atezolizumab or pembrolizumab (expectations the ERG share), but assume little expected benefit from these immunotherapies in the metastatic recurrence setting, on the BSC arm of the analysis. The ERG-corrected company analysis predicts an [redacted] incremental discounted QALY benefit in the "1st metastatic recurrence, treated" state of the comparator arm (where patients may receive atezolizumab or pembrolizumab) versus the same state in the intervention arm (where they may not). This seems to be an underestimate of the assumed benefit of atezolizumab in first metastatic recurrence in TA705, where both company and ERG assumed atezolizumab offered an expected 0.08 QALYs fewer than pembrolizumab.[70] In TA531, which led to the approval of pembrolizumab in this setting, pembrolizumab appears to have been assumed to offer an

expected benefit of 0.59 to 1.07 QALYs versus BSC.[77] Further, the ERG-corrected company analysis predicts that 1st metastatic recurrence treatment costs will be reduced by [redacted] if adjuvant atezolizumab is introduced. As such, and confidential financial agreements for pembrolizumab notwithstanding, contra to NICE TA705 and TA531 decision-making and to the benefit of adjuvant atezolizumab in this appraisal, the company's model roughly predicts that the ICER associated with the availability of immunotherapies at 1st metastatic recurrence is [redacted] per QALY gained [redacted]

The company draw heavily on data from outside of IMpower010. However, where this is done, the data identification and selection process is often unclear and/or poorly justified. Company modelling choices in using these data are then often similarly poorly justified, and in some cases introduce bias. For example, as described in Section 4.2.6.3, after seeking clarification of the post-DFS disease recurrence and mortality data identification process in clarification question B32, the ERG remained unsure that the most appropriate data sources have been used. Once identified, the company assumed an exponential model fit to all post-DFS time-to-event data, without presenting any evidence to support this choice. In fact, ERG exploratory analyses in Section 4.2.6.3 suggest an exponential model is inappropriate for most of the study data used. Further, the ERG identified an error in the company's calculation of exponential cycle probability estimates from median DFS and OS estimates.

ERG corrections and preferred amendments to the company's preferred analysis, documented throughout Section 6, address bias and inaccuracy in the company's model to an extent. The ERG's optimistic preferred analysis removes some inflationary post-hoc adjustments to DFS, including the company's "ramping up" adjustment, and addresses various biases in the company's approach to costs. Most important among these are the biases caused by the company's approach to metastatic recurrent treatment costs. While the company's metastatic treatment options are inaccurate and naïve to the complexity of the NHS treatment pathway, despite data sharing between the ERG and company, via NICE, the company-preferred assumption of zero treatment discontinuation within metastatic recurrence health states clearly biases the company's analysis in favour of adjuvant atezolizumab.

The ERG is confident that the ERG-preferred optimistic analysis presents an optimistic estimate of the cost-effectiveness of atezolizumab for post-resection PD-L1 ≥50% TC Stage II–IIIA NSCLC patients. This analysis maintains the company assumption that 91.5% of patients who are estimated remain disease-free at five years are no longer at risk of disease recurrence; in

the deterministic iteration of this analysis, 53.8% of atezolizumab patients are predicted to be disease-free at five years, and 91.5% of these patients; 49.2% of all patients; are assumed to be cured. Further, (ERG-corrected) company-preferred post-DFS disease recurrence and mortality rate assumptions remain unchanged in this analysis.

The ERG's alternative preferred analysis is less optimistic, but whether it is pessimistic is not clear. This analysis differs from the optimistic analysis in the use of a different but equally plausible parametric model fit to the observed IMpower010 DFS KM data, and in delaying cure assumptions to eight years. In the deterministic iteration of this analysis, 24.7% of atezolizumab patients are predicted remain disease-free at eight years, an effective cure probability of 22.6%.

Both ERG-preferred analyses remained subject to further assumptions and limitations highlighted throughout Section 4. Perhaps the most important uncertainty not tested fully within ERG exploratory analysis, and difficult to address within the company's chosen model structure, is the substantial uncertainty around the likely overall survival benefit of using a PD-L1-targeting immunotherapeutic agent in the adjuvant Stage II–IIIA, post-resection setting, as opposed to at metastatic recurrence. While the OS KM data in the PD-L1 ≥50% TC Stage II–IIIA population are promising in the short term, the overall effect across NHS England patients may be tempered by the inability to harness PD-L1 or PD-1 targeting immunotherapeutic treatments at metastatic recurrence. The less optimistic of the ERG-preferred deterministic analyses still predicts a 1.67 year overall survival benefit for adjuvant atezolizumab (translating to a [redacted] discounted QALY benefit, as shown in Table 22). As illustrated in Section 4.2.6.4, the company's model provides survival projections that are a poor fit to the observed PD-L1 ≥50% TC Stage II–IIIA OS KM data. In response to clarification question B10, the company provided a scenario in which parametric model fits to these OS data were used. Though the ERG place little weight in this scenario, it is notable that this company scenario predicted a survival benefit for BSC over atezolizumab.

Other assumptions in the company's economic analysis that ERG exploratory analyses and amendments do not address include: the company assumption that patients who do not complete the full 16 cycles of adjuvant atezolizumab are no different in outcomes to those who do (Section 4.2.3); the company assumption that patients who experience locoregional recurrence cannot subsequently experience metastatic recurrence (Section 4.2.4); uncertainty around patient utility assumptions, drawn from various published sources each with limitations for use in NICE appraisals in general and as proxy data for NSCLC patients in absence of

HRQL data in IMpower010, specifically (Section 4.2.7); and, the NHS cost implications of earlier PD-L1 status testing, to inform adjuvant atezolizumab eligibility if made available (Section 4.2.8).

Overall, the cost-effectiveness of adjuvant atezolizumab is highly uncertain, and the decision uncertainty in this appraisal is not fully captured by the economic analysis results in this report. This section has summarised limitations and uncertainties not addressed within the company's analysis nor within the scope of the ERG's review. In addition, the results presented throughout Sections 5 and 6 reflect a confidential discount for atezolizumab but do not reflect confidential discounts for treatments later in the pathway, with most consequence for patients experiencing 1st metastatic recurrence on the BSC arm; as such, the results presented in this report over-estimate the cost-effectiveness of adjuvant atezolizumab.

Much of the decision uncertainty for this appraisal can be reduced with further data collection. Continued follow-up of PD-L1 ≥50% TC Stage II–IIIA IMpower010 patients can provide evidence on the likelihood of modelled DFS projections, and more mature evidence on the likely OS implications of adjuvant atezolizumab. Data collection from NHS England patients treated with adjuvant atezolizumab could address uncertainty around the generalisability of IMpower010 PD-L1 ≥50% TC Stage II–IIIA sample clinical effectiveness data to outcomes in routine NHS use.

7. END OF LIFE

The company did not present a case for adjuvant atezolizumab meeting end-of-life criteria. This is consistent with life expectancy estimates for the affected patient group in absence of atezolizumab, which in the ERG-corrected, company-preferred economic analysis is over 10 years.

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National Institute for Health and Care Excellence

Centre for Health Technology Evaluation

ERG report – factual accuracy check and confidential information check

Atezolizumab for adjuvant treatment of resected non-small-cell lung cancer [ID3852]

'*Data owners will be asked to check that confidential information is correctly marked in documents created by others in the technology appraisal process before release; for example, the technical report and ERG report.*' (Section 3.1.29, Guide to the processes of technology appraisals).

You are asked to check the ERG 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 12 April 2022** 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 separately highlight information that is submitted as 'commercial in confidence' in turquoise, all information submitted as 'academic in confidence' in yellow, and all information submitted as 'depersonalised data' in pink.

Issue 1 Immaturity of IMpower010 clinical effectiveness data

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 16 **Key Issue 1. Immaturity of IMpower010 clinical effectiveness data** "OS data were immature in the pivotal IMpower trial. Median OS could not be estimated in either arm. Although OS data were presented, OS was not formally tested, and DFS was instead used as a surrogate outcome for clinical effectiveness in the health economic model. OS is the gold standard outcome for oncology trials. Moreover, in the PD-L1 ≥ 50% TC Stage II–IIIA population, DFS was also immature, due to the smaller sample size available compared to the company's original PD-L1 ≥ 1% TC Stage II–IIIA population, as reflected in the very small number of patients 2 vs 1 remaining in the tail of the KM distribution. Data immaturity is an intrinsic issue in the available evidence, which has been exacerbated through the narrowing of the population due to regulatory reasons, and the consequent reduction in the sample size. The ERG does not consider this issue can be resolved with the available evidence, although future	Please remove: 1st paragraph – "DFS was also immature" 2nd paragraph – "Data immaturity is an intrinsic issue in the available evidence"	Disease free survival in the PD-L1 ≥50% stage II-IIIA population was a prespecified endpoint and part of the pre-specified DFS interim analysis plan. Whilst the interim analysis for DFS was powered on the PD-L1≥1% population, the plan was to have 190 DFS events (193 were observed), which accounts for 80% of the number of events we expect to see at the final DFS analysis. In time to event analysis, uncertainty is driven by the number of events observed. In the PD-L1 ≥50% subgroup, the number of DFS observed relative to the sample size is just 5% less compared to what was observed for the PD-L1≥1% population, based on which the interim analysis was planned. Whilst further data cuts will increase certainty, as more events will be observed, relative to sample size, it is factually inaccurate to say that the data is immature due to the number of events observed which is in line with the statistical analysis plan. As mentioned, in the PD-L1 ≥1% population, 40% of patients had an	The ERG does not consider this to be a factual error. The ERG considers that the data for key clinical outcomes are immature. The fact that it is not uncommon for there to be very few patients in the tail of the K-M distribution does not preclude the fact this indicates data immaturity.

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
data cuts may help resolve the uncertainty.”		event, compared to 35% of patients in the PD-L1≥50% population. The atezolizumab arm drove the difference in the percentage of events between the two PD-L1 populations. The number of events are similar between the BSC arm for both populations, whereas, DFS events were higher in the atezolizumab arm (35.5%) for the PD-L1≥1% population, compared with the atezolizumab arm for the PD-L1≥50% population (24.3%), as atezolizumab is more efficacious in the PD-L1≥50% group of patients. Concerning the Kaplan-Meier curve, there are always few patients remaining at risk at the end of an observation period. For the PD-L1≥50% population, the median follow-up was 34 months. The last events were observed at 42 months for the atezolizumab arm and 37 months for the BSC arm. Therefore, after 42 months, there were no events and at this point there were only 22 patients at risk, which accounts for approximately 10% of the patients. After the 42-month point, the KM estimates become very	

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
		uncertain.	
Page 38 "The company used DFS as the clinical input to the health-economic model, citing immaturity in the OS data (see Section 4.2.6.4). The CS also states that 'DFS was used as a surrogate for OS in the economic model' (Document B, p75), but in response to clarification question B24 indicates that this was meant 'not in terms of the survival curves but in relation to the use of DFS as a surrogate endpoint to OS as an earlier indicator of efficacy'" ERG Clarification B24: "the ERG expects the DFS survival curve to decrease more rapidly than the OS survival curve (since DFS indicates the waiting time for death *or* progression), and observes this in the curves shown in Document B Figures 20 and 21" In the company response to this question, we agree that the survival curves for OS and DFS will differ, in agreement with the ERG. Which is what we meant by "not in terms of survival curves", as in the survival curves will not completely match each other. This quote from the response to the clarification question	Remove sentence "The CS also states that 'DFS was used as a surrogate for OS in the economic model' (Document B, p75), but in response to clarification question B24 indicates that this was meant 'not in terms of the survival curves but in relation to the use of DFS as a surrogate endpoint to OS as an earlier indicator of efficacy'"	Currently this sentence misquotes the company.	The ERG has amended aligned with the company's proposed revision.

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
seems to be taken out of context when referenced in isolation.			

Issue 2 Approach to model DFS patient outcomes

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 17, Key Issue 2 Table, Row - What alternative approach has the ERG suggested? "Removing a selective assumption that adjuvant atezolizumab influences DFS event type (metastatic vs locoregional recurrence)"	Amend wording to accurately reflect the information provided by the company. "Therefore the claim that the proportion of patients experiencing metastatic relapses is different across treatment arms is supported as explained in the Description of Problem section."	Correctly reflect the information provided by the company.	This is not a factual inaccuracy. No amendment warranted.
Page 77 "The ERG requested clarification on the company's justification for this assumption; specifically, analysis of whether type of DFS event was significantly associated with treatment arm; in clarification question B11. In response, the company provided analysis of differences in time to metastatic events (as first DFS event) across arms, but not analysis of the association of treatment arm with type of DFS event, as requested..... Overall,	Please include the previously company provided rationale as response to B11 for why the analysis of the association of treatment arm with type of DFS events were not provided and accurately represent what was provided.	Current wording implies Roche chose to not provide analyses in order to mislead the ERG. This is not true. In the clarification questions B11, Roche performed a time-to-event analysis to account for (1) censoring and (2) competing events (death and other types of relapse). This analysis shows a reduction of the risk of metastatic relapse for atezolizumab compared to BSC in the PD-L1 ≥ 1% stage II-IIIA population. If fewer patients experienced distant	This is not a factual inaccuracy. No amendment warranted.

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
the ERG feels there is insufficient evidence to assume a treatment effect upon type of DFS event, on top of capturing a treatment effect upon DFS.”		metastasis with atezolizumab compared to BSC and the number of patients experiencing locoregional relapses only is similar in both treatment arms (35 atezolizumab arm vs 42 BSC arm), these results support the claim that the proportion of patients experiencing metastatic relapses is different across treatment arms. The reason for not providing the "analysis of the association of treatment arm with type of DFS event, as requested", was due to competing events in the trial, namely the different types of DFS events. As explained in the response to clarification questions.	
Page 50 “The ERG was unable to evaluate if appropriate tools for trial quality assessment were chosen by the company due to poor reporting.”	-	We agree that some elements of reporting the SLRs were omitted from the appendices, to keep the size of the document manageable. If requested, the full SLR reports including the screening, data extraction, and QA tables could have been provided at ERG clarification stage.	The ERG acknowledge that the information could have been requested during clarification. The wording has been adjusted to reflect no detail was reported within the CS or Appendices. The ERG does not consider this to be a significant issue. Refer to p.50

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 57/58 "Importantly, and not indicated by Figure 4, some key transition probability parameters and assumptions around care and treatment received after leaving the DFS health state are assumed to differ by model arm."	Change wording to "Importantly, and not indicated by Figure 4, some key transition probability parameters and assumptions around care and treatment received after leaving the DFS health state are assumed to differ by the treatment options after disease recurrence."	The transition probabilities are not conditional on treatment arm but on the treatment options that patients receive after disease recurrence. The market shares of treatment options are exactly the same for patients in the BSC arm, and for patients in the ATZ arm who can re-challenge with CITs after recurrence (although the model assumes no re-challenge with immunotherapies occur, as noted by the company and communicated with the ERG and NICE after receiving the ERG report, the model erroneously allows rechallenging after 12 months - this has now been updated in the ERG-adjusted model). Patients in the ATZ arm who cannot re-challenge face different transition probabilities (higher probabilities for disease progression and death) as they are prohibited from re-challenging, and can only treat with chemotherapy.	This is not a factual inaccuracy. No amendment warranted.
Page 58 "(i) time-invariant estimates of the probability of death, for each arm, (with the time-variant	Edit sentence to include that: "when background mortality is greater than the probability calculated with the trial data, the model switches to using background mortality, which is time variant"	In the company model, when background mortality is greater than the probability calculated with the trial data, the model switches to using background mortality,	The ERG note the company's point and have amended the sentence accordingly.

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
remainder of DFS event probability each arm assumed to represent non-death DFS event probability)...all transitions between health states bar a proportion of those from the disease-free survival state are assumed to be time-invariant"		which is time variant. The model also defines the probability of death of patients who are cured with background mortality statistics, which account for 91.5% of patients after cure adjustment is activated. We can thus expect the impact of this to be minimal which should also be made clear.	
Page 59 "The ERG reiterated that the company assume that the proportion of the cohort in the "locoregional recurrence (palliative or no treatment)" can only (i) experience the health-related quality of life and costs associated with this state, or (ii) enter the death state. The assumption that these patients have zero probability of experiencing the health-related quality of life and costs associated with metastatic disease is a strong structural assumption chosen by the company "	Remove or amend sentence: "The assumption that these patients have zero probability of experiencing the health-related quality of life and costs associated with metastatic disease is a strong structural assumption chosen by the company."	The wording used here implies that Roche have overinflated quality of life for these patients. The HRQoL of patients who receive palliative intent or no treatment in the locoregional recurrence (0.62, Van den Hout et al. 2006), is lower than that of patients who receive treatment in the metastatic recurrence health states (first-line metastatic recurrence - 0.71 for progression-free, from IMpower150 and second-line metastatic recurrence - 0.69 for progressed, from IMpower150). This captures the lower health status of patients with locoregional recurrence who cannot treat with curative intent, and any disease progression they may experience before death, regardless of the fact that their	This is not a factual inaccuracy. No amendment warranted.

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
		health state membership stops at locoregional recurrence. As scenario analyses show in Table 84 of the company additional evidence dossier, changing the sources of utility inputs does not significantly impact the ICER.	
Page 61 "Importantly, and as described across Sections 4.2.6.2, 4.2.6.3 and 4.2.6.4 below, in some instances in their preferred analysis, the company opted not to use available data from IMpower010"	Change wording to: "Importantly, and as described across Sections 4.2.6.2, 4.2.6.3 and 4.2.6.4 below, in some instances in their preferred analysis, the company did not use available data from IMpower010 (i.e. OS data)"	The word "opted" is misleading. As outlined throughout the CS, Roche used all available trial data where possible within the economic model and only supplemented with published literature and expert opinion where it was not possible to be informed by the trial. Section 4.2.6.2 refers to Disease Free Survival. The model uses data from the trial to model DFS. The trial does not contain the data to allow us to model the cure adjustment and treatment effect adjustment in the model. Thus, external sources and expert opinions had to be utilised with the process documented and justified. Section 4.2.6.3 refers to the post-DFS health states. As per	This is not a factual inaccuracy. No amendment warranted.

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
		response to ERG clarification questions, the trial did not collect the data required to model the prognosis of patients after a DFS event (e.g. disease progression of patients who have locoregional recurrence or metastatic recurrence). The external sources used were identified from a real-world evidence literature review (Appendix M of CS) and a focussed literature search in PubMed. Section 4.2.6.3 refers to overall survival. The ERG had asked via the clarification questions if Roche could include OS data from the trial in the model and run a "partitioned survival model". Given that the trial does not contain the data required to run a partitioned survival model, it was agreed to run a OS scenario analyses where the probability of patients who die in each cycle is determined by the trial – implying that all patients face a similar probability of death across health states. We are aligned in the opinion that such a scenario is not a realistic predictor of OS for the	

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
		model due to immaturity of OS data, however we provided the scenario for transparency. Given the above, it is unclear what data the ERG believe Roche have chosen not to use in the model and request more clarity for the ERG to substantiate their claims.	
Page 63 "The company implicitly assume that structural assumptions assumed for PD-L1 ≥1% TC Stage II–IIIA DFS projections in the November 2021 CS hold for the MHRA-approved PD-L1 ≥50% TC Stage II–IIIA patient group."	Remove this sentence: "The company implicitly assume that structural assumptions assumed for PD-L1 ≥1% TC Stage II–IIIA DFS projections in the November 2021 CS hold for the MHRA-approved PD-L1 ≥50% TC Stage II–IIIA patient group."	This is not the case. As per the PD-L1 ≥1% population during initial ERG clarifications, all information for the PD-L1 ≥50% population were provided to the ERG, including hazard plots (Appendix B of the company additional evidence dossier) demonstrating that the proportional hazards assumption does not hold in the PD-L1 ≥50% population. Roche acknowledge a full interpretation similar to the CS could have been provided, however, this was omitted due to time constraints owing to the late change in the indication wording.	This is not a factual inaccuracy. No amendment warranted.
Page 64 "For interpretation of plausible extrapolations, the company	Remove "The ERG struggled to follow the company's logic here: if there is insufficient published data on DFS in early NSCLC to draw conclusions, how can the company conclude	Roche do not understand the logic of including a rhetorical question within the report. Furthermore, Roche believe the ERG have	This is not a factual inaccuracy. No amendment warranted.

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
referred to the literature. On page 73 of the CS (Document B), the company write both “these parametric curves […] underestimated DFS as observed in the literature” and “There is a paucity of literature available reporting DFS in patients with early NSCLC”. The ERG struggled to follow the company’s logic here: if there is insufficient published data on DFS in early NSCLC to draw conclusions, how can the company conclude that their own DFS results are drawn into question by the published data?”	that their own DFS results are drawn into question by the published data?"	made unsubstantiated assumptions in their interpretation of the narrative and imply that Roche have claimed "there is insufficient published data on DFS in early NSCLC to draw conclusions". In no part of the CS did Roche make this claim. As quoted by the ERG, Roche stated within the CS that “There is a paucity of literature available reporting DFS in patients with early NSCLC”. In this case, this should be interpreted as there being a small number of studies reporting DFS in patients with early NSCLC. As outlined in the CS, the values within the studies for benchmarking were validated with UK clinicians, which should be made clear by the ERG.	
Page 66 “the company has not provided sufficiently considered justification for the assumption that 91.5% of patients who remain disease-free for five years post-resection and post-adjuvant chemotherapy are no longer at risk of disease recurrence or disease-related	Amend sentence to: “the company only provided one source (Sonoda et al. 2019), validated by clinicians, to support assumption that 91.5% of patients who remain disease-free for five years post-resection and post-adjuvant chemotherapy are no longer at risk of disease recurrence or disease-related mortality.”	As stated in Section B.3.3.3.5 of the CS, the evidence from Sonoda et al. 2019 was validated with UK clinicians who were in agreement that after five years, some patients can be considered cured.	This is not a factual inaccuracy. No amendment warranted.

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
mortality”			
Page 67 “The ERG assumed this was a modelling error, and that the company intended to assume 91.5% of the DFS state are cured five years from baseline.”	Remove the sentence: “The ERG assumed this was a modelling error, and that the company intended to assume 91.5% of the DFS state are cured five years from baseline.”	This is not an error - as described in Section B.3.3.4 of the CS, we introduce a ramping up period for the proportion of patients not at risk of DFS event to linearly increase from year 3 to year 6 where the proportion reaches a maximum of 91.5%.	This is not a factual inaccuracy. No amendment warranted.
Page 68 “The ERG found no justification for this inflation of lifetime DFS projections across model arms and noted that the visual implications of the company’s “ramping up” adjustment were not presented in isolation anywhere in the CS.”	Amend sentence to: “The ERG noted that the visual implications of the company’s “ramping up” adjustment were not presented in isolation anywhere in the CS but were provided in slides presented to clinical experts in July/August 2021.”	In Section B.3.3.4 of the CS, it is stated that Roche "validated cure assumption survival outputs with identified literature and UK clinical expert opinion". Roche provided minutes and slides from clinical expert 1:1s in July and August 2021 where these cure assumptions were discussed. These materials were provided during ERG clarifications (Question B23).	This is not a factual inaccuracy. No amendment warranted.
Page 69 “Overall, the ERG found the company’s presentation of their chosen treatment effect adjustment misleading.”	Remove or amend sentence: “Overall, the ERG found that the company’s presentation of their chosen treatment effect adjustment had uncertainties”	Roche do not understand how the presentation of this adjustment could be misleading. The CS states "There is currently a lack of data from IMpower010 and external evidence to inform at what time point the treatment effect of atezolizumab ceases. Thus, the model assumes that it	This is not a factual inaccuracy. No amendment warranted.

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
		ceases at year 5 or the same year at which the proportion of cured patients reaches its maximum." In response to ERG clarifications B28, Roche agreed that the results from switching to "Maintained over Time" is illogical and are not misleading the ERG or the Committee.	

Issue 3 Approach to model post-DFS patient outcomes

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 70 "Overall, the ERG found the company's post-hoc adjustments to NICE DSU TSD-recommended parametric survival modelling and choice of final DFS projection to be poorly justified, and note that each post-hoc adjustment - bar the standard practice of limiting survival chances to be no better than the age-equivalent general population - inflates the absolute and relative lifetime DFS projection for the atezolizumab arm of the model."	Change sentence to: "Overall, the ERG found the company's post-hoc adjustments to NICE DSU TSD-recommended parametric survival modelling and choice of final DFS projection to be poorly justified, and note that each post-hoc adjustment - bar the standard practice of limiting survival chances to be no better than the age-equivalent general population - may increase the absolute and relative lifetime DFS"	This wording implies that Roche are intentionally inflating the lifetime DFS projection without any evidence. However, the literature and clinical validation and rationale for the cure assumptions are provided in Section B.3.3.4 of the CS.	This is not a factual inaccuracy. No amendment warranted.

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 71 "Given this feedback, in estimating a DFS QALY benefit of adjuvant immunotherapy ([redacted] discounted QALYs) that is more than 11 times greater than the post-DFS QALY benefit of immunotherapy (in the comparator arm; [redacted] discounted QALYs), the ERG was concerned that the company's approach may be underestimating the post-adjuvant relative benefit of available immune-check-inhibitor treatments, including atezolizumab, and in doing so, bias results in favour of adjuvant atezolizumab."	We were unable to replicate the values described here. Please provide clarity around where these values originate.	This result is driven by a base case parameter error for rechallenging with CITs in the atezolizumab arm of the model discovered by Roche when going through the ERG-adjusted model that has been part of the model since the original CS.	To replicate the values cited, the company can recreate the company's January 2022 base case within sheet "ERG" of the latest ERG-adapted company model, following instructions in cell B:30 of said sheet. The values can then be found in cells I:42 and I:57 of sheet "Results Table". The cited text refers to the company's January 2022 evidence submission, and is true to the company's base case as presented by the company. The ERG have corrected for the company's base case parameter error, enveloping this amendment into ERG corrections to the company base case, as reflected in changes to Sections 1, 4, 5 and 6 of the ERG report.
Page 72 "Overall, the ERG was not confident that the most appropriate data sources were selected by the company to inform post-DFS health state transition assumptions."	Remove or amend sentence.	The ERG have not provided any evidence to back-up this statement. As outlined by the ERG, a number of transitions were informed by Roche-led pivotal studies which were the basis for previous HTA submissions and whereby Roche would have greater access to data to inform transition probabilities. This was	This is not a factual inaccuracy. No amendment warranted.

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
		given as strong justification for their use. Furthermore, it should be made clear that Roche accepted that whenever parameters need to be sourced from published literature instead of the pivotal clinical trial there is uncertainty. As a result, this was tested via scenario analyses to quanitfy the uncertainty and understand the potential bias these specific inputs can impact of the model results.	
Page 73 "Despite this data availability, the company's analysis of these data was limited to fitting exponential survival models. No exploration of the appropriateness of the exponential model for fitting to external data was presented in the CS, and no survival models other than exponential were fitted. In each case, the company commented in a footnote that "This was a simplifying assumption as using a different parametric distribution would make it time varying" (CS, Document B, Section B.3.3.6). The ERG reiterate that it was the	Include sentence: "However, the company tested the probabilities in sensitivity and scenario analyses and ICERs remained within the cost-effectiveness threshold".	Whilst exploration of different fitting survival models was not possible due to the justified model structure, it should be made clear that the probabilities here were tested within sensitivity and scenario analyses to quantify the uncertainty and ICERs remained within the threshold, however, we understand the potential bias these specific inputs can have.	This is not a factual inaccuracy. No amendment warranted.

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
company's choice to specify a cohort-level, discrete-time approach to modelling using spreadsheet logic (refer also to Section 4.2.4)."			
Page 78 "To summarise the ERG's perspective on the company's post-DFS health state transition assumptions, the ERG are concerned that the company's approaches to data identification, selection and analysis and other modelling assumptions fall short of the standards set out in the NICE Guide to the Methods of Technology Appraisal."	Amend sentence to specify which standards the company falls short on and quantify the impact of this.	It is not clear from this statement which standards the ERG believe the analysis falls short on. The ERG should also provide a statement to quantify the impact of this to aid the committee's interpretation for decision making.	This is not a factual inaccuracy. No amendment warranted.
Page 79 "The company's base case OS projections are shown in Figure 16, alongside the OS KM data shown in the ERG-generated Figure 15. Figure 16 illustrates how the company's approach to capture post-DFS events produces OS projections that are markedly below the observed KM data on both treatment arms, and implying a	Change sentence to: "Figure 16 illustrates how the company's approach to capture post-DFS events produces OS projections that are markedly below the observed KM data on both treatment arms."	As outlined by the ERG, the base case uses a simplified calculation of post-DFS events based on median PFS/OS which produces a slight under prediction of OS in both arms. It should be noted that a scenario using the digitised KM data instead of medians produces OS data comparable to OS. As previously outlined, the OS data is immature in respect to the adjuvant setting, making it difficult	This is not a factual inaccuracy. No amendment warranted.

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
sizeable relative lifetime OS benefit, far beyond the observed data."		to infer conclusions on long term OS for patients. However, the statement provided by the ERG implies that no relative lifetime OS benefit should be observed beyond the immature OS from the trial and is misleading.	
Page 79 "As described in Section 4.2.6.2, the company base case assumed a proportion of patients yet to experience a DFS event face general population-weighted mortality risks, increasingly linearly from 0% at 36 months to 91.5% at 72 months."	Amend sentence to: "As described in Section 4.2.6.2, the company base case assumed a proportion of patients yet to experience a DFS event only face adjusted general population-weighted mortality risks, increasingly linearly from 0% at 36 months to 91.5% at 72 months, with an adjustment to the general population mortality throughout the model."	The statement provided by the ERG does not make clear that the general population mortality is significantly adjusted throughout the model and at no point do any of the cohort return to actual general population levels of risk.	This is not a factual inaccuracy. No amendment warranted.

Issue 4 Approach to capture lifetime treatment pathway expectations

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
-	-	-	No problem was raised. Therefore, no changes are required.

Issue 5 Approach to capture incremental cost differences aside from NSCLC treatment acquisition costs

Description of problem	Description of proposed amendment	Justification for amendment	ERG response

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 32 "Following a review of all the materials provided, the ERG determines that the discussion was not appropriately framed in terms of the PD-L1 TC ≥50% Stage II–IIIA population in the questions put to clinical advisors" The wording of the comment above appears that we framed a conversation in a particular way. The materials provided to the ERG were advisory board documents and 1:1 conversations held with Clinicians when we were pursuing a licence in the PD-L1 TC ≥1% Stage II–IIIA population.	Remove and amend to: "As the advisory board was prior to the change in marketing authorisation to limit to PD-L1 TC ≥50% Stage II–IIIA population, discussions were based on the PD-L1 TC ≥1% Stage II–IIIA population. However, further discussions were conducted with clinicians to check validity in the updated PD-L1 TC ≥50% Stage II–IIIA population."	To be transparent that the company provided materials that were relevant to the target population at the time and that these were further checked with clinicians, something the ERG makes reference to later in the report.	The ERG has made the following edits: "Following a review of all the materials provided, the ERG noted that the discussion was set in context of the PD-L1 TC ≥1% Stage II–IIIA population aligned with the planned marketing authorisation.

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 56 "From June 2016 to the date of correspondence, 09 November 2021, the advising pharmacist's unit had recorded three uses of a second atezolizumab vial to remake a batch for a patient, in each case due to particles. This pharmacist reported making around 45 atezolizumab batches each year. Taking the period 01 June 2016 to 09 November 2021 inclusive, the time-period in question is 1,987 days, or 5.44 years (to 2 decimal places (2dp)). The estimated number of remakes per year, or per 45 batches, is three vials / 5.44 (2dp) years = 0.55 (2dp) vials, and the expected number of vials per administration is one vial + 0.55 (2dp) vials / 45 batches = 1.012 (to four significant figures (4sf)) vials."	Should it be deemed warranted, analyses should be updated to apply the same level of adjustment to all drugs within the model. If not, the ERG should provide justification for only applying this to atezolizumab.	Whilst we appreciate the accuracy of this adjustment, there is no precedence for this level of adjustment in previous technology appraisals for atezolizumab or similar products. Secondly, the ERG have only applied this adjustment to atezolizumab and no other modelled immunotherapies. Clearly, this biases against the atezlizumab arm as a quick calculation applying the same adjustment to only the vial cost of pembrolizumab would reduce the ICER.	This is not a factual inaccuracy. No amendment warranted.
Page 56 "The company use the time-to-treatment-discontinuation data to inform treatment acquisition cost assumptions in the analysis, but otherwise assumed that when a patient discontinues treatment	Suggest to remove the paragraph entirely.	As outlined in the CS, the DFS in the model is defined by both the patients who did and did not complete the whole 16 cycles of treatment. Given that DFS is allowed to be time variant, this accounts for the effect that a	This is not a factual inaccuracy. No amendment warranted.

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
early, the patient is no different to a patient who completes the intended 16 cycles of treatment, in terms of their quality of life, disease management costs and long-term prognosis, unless a DFS event occurs."		different mix of individuals in DFS would have (i.e. those who did and did not complete the 16 cycles), if we can assume that both types of patients have different long-term prognoses. In terms of disease management costs, the costs of individuals who did not complete the whole 16 cycles is 0 (apart from follow-up costs), but we can assume that some may go onto other forms of treatment. Thus, this limitation biases against atezolizumab in increasing the ICER due to the other treatments. In terms of HRQoL, there is no evidence to suggest whether patients who did and did not complete the whole 16 cycles have a different QoL (none of the studies identified in the SLR split patients according to whether they completed adjuvant treatment or not – and would only consider adjuvant chemotherapy patients, which may bias the results even further). Regardless, changes in both disease management costs and quality of life would be indirectly impacted as a result of differing DFS due to disease progression.	

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 87 "The ERG's clinical advisor estimated that each visit would involve a blood test, to ensure the patient is safe to proceed; the patient would then attend as a day case in a separate visit, to receive the treatment. The ERG asked the company to amend the assumed administration cost of adjuvant atezolizumab in line with this independent advice (clarification question B13)."	Should it be deemed warranted, analyses should be updated to apply the same level of adjustment to all immunotherapies within the model. If not, the ERG should provide justification for only applying this to atezolizumab.	Whilst Roche have been happy to include the additional costs for atezolizumab in the adjuvant setting, it is unclear if the ERG also validated these same assumptions for later line treatments i.e. patients receiving pembrolizumab in first line metastatic or if this would only be applicable for atezolizumab in the adjuvant setting.	This is not a factual inaccuracy. No amendment warranted.
Page 89 "In response, the ERG provided a pragmatic scenario analysis in which a cost estimate of £7,508 is assumed for any adjuvant AE management; an inflation-adjusted cost for febrile neutropenia sourced from NICE TA531 ("Pembrolizumab for untreated PD-L1-positive metastatic non-small-cell lung cancer"), used to inform adverse event assumptions for treatment of metastatic recurrence in the company's base case analysis."	Replace sentence with: "In response, the company provided a pragmatic extreme scenario analysis in which a cost estimate of £7,508 is assumed for any adjuvant AE management; an inflation-adjusted cost for febrile neutropenia sourced from NICE TA531 ("Pembrolizumab for untreated PD-L1-positive metastatic non-small-cell lung cancer"), used to inform adverse event assumptions for treatment of metastatic recurrence in the company's base case analysis (Increases ICER from [redacted] to [redacted] per QALY). However, this is highly likely an overestimate of the impact due to the use of a high cost adverse event to represent all adverse events and should therefore be interpreted as an extreme scenario."	The pragmatic AE scenario was provided by Roche, not the ERG. It should be noted that this scenario was agreed with the ERG during clarification questions call and that the scenario was provided using the cost for febrile neutrpenia to represent all AEs as an extreme scenario using the most expensive AE likely to be experienced by patients and therefore is overly conservative. The ERG should also make clear the expected and actual impact on model results of AE in this setting.	The ERG thanks the company for highlighting this; the text has been corrected to state that the scenario was provided by the company.

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 90 "However, from reporting in the company-amended economic model, it appeared that these are Grade 2 event rates (the data appear under "IMpower010 Grade 2 events" headings, in sheet "AE ERG scenario"), as opposed to Grade 2+ event rates, and the ERG was concerned that this approach may have omitted Grade 3+ events."	Replace sentence with: "However, from reporting in the company-amended economic model, it appeared that these are Grade 2 event rates (the data appear under "IMpower010 Grade 2 events" headings, in sheet "AE ERG scenario"), as opposed to Grade 2+ event rates, and the ERG was concerned that this approach may have omitted Grade 3+ events. The company have since confirmed these were Grade 2+ event rates."	Roche agree this was not reported clearly, however, the report should state Grade 2+ AEs, which is what was reported in the ERG clarifications response and in the model.	The ERG has amended the text accordingly, to state the company's confirmation that the data refer to Grade 2+ AEs.
Page 90 "As noted in Section 4.2.6.3 of this report, the company assume that 80% of patients experiencing locoregional recurrence will receive active treatment with curative intent, with the remaining 20% receiving palliative care only."	Replace sentence with: "As noted in Section 4.2.6.3 of this report, the company use Sonoda et al. 2020 as the source to support that 80% of patients experiencing locoregional recurrence will receive active treatment with curative intent, with the remaining 20% receiving palliative care only."	This was informed by Sonoda et al. 2020 rather than a Roche assumption	This is not a factual inaccuracy. No amendment warranted.
Page 93/94 "Within this group, the ERG expects that around 70% will have stable disease, and therefore be likely to receive	Include evidence used to inform percentages.	It is unclear what evidence the ERG have used to inform their preferred percentages outlined. Please could the ERG provide clarity.	The ERG has amended the text to clarify the source of ERG expectations.

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
pembrolizumab or atezolizumab as monotherapy, with a roughly even split between these treatments. The ERG expects the remaining 30% would have more rapidly progressive disease that would prompt combination immuno-chemotherapy. Of those not eligible for immunotherapy but fit for chemotherapy, the ERG expects that nearly all would be treated with doublet chemotherapy."			
Page 95 "The ERG noted that the atezolizumab cohort spend 3.504 months (2.917 time-discounted months) in the "1st metastasis, on treatment" health state in the company base case, while the BSC cohort spend 5.757 months (5.118 time-discounted months) in this state; as such, the implications of the company's assumptions in this area are time-limited."	Please provide clarity on the point being made.	Roche are unsure what statement the ERG are trying to make here. The time within "1st metastasis, on treatment" health state would be expected to be higher within the BSC cohort due to 1) more of the cohort progressing to this state earlier 2) BSC cohort having access to CITs which would result in longer time to progression and therefore on treatment.	This is not a factual inaccuracy. No amendment warranted.
Page 95 "In this, the ERG was concerned that the company's approach to	Please include specific concerns of the company's approach.	The differences in time in the health state are logical based on the previous response. The ERG	This is not a factual inaccuracy. No amendment warranted.

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
1st metastatic treatment assumptions biases cost-effectiveness results in favour of atezolizumab adjuvant therapy."		should provide further clarity in order to substantiate their claims.	
Page 97 "The company provide no further justification; the result of their approach is an assumed monthly AE management cost of £87.07 in the atezolizumab arm and £93.45 in the BSC arm for first-line metastatic treatment, and £308.41 across model arms for second-line metastatic treatment."	Change sentence to: "The company provide no further justification beyond their choice the use of pivotal atezolizumab trials; the result of their approach is an assumed monthly AE management cost of £87.07 in the atezolizumab arm and £93.45 in the BSC arm for first-line metastatic treatment, and £308.41 across model arms for second-line metastatic treatment."	Roche believe justification for this was provided. IMpower010 does not collect information needed to define the cost of adverse event management for patients on 2L metastatic treatment. Therefore, pivotal trials for atezolizumab were deemed the best possible option. The use of 'assumed' implies that the value used is poorly justified when the reality is that the value is based on the previously and recently approved calculations within technology appraisals for atezolizumab in this specific setting.	This is not a factual inaccuracy. No amendment warranted.
Page 98 "Further, the ERG are not convinced by the company's unjustified assumption that the NHS and PSS cost of terminal care is zero for lung cancer patients who are recorded as experiencing "all cause" death, as opposed to £4,598.01 for lung cancer patients recorded as	Change sentence to: "Further, the ERG are not convinced by the company's assumption that the NHS and PSS cost of terminal care is zero for lung cancer patients who are recorded as experiencing "all cause" death, as opposed to £4,598.01 for lung cancer patients recorded as experiencing disease-related death."	Whilst Roche do not see costs related to type of death as a significant value driver for atezolizumab in the adjuvant setting, we do believe the assumptions in the base case were fairly justified and that the description by the ERG implies that terminal care costs were specifically applied differently in the atezolizumab and BSC arms,	This is not a factual inaccuracy. No amendment warranted.

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
experiencing disease-related death.		when in reality this is based on health state occupation. Terminal care costs for non-NSCLC are not included for transitions from the disease free health state as they are not related to NSCLC. It would be incorrect to assume the same terminal care costs for patients from progressed health states with diagnosed NSCLC and those who have been disease free and defined as cured for a significant number of years. Including the same terminal care costs within the disease free health state is to assume that death is related to NSCLC. Any assumption on future causes of death would be including non-NSCLC related healthcare costs into the model, outside of the reference case.	

Issue 6 Issues and uncertainties from technical review of the cost-effectiveness analysis

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 104 "Company's approach to post-hoc inflation of DFS projections (EAs #3 and #4)"	Change bullet to: "Company's approach to post-hoc adjustment of DFS projections (EAs #3 and #4)"	The language used here could be misleading. The use of 'inflated' implies that the DFS projections were arbitrarily increased beyond what might be expected in clinical practice to look more cost-	This is not a factual inaccuracy. No amendment warranted.

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
		effective. This also suggests that this adjustment may only have been applied to the atezolizumab arm and that any adjustments would only ever benefit atezolizumab. As documented, the unadjusted DFS curves provide clinically unrealistic projections of DFS in both arms. Correct terminology would be 'adjustment' in place of language biasing 'inflation'.	
Page 104 "Company assumption that treatment arm influences DFS event type (EA #6)"	Change bullet to: "Company use of results from IMpower010 to define DFS event type (EA #6)"	It is incorrect to state that this is an assumption. The inputs used to define DFS event type is based on the results of the IMpower010 randomised control trial.	This is not a factual inaccuracy. No amendment warranted.
Page 104 "Company assumption that exactly one 1200mg vial of atezolizumab is administered at each adjuvant atezolizumab administration visit (EA #8)"	Should it be deemed warranted, analyses should be updated to apply the same level of adjustment to all drugs within the model. If not, the ERG should provide justification for only applying this to atezolizumab.	As previously stated, it is unclear why the ERG have only applied this level of adjustment to atezolizumab in a way that biases against atezolizumab. Please could the ERG provide justification for this.	This is not a factual inaccuracy. No amendment warranted.
Page 104 "Company assumption that atezolizumab administration NHS resource burden is equal to	Should it be deemed warranted, analyses should be updated to apply the same level of adjustment to all drugs within the model. If not, the ERG should provide justification for only	It is unclear why the ERG applies this amendment to atezolizumab, but for none of the other drugs. With this, the ERG assumes that the administration cost of	This is not a factual inaccuracy. No amendment warranted.

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
the NHS Reference Cost for delivery of simple parenteral chemotherapy at first attendance (EA #9)"	applying this to atezolizumab.	atezolizumab in the adjuvant setting is greater than the administration cost of all other drugs across the post-DFS health settings. Roche would assume that similar costs may apply to the use of CITs in the metastatic setting and that if the ERG believe the adjuvant setting resource use is greater, this should also apply to the metastatic setting.	
Page 105 "Company's approach to apply terminal care costs to some patients only (EA #11)"	Amend bullet to: "Company's approach to not apply terminal care costs to patients who transition to death from the DFS health state and 'all cause' mortality (EA #11)"	The language used here could be misleading. The use of 'some' implies that Roche applied these costs arbitrarily and without any justification.	This is not a factual inaccuracy. No amendment warranted.
Page 105 "Company assumption of indefinite treatment within metastatic recurrence health states (EA #14)"	Amend bullet to: "Company assumption of indefinite treatment with chemotherapies within metastatic recurrence health states (EA #14)"	This statement could be misleading. It should be made clear that this is related to treatment discontinuation and that pre-defined stopping rules, such as those for pembrolizumab, were included.	The ERG have amended the bullet accordingly.
Page 107 "Further, the CS lacked justification for the log-logistic model over alternatives as a fit to even the IMpower010 PD-L1 ≥ 1% TC Stage II–IIIA DFS	Amend sentence to: "Further, with the statistical fit to the KM data consistent across distributions, the CS justification for the log-logistic model over alternatives as a fit to the DFS data was based on clinical expert selection with the aid of published literature."	This statement implies that curve selection was arbitrary and that there are significant differences in the statistical fit of the curves to the data. The process for curve adjustment and selection was documented within the CS, with	This is not a factual inaccuracy. No amendment warranted.

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
data.”		materials from the advisory board provided to the ERG. As previously documented, statistical fit between the different curves showed little variation. It was also stated, that statistical fit only tells us how well the curves fit to the known data and gives us no information for the extrapolated period. Within the adjuvant setting, the extrapolated period is highly unlikely to follow what would be observed in clinical practice in either arm as the expected cure point has not yet been observed. As a result, all curves were validated with clinical experts with the aid of published literature as part of the curve adjustment with justification given for selection between the two deemed most clinically plausible curves. Regardless, extensive scenario analyses were provided for curve selection, including those deemed not clinically plausible, to quantify the uncertainty related to curve selection and impact of cost-effectiveness.	
Page 109 “As discussed in Section 4.2.6.2, the company’s post-hoc	Amend sentence to: “As discussed in Section 4.2.6.2, the company’s post-hoc “Ramping up” adjustment is unable to be justified by evidence	Clarity should be given around the rationale for a 'Ramping up' adjustment. Without this, the ERG	This is not a factual inaccuracy. No amendment warranted.

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
“Ramping up” adjustment is unjustified and inflates DFS projections above parametric model predictions, biasing results in favour of adjuvant atezolizumab.”	and estimates DFS projections above parametric model predictions, being favourable for adjuvant atezolizumab. Whilst there is no current observable evidence of this, the simplified "Ramping up" adjustment was implemented by the company in order to remove the less clinically plausible single time point increase in the model without it.”	are assuming that no patients may be considered 'cured' until a certain time point. At this time point, there is one time increase in the proportion of patients who are ‘cured’ and remains there for the remaining cycles; resulting in an unrealistic significant change in risk of progression in a single modelled cycle. The ramping adjustment is a simplified approach of exploring the impact of this. The ERG does not provide a reason as to why the use of the ramping up adjustment is not justified, and do not back the removal of the assumption with a rationale of their own. Furthermore, the ERG should provide clarity around the insignificant impact on cost-effectiveness within the narrative to aid interpretation.	
Page 109 “Change sentence to: “Removing the adjustment increases the ERG-corrected base case ICER by [redacted] to [redacted].”	Amend sentence to: “Removing the adjustment leads to a minor increase in the ERG-corrected base case ICER of [redacted], to [redacted] having an insignificant impact on the cost-effectiveness.”	As per EA #3, the ERG should provide clarity around the insignificant impact on cost-effectiveness within the narrative to aid interpretation.	This is not a factual inaccuracy. Regardless, this text has been edited by the ERG to reflect the latest ERG-corrected cost-effectiveness results (which correct for the company’s immunotherapy rechallenge error).

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 109 "Overall, the company provide very little justification for their base case cure assumptions."	Amend sentence to: "Overall, the company's cure assumptions were unable to be based on significant direct clinical evidence and have therefore been justified using published literature, validated with clinicians."	This statement is misleading and implies that the parameter in question was included without validation. It should be made clear here that the cure assumption timing and proportion were based on published literature and validated with clinicians who agreed that this was clinically relevant.	This is not a factual inaccuracy. No amendment warranted.
Page 110 "The different treatment mechanisms of osimertinib and atezolizumab and 48-week maximum treatment duration of adjuvant atezolizumab muddy translation of assumptions across appraisals, but the lack of evidence and uncertainty around cure assumptions in TA671 and in this appraisal are similar."	Add to this sentence: "A key distinction between the clinical evidence of osimertinib and atezolizumab that should be considered when interpreting any cure assumption is that IMpower010 provides evidence of sustained treatment effect beyond the 48-week maximum treatment duration, whereas in the ADAURA pivotal trial patients can receive osimertinib for the full study duration."	A key difference between the clinical evidence of osimertinib and atezolizumab that would impact interpretation of any cure assumption is that IMpower010 provides evidence of sustained treatment effect beyond the 48-week maximum treatment duration. This was not the case for osimertinib and would be a significant factor in the thinking of the ERG and committee when evaluating any cure assumptions. The ERG should make this distinction clear to aid committee considerations.	This is not a factual inaccuracy. No amendment warranted.
Page 110 "In EA #5, the company's cure assumption is delayed to eight	Amend sentence to: "In EA #5, the company's cure assumption is delayed to eight years on both model arms as an exploratory value to quantify the impact the uncertainty of this value	The ERG provide no justification for the use of an arbitrary eight-year cure assumption which biases against atezolizumab. This	This is not a factual inaccuracy. No amendment warranted.

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
years on both model arms."	has on the cost-effectiveness result."	implies that the treatment mechanisms of osimertinib and atezolizumab are similar, contrary to the evidence provided and previous ERG statements.	
Page 112 "6.2.8. Exploration of implications of batch remake occurrences – EA #8"	Should it be deemed warranted, analyses should be updated to apply the same level of adjustment to all drugs within the model. If not, the ERG should provide justification for only applying this to atezolizumab.	As previously stated, it is unclear why the ERG have only applied this level of adjustment to atezolizumab in a way that biases against atezolizumab. Please could the ERG provide justification for this.	This is not a factual inaccuracy. No amendment warranted.
Page 112 "6.2.9. Capturing adjuvant atezolizumab administration resource use expectations – EA #9"	Should it be deemed warranted, analyses should be updated to apply the same level of adjustment to all drugs within the model. If not, the ERG should provide justification for only applying this to atezolizumab.	As previously stated, it is unclear why the ERG have only applied this level of adjustment to atezolizumab in a way that biases against atezolizumab. Please could the ERG provide justification for this.	This is not a factual inaccuracy. No amendment warranted.
Page 118 "The effect of the company approach is to skew cost effectiveness results in favour of adjuvant atezolizumab, primarily as patients on the BSC arm of the analysis face higher expected 1st metastatic recurrence costs (as described in Sections 4.2.8.3 and 6.2.12)."	Amend sentence to: "The company approach favours adjuvant atezolizumab, primarily as patients on the BSC arm of the analysis face higher expected 1st metastatic recurrence costs (as described in Sections 4.2.8.3 and 6.2.12)."	The language here could be misleading. The use 'skew' implies that the design was implemented with the intention to skew the results of the model, which is not true.	This is not a factual inaccuracy. No amendment warranted.

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 118 "As a practical illustration, EA #14 assumes that those eligible for metastatic treatment spend half their time in metastatic recurrence health states actively receiving treatment, by applying a multiplier of 0.5 to the monthly estimated costs of metastatic recurrence treatment."	Amend sentence to: "As a practical illustration, EA #14 assumes that those eligible for metastatic treatment spend half their time in metastatic recurrence health states actively receiving treatment, by applying a multiplier of 0.5 to the monthly estimated costs of metastatic recurrence treatment. This assumption was used as an exploratory analysis to quantify the impact the uncertainty of this value has on the cost-effectiveness result."	The ERG provide no justification for the use of an arbitrary 0.5 multiplier. The ERG should make clear that this analysis is only used to quantify the uncertainty here and that the scenario has no clinical validity.	This is not a factual inaccuracy. No amendment warranted.
Page 127 "As discussed in Section 4.2.6, all aspects of the company's cure assumptions are almost completely unjustified by relevant data"	Amend sentence to: "As discussed in Section 4.2.6, the company's cure assumptions were unable to be based on significant direct clinical evidence and have therefore been justified using published literature, validated with clinicians."	As previously outlined, the statement here is untrue. The cure assumption is not 'completely unjustified' and is valid based on published literature, previous appraisals and expert clinical opinion. The language here should be toned down as to not mislead the committee.	This is not a factual inaccuracy. No amendment warranted.
Page 127 "but assume little expected benefit from these immunotherapies in the metastatic recurrence setting, on the BSC arm of the analysis"	ERG should reinterpret based on the fact that the analysis in the ERG report includes rechallenging in the atezolizumab arm after 12 months within the metastatic setting.	The ERGs interpretation of the metastatic state impact is not a like for like comparison and therefore conclusions are not wholly justified. It should also be noted that this impact would be further realised once the model has been corrected for the rechallenging input error in the model.	The ERG have amended the text based on interpretation of up-to-date ERG-corrected cost-effectiveness results (which correct for the company's immunotherapy rechallenge error).

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 127 "However, where this is done, the data identification and selection process is often unclear and/or poorly justified"	Removal of statement.	As per previous comments, we believe the conclusion that the process is 'often unclear and/or poorly justified' is unwarranted.	This is not a factual inaccuracy. No amendment warranted.
Page 128 "The ERG's optimistic preferred analysis removes some inflationary post-hoc adjustments to DFS, including the company's "ramping up" adjustment, and addresses various biases in the company's approach to costs."	Amend sentence to: "The ERG's optimistic preferred analysis removes some post-hoc adjustments to DFS, including the company's "ramping up" adjustment, and addresses various biases in the company's approach to costs."	As per previous comments on the use of 'inflationary', which should be removed.	This is not a factual inaccuracy. No amendment warranted.
Page 128 "The ERG's alternative preferred analysis is less optimistic, but whether it is pessimistic is not clear"	Amend sentence to: "The ERG's alternative preferred analysis presents a pessimistic base case."	Inconsistent use of terminology whereby previously referred to as pessimistic base case and now being questioned.	This is not a factual inaccuracy. No amendment warranted.
Page 128/129 "This analysis differs from the optimistic analysis in the use of a different but equally plausible parametric model fit to the observed IMpower010 DFS KM data, and in delaying cure assumptions to eight years. In	Justification for the 8 year value. OR Amend paragraph to: "This analysis differs from the optimistic analysis in the use of a different but equally plausible parametric model fit to the observed IMpower010 DFS KM data, and in delaying cure assumptions to eight years. The eight year delay was used as an exploratory	Justification for the 8 year value should be provided. If the assumption is not based on evidence, the narrative should be edited to add clarity that this is an exploratory scenario to quantify the uncertainty of the cure point.	This is not a factual inaccuracy. No amendment warranted.

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
the deterministic iteration of this analysis, 24.7% of atezolizumab patients are predicted remain disease-free at eight years, an effective cure probability of 22.6%.”	value to quantify the impact the uncertainty of this value has on the cost-effectiveness result. In the deterministic iteration of this analysis, 24.7% of atezolizumab patients are predicted remain disease-free at eight years, an effective cure probability of 22.6%."		

Issue 7 Additional issues

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 32 Pembrolizumab incorrectly used, atezolizumab should be referred to: ● Clinical efficacy of pembrolizumab. ● Safety profile of pembrolizumab. ● Assessment of comparative clinical effectiveness of pembrolizumab against relevant comparators.”	Pembrolizumab should be replaced with atezolizumab: “ ● Clinical efficacy of atezolizumab ● Safety profile of atezolizumab ● Assessment of comparative clinical effectiveness of atezolizumab against relevant comparators.”	The error requires correcting as the incorrect product is referred to.	Correction made. Refer to page 32

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 36 Table 6 Intervention Column Atezolizumab spelt incorrectly	Please correct spelling of atezolizumab	Atezolizumab spelt incorrectly	Correction made. Refer to page 36, Table 6
Page 37 The ERG report states that: "It should be noted that the staging and ECOG eligibility criteria for the trial were not included in either the NICE scope or the company decision problem" **Decision problem addressed in the company submission (initial submission):** "Adults with resected, Stage II–IIIA early non-small cell lung cancer (eNSCLC), expressing PD-L1 ≥ 1% of tumour cells" While it is fair to say that ECOG eligibility criteria was not included in the decision problem addressed in the company submission. Staging was included in the decision problem addressed in the company submission	Amend sentence to: "It should be noted that the ECOG eligibility criteria for the trial was not included in either the NICE scope or the company decision problem."	Whilst the ECOG eligibility criteria was not included in the either the NICE scope or the company decision problem, the staging which our licence is based on was included in the company decision problem.	Correction made. Refer to page 37 Please note that staging was not mentioned in the NICE final scope but is mentioned in the decision problem.

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 43 of the ERG report "At the 21 January 2021 data cut, the proportion of patients in the atezolizumab arm who experienced disease recurrence or death was 2.43% compared to 45.6% in the BSC arm"	Amend to: "At the 21 January 2021 data cut, the proportion of patients in the atezolizumab arm who experienced disease recurrence or death was 24.3% compared to 45.6% in the BSC arm"	Incorrect value for disease recurrence or death in atezolizumab arm.	Correction made. Refer to page 43
Page 44 "The DFS KM curve for the PD-L1 ≥ 1% TC Stage II–IIIA population is shown below (Figure 3)."	Amend to: "The DFS KM curve for the PD-L1 ≥ 50% TC Stage II–IIIA population is shown below (Figure 3)."	Currently refers to the wrong population.	Correction made. Refer to page 44

Issue 8 Confidential marking

Location of incorrect marking	Description of incorrect marking	Amended marking	ERG response
Page 24 ERG report	The CIC marking can now be removed from the licensed indication as it is now approved by the MHRA	The Medicine and Healthcare products Regulatory Agency (MHRA), [redacted] Tecentriq® as monotherapy is indicated as [redacted]	CIC marking has been updated aligned with the company's amended marking

		[redacted]. Amend to: the Medicine and Healthcare products Regulatory Agency (MHRA), restricted the indication to the PD-L1 ≥ 50% Stage II–IIIA population with the following proposed updated indication wording: ● Tecentriq® as monotherapy is indicated as adjuvant treatment following complete resection for adult patients with Stage II to IIIA (7th edition of the Union for International Cancer Control [UICC]/ American Joint Committee on Cancer [AJCC]-staging system) non-small cell lung cancer (NSCLC) whose tumours have PD-L1 expression on ≥50% of tumour cells (TC) and whose disease has not progressed following platinum-based adjuvant chemotherapy.	
Page 27 ERG report	The CIC marking can now be removed from the licensed indication as it is now approved by the MHRA	([redacted]) Amend to: (PD-L1 ≥50% TC Stage II–IIIA)	CIC marking has been updated aligned with the company's amended marking

Page 28 – ERG report – Table 4 – Population Row	The CIC marking can now be removed from the licensed indication as it is now approved by the MHRA	The PD-L1 ≥50% population is in line with [redacted] Amend to: The PD-L1 ≥50% population is in line with the marketing authorisation granted by the MHRA	CIC marking has been updated aligned with the company's amended marking. Correction has been made to the text to remove the word "proposed"
Page 30/31 – Table 4 – Subgroup Row	The CIC marking can now be removed from the licensed indication as it is now approved by the MHRA	[redacted]. Amend to: PD-L1 ≥50% Stage 2 and Stage 3A in line with indication wording.	CIC marking has been updated aligned with the company's amended marking. Correction has been made to the text to remove "the proposed updated"
Page 32		[redacted] Amend to: Following a review of all the materials provided, the ERG determines that the discussion was not appropriately framed in terms of the PD-L1 TC ≥50% Stage II–IIIA population in the questions	CIC marking has been updated aligned with the company's amended marking.

		put to clinical advisors	
Page 36 – Table 7 – Analysis Population Column	The CIC marking can now be removed from the licensed indication as it is now approved by the MHRA	[redacted] Amend to: Marketing authorisation: Stage II–IIIA + SP263 TC ≥50% participants	CIC marking has been updated aligned with the company's amended marking.

(Please add further lines to the table as necessary)

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single technology appraisal

Atezolizumab for adjuvant treatment of resected non-small-cell lung cancer [ID3852]

Additional company evidence

Company evidence submission

January 2022

File name	Version	Contains confidential information	Date
ID3852_Atezolizumab_eNSCLC_AdditionalEvidence_v1_Mar2022	V2.0	Yes	8Mar2022

Contents

1. Clinical effectiveness

1.1 Introduction and Rationale for Supplementary Data Package

The initial submission to NICE in October 2021, covered the technology's full, proposed marketing authorisation for the indication at that time: Tecentriq® (atezolizumab) as monotherapy is indicated as [redacted]

However when the indication was undergoing review by the Medicine and Healthcare products Regulatory Agency (MHRA), [redacted]atezolizumab in patients whose tumours have PD-L1 expression on [redacted]

Therefore, the MHRA has [redacted]

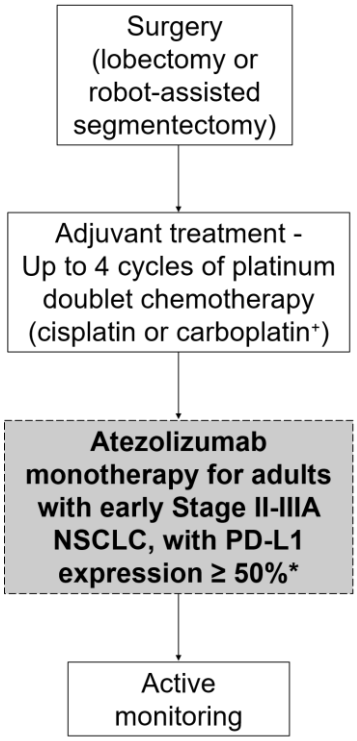
- Tecentriq as monotherapy is indicated as adjuvant treatment following complete resection for adult patients with Stage II to IIIA (7th edition of the UICC/AJCC-staging system) non-small cell lung cancer (NSCLC) whose tumours have PD-L1 expression on ≥ 50% of tumour cells (TC) and whose disease has not progressed following platinum-based adjuvant chemotherapy.

Consequently, this supplementary data package presents data in the PD-L1 ≥ 50% Stage II–IIIA patient population, the updated patient population for this submission.

1.2 Disease management pathway

The information presented in Figure 1 is based on the NICE guidelines for the diagnosis and management of lung cancer (1). This was further confirmed by clinical experts, who agreed that the current NICE management pathway is in line with UK clinical practice (Data on File) (2).

Figure 1: Current treatment pathway for early NSCLC adult patients (including atezolizumab positioning)



***** The current NICE lung cancer management guidelines for adjuvant NSCLC are not defined by PD-L1 expression, as there are currently no PD-1/L1 inhibitors licensed in the adjuvant setting. Additionally, the guidelines are not defined by EGFR/ALK status, as there were no licensed targeted treatments for these mutations in the adjuvant setting at the time of guideline development. However, osimertinib is now available under the CDF (3).

+ Carboplatin is used in the current clinical practice, but usage varies greatly across the country. It is not currently recommended by NICE (1) and was not included as an intervention in the IMpower010 trial.

The grey box indicates the proposed positioning of adjuvant atezolizumab.

Abbreviations: ALK, anaplastic lymphoma kinase; EGFR, epidermal growth factor receptor; NSCLC, non-small cell lung cancer.

Source: Clinician interviews conducted by Roche (2, 4, 5).

1.3 Summary of methodology of the relevant clinical effectiveness evidence

1.3.1 Endpoints and assessments

The primary efficacy endpoint was duration of DFS as assessed by the investigator:

- 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

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 randomization])
- 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)

The primary efficacy endpoint was duration of DFS as assessed by the investigator. Data presented in this updated document, focuses on PD-L1 ≥ 50% TC Stage II – IIIA population, which was a secondary efficacy endpoint in the IMpower010 study and the population of interest for this submission. Disease free-survival excluding patients with EGFR/ ALK mutations and overall survival will also be presented for the PD-L1 ≥ 50% TC Stage II – IIIA population, however it is important to note that this was an exploratory analysis.

1.3.2 Baseline characteristics

Between 26 February 2016 and 16 January 2019, 1280 patients were recruited from 227 centers 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 were generally well-balanced between treatment arms in the PD-L1 ≥ 50% TC Stage II – IIIA population and generally consistent with that expected for the target patient population (Table 1). There is however, a slightly higher proportion of males and Asians in the atezolizumab arm compared to the BSC arm, for the PD-L1 ≥ 50% TC Stage II – IIIA population.

Table 1: Patient demographics and baseline characteristics by groups (PD-L1 TC ≥ 1% stage II-IIIA, PD-L1 TC ≥ 50% stage II-IIIA)

Characteristic, n (%)		PD-L1 TC ≥1% stage II-IIIA[a]		PD-L1 TC ≥50% stage II-IIIA[a]	
		Atezo (n=248)	BSC (n=228)	Atezo (n=115)	BSC (n=114)
Age	Median (range), y	61 (34-81)	62 (26-84)	[redacted]	[redacted]
	≥65 y	92 (37)	97 (43)	[redacted]	[redacted]
Sex	Male	171 (69)	147 (64)	89 (77)	78 (68)
Race[b]	White	162 (65)	166 (73)	[redacted]	[redacted]
	Asian	78 (31)	56 (25)	[redacted]	[redacted]
ECOG PS	0	146 (59)	133 (58)	[redacted]	[redacted]
	1	102 (41)	95 (42)	[redacted]	[redacted]
Histology	Squamous	96 (39)	85 (37)	47 (41)	45 (39)
	Non-squamous	152 (61)	143 (63)	68 (59)	69 (61)
Stage	II	131 (53)	113 (50)	62 (54)	57 (50)
	IIIA	117 (47)	115 (50)	53 (46)	57 (50)
Tobacco use history	Never	51 (21)	41 (18)	16 (14)	15 (13)
	Current/previous	197 (79)	187 (82)	99 (86)	99 (87)
***EGFR* mutation status**[c]	Positive	23 (9)	20 (9)	[redacted]	[redacted]
	Negative	123 (50)	125 (55)	[redacted]	[redacted]
	Unknown	102 (41)	83 (36)	[redacted]	[redacted]
***ALK* rearrangement status**[c]	Positive	12 (5)	11 (5)	[redacted]	[redacted]
	Negative	133 (54)	121 (53)	[redacted]	[redacted]
	Unknown	103 (42)	96 (42)	[redacted]	[redacted]

Some categories may add to >100% due to rounding

[a] 23 patients in the stage II-IIIA population had unknown PD-L1 status as assessed by SP263.

[b] Patients with other/unknown race are not shown.

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

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

1.4 Clinical effectiveness results from IMpower010

1.4.1 Overview of efficacy

The primary efficacy outcome measure was disease-free survival (DFS) as assessed by the investigator. 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. Previously, data for the PD-L1 ≥ 1% Stage II – IIIA population was presented, in line with the anticipated license at the time. The PD-L1 ≥ 1% Stage II – IIIA population demonstrated a statistically significant and clinically meaningful improvement in DFS (stratified HR 0.66, 95% CI 0.50-0.66) for the atezolizumab arm compared to the BSC arm (Table 2). However, an extended analysis of PD-L1 subgroups in the Stage II – IIIA population demonstrates a higher magnitude of benefit from adjuvant atezolizumab in patients with PD-L1 expression ≥50 (Table 2). As we anticipate a license for the PD-L1 ≥ 50% Stage II – IIIA population for the IMpower010 regimen, efficacy data for the PD-L1 ≥ 50% Stage II – IIIA population will be provided as it is the patient population of interest for this submission.

Table 2: DFS and OS efficacy results for PD-L1 ≥ 1% Stage II – IIIA population and PD-L1 ≥ 50% Stage II – IIIA population

PD-L1 populations	**PD-L1 ≥ 1% Stage II – IIIA**		**PD-L1 ≥ 50% Stage II – IIIA**	
	Atezolizumab (n=248)	**BSC (n=228)**	**Atezolizumab (n=115)**	**BSC (n=114)**
mDFS (months)	NE	35.3	NE	35.7
HR (95% CI)	0.66 (0.50-0.66)*		0.43 (0.27, 0.68)+	
mOS	NE	NE	[redacted]	[redacted]
HR (95% CI)	0.77 (0.51, 1.17)		0.37 (0.18, 0.74)	

BSC; Best supportive care, mDFS; median disease free survival, NE; not evaluable, HR; Hazard ration, CI; Confidence interval. * Stratified hazard ratio, + Unstratified hazard ratio. Clinical cut off date (CCOD): 21 January 2021

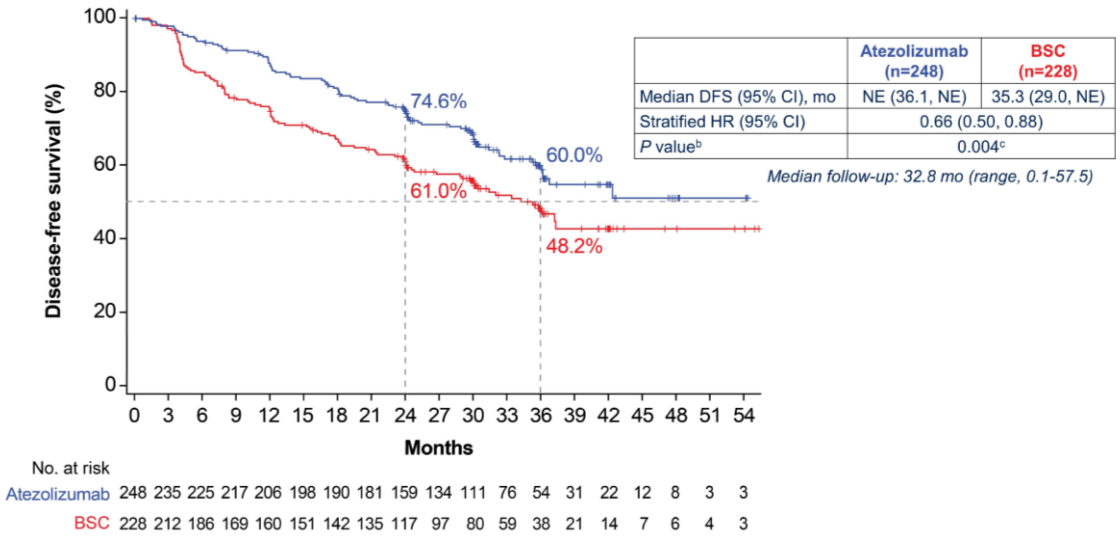
1.4.2 Primary Endpoint - DFS in PD-L1 ≥ 1% TC Stage II–IIIA population

In IMpower010, 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%. At the CCOD on 21 January 2021, 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% relative risk reduction of a DFS event with atezolizumab compared to BSC.

The Kaplan-Meier (KM) estimated median DFS was not reached in the atezolizumab arm due to the low number of events 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 2).

Figure 2: Kaplan-Meier plot of DFS (PD-L1 ≥ 1% TC Stage II–IIIA population) (6)



[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

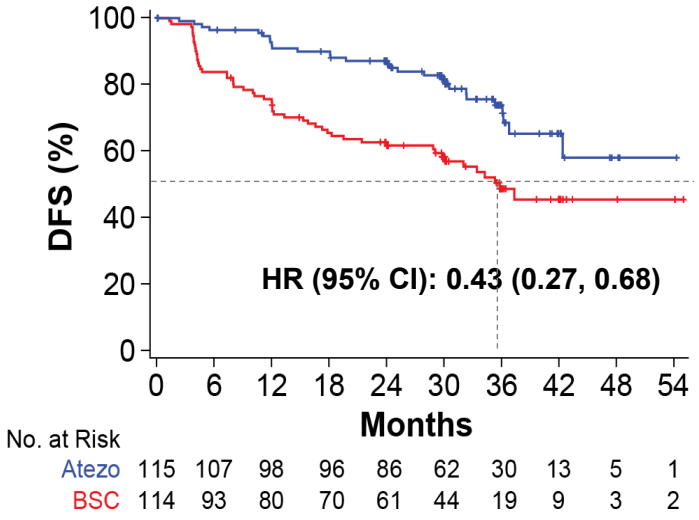
1.4.3 Secondary Endpoint - DFS in PD-L1 ≥ 50% TC Stage II–IIIA population, including patients with EGFR/ALK mutations

Analysis of DFS in the PD-L1 ≥ 50% TC Stage II–IIIA population (n=229) was a secondary endpoint. Median follow-up was 34.2 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 ≥ 50%. At the CCOD on 21 January 2021, a higher proportion of patients in the BSC arm (45.6%) compared to the atezolizumab arm (24.3%) had experienced disease recurrence or death (6, 7).

The unstratified HR was 0.43 (95% CI: 0.27, 0.68; p = 0.0002), which corresponds to a 57% relative risk reduction of a DFS event with atezolizumab compared to BSC (6, 7).

The Kaplan-Meier (KM) estimated median DFS was not reached in the atezolizumab arm due to the low number of events, and was 35.7 months in the BSC arm (95% CI: 29.7, NE). The KM curves began to separate at approximately 4 months (corresponding to the first scheduled tumour assessment) after randomisation in favour of the atezolizumab arm and was maintained thereafter (Figure 3).

Figure 3: Kaplan-Meier plot of DFS (PD-L1 ≥ 50% TC Stage II–IIIA population) (6, 7).



PD-L1 TC ≥ 50% Stage II-IIIA		
	Atezo (n=115)	BSC (n=114)
mDFS,	NE	35.7
DFS HR (95% CI)	0.43 (0.27, 0.68)	

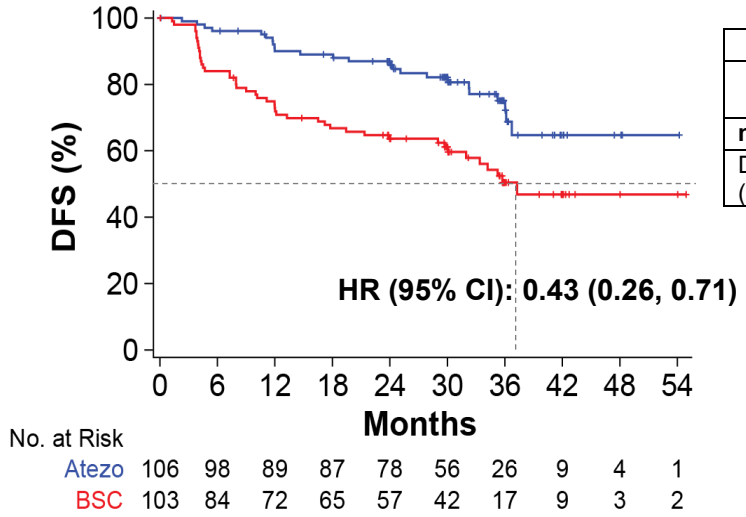
Clinical data cut-off date (CCOD): 21 Jan 2021
Unstratified HRs are reported. mDFS, median DFS; NR, not evaluable.

1.4.4 Secondary Endpoint - DFS in PD-L1 ≥ 50% TC Stage II–IIIA population, *excluding patients with EGFR/ALK mutations*

At the time of IMpower010 study design and initiation in 2015, patients with EGFR/ALK+ NSCLC were enrolled since efficacy of anti-PD-L1 therapies in these subgroups were unknown, hence there was no clear rationale for excluding these populations. Additionally, besides from chemotherapy there were no other adjuvant treatment options for early stage NSCLC patients who had EGFR/ALK mutations. Adjuvant osimertinib is now licensed for EGFR+ early NSCLC following resection (8) and represents a new standard of care for these patients. Other Phase III studies, such as ALINA, are underway to investigate the use of targeted therapies in the adjuvant setting for ALK+ early NSCLC (9). Therefore, it is not expected that the IMpower010 regimen will replace osimertinib as a standard of care for these patients. DFS was analysed excluding patients with EGFR/ALK mutations, to better reflect the target population for the IMpower010 regimen.

In this exploratory, post-hoc analysis, when EGFR/ALK positive patients were excluded the DFS HR was 0.43, for the PD-L1 TC ≥50% Stage II–IIIA population (Figure 4). Therefore, whether EGFR/ALK positive patients are included or excluded from the DFS analysis for the PD-L1 TC ≥50% Stage II – IIIA population, the DFS HR remains the same, with minor widening of the confidence intervals (HR 0.43) (10).

Figure 4: Kaplan-Meier plot of DFS (PD-L1 ≥ 50% TC Stage II–IIIA population, excluding EGFR/ALK mutations) (10)



PD-L1 TC ≥ 50% Stage II-IIIA		
	Atezo (n=106)	BSC (n=103)
mDFS	NR	37.3
DFS HR (95% CI)	0.43 (0.26, 0.71)	

Clinical data cut-off date (CCOD): 21 Jan 2021
Unstratified HRs are reported. mDFS, median DFS; NR, not reached.

1.4.5 Overall Survival Results

1.4.5.1 OS in the PD-L1 ≥ 50% TC Stage II–IIIA population,

OS in the intention to treat population (ITT; ITT population includes the all-randomised stage IB-IIIA population in the IMpower010 trial) was included as a key secondary endpoint in IMpower010. OS was not formally tested at the time of analysis, as statistical significance for DFS was not met in the ITT population (Company submission, Appendix H).

However, an exploratory analysis of OS was performed in the PD-L1 ≥ 50% TC Stage II–IIIA population.

[redacted] (Data on File). Exploratory analysis of OS suggested a trend in favour of atezolizumab over BSC in the PD-L1 ≥50% TC Stage II–IIIA population. The unstratified HR was 0.37 (95% CI: 0.18, 0.74), which corresponds to a [redacted] (Figure 5). These data should be interpreted with caution as they were [redacted]. The median OS [redacted]. OS analyses will continue to be followed up as data matures.

Figure 5: Kaplan-Meier plot of OS (PD-L1 ≥ 50% TC Stage II–IIIA population)

Clinical data cut-off date (CCOD): 21 Jan 2021
Clinical cutoff: 21 January 2021. Unstratified HRs are reported. CI, confidence intervals, mOS, median overall survival; NE, not evaluable.

1.4.6 Disease Relapse

In current clinical practice, between a third and two thirds of patients with early NSCLC who undergo resection experience relapse (11). Therefore, it is important that treatment not only prevents disease relapse but also relapse, as delaying relapse is commonly associated with a positive impact for patients, such as improvement in quality of life by delayed presentation of advanced or metastatic disease, which is associated with substantial morbidity.

A post-hoc exploratory analysis was conducted to investigate the incidence of disease relapse (Table 3) and the sites of relapse (Table **4**) (Data on File).

1.4.6.1 Incidence of disease relapse in the PD-L1 ≥ 50% TC Stage II–IIIA population

As an exploratory, post-hoc analysis, rate of relapse was evaluated in all randomised patients (after surgery and chemotherapy) whose DFS event was that of disease recurrence (Data on File). In the PD-L1 ≥ 50% TC Stage II–IIIA population, 22% of patients experienced relapse in the atezolizumab arm compared with 44% in the BSC arm (Data on File), within the current follow-up period (Table 3).

Table 3: Disease Recurrence

Disease Recurrence	
Atezolizumab (n=115)	**Best Supportive Care (n=114)**
25 (22%)	50 (44%)

Presented as an exploratory post-hoc descriptive analysis.
Clinical data cut-off date (CCOD): 21 Jan 2021.

1.4.6.2 Sites of relapse in the PD-L1 ≥ 50% Stage II–IIIA population

In a further post-hoc analysis, the sites of disease recurrence were analysed for patients who had disease recurrence (atezolizumab arm n=25, best supportive care arm, n=50) in the PD-L1 TC ≥ 50% Stage II–IIIA population (Data on File). For patients who had disease recurrence in the atezolizumab arm, a higher proportion of patients had loco-regional recurrence only (60%) compared to distant only recurrence (24%). Whereas for patients who had disease recurrence in the BSC arm, a higher proportion of patients had distant recurrence (42%) compared to loco-regional recurrence only (34%).

Table 4**: Sites of disease recurrence for patients with protocol defined disease recurrence in the PD-L1 ≥ 50% Stage II–IIIA population**

Sites of disease recurrence		
	Atezolizumab (n=25)	**Best Supportive Care (n=50)**

Loco Regional Only	15 (60%)	17 (34%)
Distant Only	6 (24%)	21 (42%)
Loco Regional + Distant	4 (16%)	9 (18%)
CNS	1 (4%)	7 (14%)

Presented as an exploratory post-hoc descriptive analysis.
Abbreviations: LR, locoregional; CNS, Central Nervous System.

1.4.7 Subgroup analysis for DFS in the PD-L1 ≥ 50% TC Stage II–IIIA population

The generalisability of the observed DFS treatment effect with atezolizumab relative to BSC in the PD-L1 ≥ 50% TC Stage II–IIIA population was investigated in pre-defined subgroups based on key baseline demographics, baseline disease characteristics and biomarker status. Results from the PD-L1 ≥ 50% TC Stage II–IIIA key patient population are presented below (Data on File).

In the subgroup analyses, the atezolizumab treatment effect on DFS was consistent across the majority of pre-defined subgroups, and consistent with the benefit observed in the overall PD-L1 ≥ 50% TC Stage II–IIIA population (Table 5). Patients who were treated with

[redacted]

[redacted] Results for the subgroups analysis should be interpreted with caution due to the small sample size.

Table 5: Subgroup analysis of DFS in the PD-L1 ≥ 50%[a] TC Stage II–IIIA population by disease characteristics

[redacted]

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

1.5 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. The full safety analysis was presented in the initial company submission. Additional safety data presented below consists of Grade 3-4 AEs for the PD-L1 ≥ 50% Stage II-IIIA population.

1.5.1 Treatment-related Grade 3–4 AEs in the PD-L1 TC ≥50% Stage II–IIIA population

Safety in PD-L1 TC ≥50% stage II-IIIA pts was consistent with that of the overall study population and known safety profile of atezolizumab. In this patient population, the most common atezolizumab-related Grade 3-4 AEs was [redacted] (Data on File).

Table 6: Treatment-related Grade 3–4 AEs/SAEs (PD-L1 ≥ 50% TC Stage II–IIIA population)

	Atezolizumab (n=115)
Number of occurrences of Grade 3-4 AEs/SAEs, n (%)	
Alanine aminotransferase increased	[redacted]
Aspartate aminotransferase increased	[redacted]
Asthenia	[redacted]
Axonal neuropathy	[redacted]
Colitis	[redacted]
Demyelinating polyneuropathy	[redacted]
Diarrhoea	[redacted]
Drug eruption	[redacted]
Drug-induced liver injury	[redacted]
Dyspepsia	[redacted]
Encephalitis	[redacted]
Gait disturbance	[redacted]
Gastritis	[redacted]
Genital rash	[redacted]
Hepatic function abnormal	[redacted]
Hyperglycaemia	[redacted]
Hypersensitivity	[redacted]
Hyponatraemia	[redacted]

	Immune-mediated adverse reaction	[redacted]
	Inappropriate antidiuretic hormone secretion	[redacted]
	Interstitial lung disease	[redacted]
	Leukopenia	[redacted]
	Meningitis	[redacted]
	Multiple organ dysfunction syndrome	[redacted]
	Myalgia	[redacted]
	Myocarditis	[redacted]
	Neuropathy peripheral	[redacted]
	Neutropenia	[redacted]
	Parapsoriasis	[redacted]
	Platelet count decreased	[redacted]
	Pneumonia	[redacted]
	Pneumonitis	[redacted]
	Pyrexia	[redacted]
	Rash	[redacted]
	Rash maculo-papular	[redacted]
	Sarcoidosis	[redacted]
	Secondary adrenocortical insufficiency	[redacted]
	Septic shock	[redacted]
	Thrombocytopenia	[redacted]
	Vomiting	[redacted]

*The difference in patient population (n=244 vs n=248) was due to four patients not receiving at least one dose of atezolizumab after randomisation.
Abbreviations: AE, adverse event; SAE, serious adverse event.

1.6 Ongoing studies

Analyses in IMpower010 are event-driven; therefore, it is difficult to provide exact timings on when further analyses will become available. However, patients will continue to be followed up. Final analyses are planned for DFS in the ITT population (which did not cross the threshold for significance at the DFS interim analysis) and OS (which were immature at the time of the interim DFS analysis).

1.7 Innovation

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 (12).

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 (13). Adjuvant chemotherapy can provide further benefit; however, it only provides a modest 5% improvement in OS at 5 years

(HR 0.89) (14). Aside from chemotherapy, no other adjuvant treatment options are available other than osimertinib for patients with EGFR+ early NSCLC (15), however EGFR+ patients are only a small subset of NSCLC patients (16-18).

Though surgery represents a potential cure for resectable early NSCLC patients, recurrence rates remain high, with an approximate rate of recurrence of 41–68% for patients with Stage I–III NSCLC. Upon locoregional recurrence, patients may receive a potentially curative treatment with chemo-radiation. However, if patients progress to metastatic disease, the aim of treatment is no longer cure, but to prolong life and reduce disease burden. Additionally, as NHS England implement lung cancer screening programmes, the proportion of early NSCLC patients are likely to increase in the UK. This further highlights the urgent need for more effective treatment options, especially in this potentially curative setting.

Cancer immunotherapy alone, or in combination with chemotherapy, has demonstrated an overall survival benefit in unresectable, Stage III NSCLC, and in Stage IV NSCLC. Recently, trials of cancer immunotherapy in the neoadjuvant setting for NSCLC have also been positive (19, 20). In the adjuvant setting, atezolizumab offers an innovative approach to therapy. By targeting PD-L1 expression, anti-tumour mechanisms are reactivated. This stimulates T-cells to monitor for residual tumours cells, potentially eliminating the formation of micro-metastases following complete surgical resection. This results in a prolonged anti-tumour immune response, to reduce the risk of recurrence.

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. The primary endpoint, showed that atezolizumab reduced the risk of recurrence, new primary NSCLC, or death by 34% (DFS HR 0.66) compared to BSC, in the PD-L1 ≥ 1% Stage II–IIIA population. For the secondary endpoint of DFS in PD-L1 ≥ 50% Stage II–IIIA population, a greater magnitude of benefit was observed compared to BSC, with an unstratified HR was 0.43 (95% CI 0·27–0·68). In addition, there were no new safety signals for atezolizumab in IMpower010, with the safety profile consistent with that established for atezolizumab monotherapy (6).

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 positive 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.

Due to the positive results of IMpower010 and the potential for a paradigm shift in the management of early NSCLC, adjuvant atezolizumab was granted priority review under the FDAs Real-Time Oncology Review programme. Which has led to the recent FDA approval of atezolizumab for the adjuvant treatment of Stage II–IIIA NSCLC, whose tumours have PD-L1 expression on ≥ 1% of tumour cells, following resection and platinum-based chemotherapy. Therefore, atezolizumab is the first and only cancer immunotherapy currently available for adjuvant treatment of NSCLC. The review was conducted under the Project Orbis initiative due to its innovative and clinical significance. In addition, atezolizumab has been granted an 'Innovation Passport' through MHRA's Innovative Licensing and Access Pathway (ILAP).

[redacted]

1.8 Interpretation of clinical effectiveness and safety evidence

1.8.1 Atezolizumab vs BSC

The IMpower010 trial met its primary endpoint, demonstrating statistically significant and clinically meaningful DFS improvement in patients receiving adjuvant atezolizumab compared with BSC in the PD-L1 TC ≥ 1% Stage II–IIIA population.

The aim of offering adjuvant atezolizumab after chemotherapy is to prevent or delay relapse. In the primary analysis, the efficacy boundary for patients with PD-L1 ≥ 1% Stage II–IIIA NSCLC was crossed, demonstrating a 34% reduction in risk of disease recurrence, formation of new NSCLC, or death (DFS HR 0.66) in favour of atezolizumab compared with BSC. For the secondary endpoint of DFS in PD-L1 ≥ 50% Stage II–IIIA population, a greater magnitude of benefit was observed compared to the PD-L1 ≥ 1% population, with an unstratified HR of 0.43 (95% CI 0·27–0·68) in favour of atezolizumab (the target patient population for this submission).

Although highly immature and unstable at this time due to the low number of events, the exploratory analysis of OS in PD-L1 ≥ 50% Stage II–IIIA population demonstrated a trend indicating in favour of atezolizumab, with a 63% reduction in risk of death for atezolizumab compared with BSC (OS HR 0.37; 95% CI: 0.18, 0.74). These data will require longer-term follow-up and patients will be monitored as survival data matures.

Due to the high recurrence rates in early NSCLC following resection, it is clinically important to understand when relapse occurs, as delaying relapse is associated with a positive impact

for patients. In the exploratory post-hoc analysis, 22% of patients experienced relapse for atezolizumab compared with 44% in the BSC arm. This is reflected in the DFS benefit observed in the PD-L1 ≥ 50% Stage II–IIIA population.

The safety profile for atezolizumab monotherapy was consistent with previous clinical studies (21-24), and no new safety signals were identified. Immune-mediated adverse events occurred more frequently in patients treated with atezolizumab, which was expected as these were known risks with checkpoint inhibitors (21). Approximately half of the adverse events that led to discontinuation were Grade 1–2, which might indicate that investigators had a lower threshold for discontinuing treatment in patients with early NSCLC due to treatment-related toxicity compared to what might be observed in the metastatic setting. Overall, more toxicity was observed in atezolizumab compared with BSC, as expected since the latter was comprised of active monitoring only. 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 PD-L1 ≥ 50% Stage II–IIIA population appeared to be favourable. 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.

1.8.2 Strengths and limitations of IMpower010

The IMpower010 study was a robust Phase III study that included a large global patient population with well-balanced baselines characteristics between treatment arms, standardised adjuvant chemotherapy, and standardised endpoints powered to show differences between treatment arms.

In terms of limitations, IMpower010 included an open-label design and lack of placebo control. The open-label study design was chosen for safety considerations, in the context of the standard of care at the time. To minimise the potential bias of the open-label design, Good Clinical Practice (GCP), NCCN and ESMO guidelines were adhered to ensure standard patient care. A placebo arm was not included in the adjuvant setting to avoid placing the burden of one year of 3-weekly intravenous treatment visits on patients who had undergone potentially curative resection and adjuvant chemotherapy.

In addition, the SP142 assay was used during screening and enrolment initially, however, in line with the changing landscape of PD-L1 testing, the SP263 PD-L1 IHC assay was used to define the primary analysis population. Of note, the proportion of baseline PD-L1 expression

by SP263 and baseline characteristics by SP142 were similar and well-balanced between study arms and within the Stage II–IIIA PD-L1 TC ≥ 50% population. This shows that the analyses were adequately powered to investigate the DFS benefit of atezolizumab vs BSC in the PD-L1 positive patient population defined by the SP263 assay.

2. Cost-effectiveness

The cost-effectiveness model results presented in this section are for the following subgroups:

- Adult patients with Stage II to IIIA with NSCLC whose tumours have PD-L1 expression on ≥50% of TCs and whose disease has not progressed following platinum-based adjuvant chemotherapy, including the EGFR mutation or ALK-positive population
- Adult patients with Stage II to IIIA with NSCLC whose tumours have PD-L1 expression on ≥50% of TCs and whose disease has not progressed following platinum-based adjuvant chemotherapy, excluding the EGFR mutation or ALK-positive population

2.1 Economic analysis

2.1.1 Intervention technology and comparators

The intervention technology, atezolizumab (1200 mg every 21 days; for 16 cycles or ~1 year), and the comparator, BSC (observation and regular scans for disease recurrence), in the IMpower010 trial are consistent with the final NICE scope outlined in Section B.1.1 of the company submission document B.

In this additional evidence document, the NSCLC population of interest is PD-L1 TC ≥ 50% Stage II–IIIA, as the MHRA is anticipated to grant license for:

- Tecentriq as monotherapy is indicated as adjuvant treatment following complete resection for adult patients with Stage II to IIIA (7th edition of the UICC/AJCC-staging system) non-small cell lung cancer (NSCLC) whose tumours have PD-L1 expression on ≥50% of tumour cells (TC) and whose disease has not progressed following platinum-based adjuvant chemotherapy

This approval was based on the interim DFS analysis, where the significant boundary was crossed for the PD-L1 TC ≥ 1% Stage II–IIIA population, with the greatest benefit in the PD-L1 TC ≥ 50% subgroup (unstratified HR, 0.43; 95% CI: 0.27, 0.68) (25).

Osimertinib was recently recommended for use within the Cancer Drugs Fund (CDF) for the Stage IB–IIIA population whose tumours have EGFR exon 19 deletions or exon 21 (L858R) substitution mutations and UK clinical oncologists advised that an immunotherapy is unlikely to be used in the PD-L1 TC ≥ 50% Stage II–IIIA population with EGFR mutations, if osimertinib is available (3). For this reason, we have included the cost-effectiveness results for the PD-L1 TC ≥ 50% Stage II–IIIA population, excluding EGFR or ALK-positive mutations in Section 2.6.

2.2 Clinical parameters and variables

2.2.1 Adaptation of the economic model to the PD-L1 TC ≥ 50% Stage II–IIIA population

Data for the PD-L1 TC ≥ 50% Stage II–IIIA population, both including and excluding EGFR mutation or ALK-positive have been incorporated into the existing economic model which was submitted for the ERG clarification response (file name: ID3852_Atezolizumab_eNSCLC_CE_Model_v2.1_ERG_clarifications). In addition, following advice from a UK clinical expert (from a 1:1 call in December 2021), changes were made to the treatment options for metastatic recurrence health states. The following was changed in the model as a result of this discussion:

1. Carboplatin was replaced cisplatin as this is more in line with clinical practice
2. Atezolizumab was removed as a treatment option for 2L metastatic recurrence health state; if immunotherapy was not deemed appropriate in 1L, it was unlikely to be used in 2L
    - As a result, for the 2L metastatic recurrence health state, only chemotherapy treatment options were included (see Table 12). The market shares were calculated using the proportions from the TAE survey carried out August 2021

These changes apply for whether the populations were for PD-L1 TC ≥ 50% Stage II–IIIA or PD-L1 TC ≥ 1% Stage II–IIIA populations. Although market shares may be different for these populations, regional variations make it difficult to accurately portray these proportions, however, sensitivity analysis shows that varying these proportions has little impact on the

ICER (Section 2.5). Making these changes to the treatment options and market shares in the economic model (file name: ID3852_Atezolizumab_eNSCLC_CE_Model_v2.1_ERG_clarifications) as a result of the 1:1 with a UK clinical expert, resulted in revised ICERs (with PAS) as follows:

- PD-L1 TC ≥ 1% Stage II–IIIA population, including EGFR/ALK+ mutations: from [redacted] to [redacted] per QALY
- PD-L1 TC ≥ 1% Stage II–IIIA population, excluding EGFR/ALK+ mutations: from [redacted] to [redacted] per QALY

Changes to the economic model with the PD-L1 TC ≥ 50% Stage II–IIIA subgroup data and how this affects the previous base case analysis assumptions are detailed in Table 7. All of the inputs presented in the table are varied at the same time when the model sub-group is changed, linked to cell F34 (named range “pop”) within the ‘Model Settings’ sheet. Thus, the effect that any one of the inputs may have on the results, may be confounded by the other inputs.

In Table 7, the sub-group PD-L1 ≥1% Stage II-IIIA is referred to as (A), and the sub-group PD-L1 ≥50% as (B).

Table 7: The effects on the variables with the subgroup analysis for the PD-L1 ≥ 1% Stage II-IIIA (A), compared with PD-L1 ≥50% Stage II-IIIA (B), including and excluding ALK+/EGFR mutations

				Including ALK+/EGFR mutations	**Excluding ALK+/EGFR mutations**
Variable and reference to relevant sections	**Sheet**	**Cells**	**Effect**	**Interpretation**	
Time-to-off treatment (ttot_atz) *Section B.3.5.2.1 of Document B*	Atezolizumab in DFS Tx Schedule	C31:Q46	If option_ttot_atz is set to 'observed in trial', a change in the time-to-off treatment has an effect on the atezolizumab treatment cost in the DFS health state.	Completed 16 cycles of treatment (ATZ arm): (A) [redacted] < (B) [redacted] This implies that the treatment cost should be higher in (B), which is realised: (A) [redacted] < (B) [redacted]	Completed 16 cycles of treatment (ATZ arm): (A) [redacted] > (B) [redacted] This implies that the treatment cost should be higher in (A), which is realised: (A) [redacted] > (B) [redacted]
Number of patients experiencing locoregional and metastatic recurrence as first DFS event *Section B.3.3.6 of Document B*	DFS Events	E23:X24	A change in the number of patients who experience locoregional and metastatic recurrence has an effect on the proportion of patients who experience these recurrences (cells E30:T31 and variables p_dfs_lr_atz, p_dfs_mr_atz,	% locoregional recurrences (ATZ arm): [redacted] < (B) [redacted] % locoregional recurrences (BSC arm): (A) [redacted] > (B) [redacted] % metastatic recurrences (ATZ arm): [redacted] > (B) [redacted]	% locoregional recurrences (ATZ arm): [redacted] < (B) [redacted] % locoregional recurrences (BSC arm): (A) [redacted] > (B) [redacted] % metastatic recurrences (ATZ arm): [redacted] > (B) [redacted]

			p_dfs_lr_bsc, p_dfs_mr_bsc). As a consequence, this has an effect on the costs, quality-life year gains, and life-year gains for the locoregional recurrence and metastatic recurrence health states.	<u>% metastatic recurrences (BSC arm):</u> (A) [redacted] < (B) [redacted] The % of locoregional recurrences is greater in (B) than in (A) for the ATZ arm: As more patients transition first to the locoregional recurrence health state in (B), and as less patients may make it to the metastatic recurrence health states due to dying in the locoregional recurrence health state, locoregional recurrence health state costs and QALYs should be higher, and metastatic recurrence health state costs and QALYs should be lower in (B). The below results show that this is realised. <u>Locoregional health state (ATZ):</u> Cost: (A) = [redacted] < (B) = [redacted]	<u>% metastatic recurrences (BSC arm):</u> (A) [redacted] < (B) [redacted] The % of locoregional recurrences is greater in (B) than in (A) for the ATZ arm: As more patients transition first to the locoregional recurrence health state in (B), and as less patients may make it to the metastatic recurrence health states due to dying in the locoregional recurrence health state, locoregional recurrence health state costs and QALYs should be higher, and metastatic recurrence health state costs and QALYs should be lower in (B). The below results show that this is realised. <u>Locoregional health state (ATZ):</u> Cost: (A) = [redacted] > (B) = £2,516

				QALY: (A) = [redacted] < (B) = [redacted] <u>Metastatic health states (ATZ):</u> Cost: (A) = [redacted] > (B) = [redacted] QALY: (A) = [redacted] > (B) = [redacted] The % of locoregional and metastatic recurrences is negligible between (A) and (B) for the BSC arm. Thus, we only interpret the effect that a change in this input has on the ATZ arm.	QALY: (A) = [redacted] > (B) = [redacted] <u>Metastatic health states (ATZ):</u> Cost: (A) = [redacted] > (B) = [redacted] QALY: (A) = [redacted] > (B) = [redacted] The % of locoregional recurrences is greater in (A) than in (B) for the BSC arm: As more patients transition first to the locoregional recurrence health state in (A), and as less patients may make it to the metastatic recurrence health states due to dying in the locoregional recurrence health state, locoregional recurrence health state costs and QALYs should be higher. The results below show this is realised. As seen below, the difference between (A) and (B) is negligible in the metastatic health states for the *BSC arm*, thus, we only interpret the effect that a change in

					this input has on the locoregional health state. <u>Locoregional health state (BSC):</u> Cost: (A) = [redacted] > (B) = [redacted] QALY: (A) = [redacted] > (B) = [redacted] <u>Metastatic health states (BSC):</u> Cost: (A) = [redacted] > (B) = [redacted] QALY: (A) = [redacted] = (B) = [redacted]
Number of patients experiencing death as a first DFS event *Section B.3.3.6 of Document B*	DFS Events	E26:X26	A change in the number of patients who experience death as a first DFS event has an effect on the transition probability from the DFS health state to Death (cells E37:X38 and variables dfs_death_atz and dfs_death_bsc). A change in this transition probability would impact the	<u>Transition probability to death (ATZ arm):</u> (A) [redacted] > (B) [redacted] <u>Transition probability to death (BSC arm):</u> (A) [redacted] < (B) [redacted] In the ATZ arm, if there are less patients transitioning to death in (B) from DFS, we would expect the costs and QALYs to be higher than for	<u>Transition probability to death (ATZ arm):</u> (A) [redacted] > (B) [redacted] <u>Transition probability to death (BSC arm):</u> (A) [redacted] < (B) [redacted] In the ATZ arm, if there are less patients transitioning to death in (B) from DFS, we would expect the costs and QALYs to be higher than for

			costs, quality-life year gains and life year gains of all health states.	(A). The results below show this is realised <u>DFS health states (ATZ):</u> Cost: (A) = [redacted] < (B) = [redacted] QALY: (A) = [redacted] < (B) = [redacted] Due to the insignificant change in the transition probabilities in the BSC arm, an interpretation of the results will not be conducted as changes in the other inputs may confound the effect that we can expect this input to have.	(A). The results below show this is realized: <u>DFS health states (ATZ):</u> Cost: (A) = [redacted] < (B) = [redacted] QALY: (A) = [redacted] < (B) = [redacted] Due to the insignificant change in the transition probabilities in the BSC arm, an interpretation of the results will not be conducted as changes in the other inputs may confound the effect that we can expect this input to have.
Number of patients experiencing each grade 3+ treatment emergent adverse event (atezolizumab arm only) *B14 and B15 of ERG Clarification questions*	DFS Events	E50:W89	If the costs and disutilities of adverse events are considered by the model, a change in the number of patients experiencing each adverse event has an effect on the adverse event management costs and quality-life year gains in the DFS health state for the atezolizumab arm	This is not currently considered in the model, but is considered in scenario analysis with grade 2+ AEs.	This is not currently considered in the model, but is considered in scenario analysis with grade 2+ AEs.

			(refer to variables c_ae_atz and u_ae_atz).		
Kaplan-Meier statistics *Section B.3.3.4 of Document B*	DFS Kaplan-Meier	C15:X177; C190:X416	If the model uses the Kaplan-Meier curve + parametric tail to model DFS, a change in these statistics affects the proportion of patients who are in the DFS health state in each cycle and, consequently, costs, quality-life year gains, and life-year gains of all health states. Moreover, if option_ttot_atz is set to 'until progression or death', a change in these statistics have an effect on the atezolizumab treatment cost in the DFS health state.	This input is not currently used to model DFS or time-to-off treatment.	This input is not currently used to model DFS or time-to-off treatment.

Kaplan-Meier statistics *Section B.3.3.5.1 of Document B*	OS Kaplan-Meier	C15:AF57; C81:AF128	If the model uses the OS Kaplan-Meier curve model OS, a change in these statistics affects the proportion of patients who survive in each cycle and, consequently, costs, quality-life year gains, and life-year gains of all health states.	This input is not currently used in the base case analysis but is considered in scenario analysis.	This input is not currently used in the base case analysis but is considered in scenario analysis.
Estimated parameters from survival analysis (DFS) *Section 1.4.1 of this dossier*	DFS Survival Analysis	C16:BH29; C38:BH51	A change in these estimates affects the extrapolation of DFS (proportion of patients in DFS in each cycle) and, consequently, the costs, quality-life year gains and life-year gains of all health states.	The analysis of DFS of (B) shows that the hazard ratio is lower than (A) (refer to Section 1.4.1). Thus, an even greater improvement of DFS in this subgroup of patients should result in less overall costs and more QALYs across the ATZ and BSC arms. In relative terms, even less patients in the ATZ arm vs. the BSC arm would experience recurrence. The results below show that this expectation is realised. <u>Cost Difference:</u> (A) [redacted] > (B) [redacted]	The analysis of DFS of (B) shows that the hazard ratio is lower than (A) (refer to Section 1.4.4 and Document B Section B.2.7.2). Thus, an even greater improvement of DFS in this subgroup of patients should result in a less overall costs and more QALYs across the ATZ and BSC arms. In relative terms, even less patients in the ATZ arm vs. the BSC arm would experience recurrence. The results below show that this expectation is realised. <u>Cost Difference:</u> (A) [redacted] > (B) [redacted]

				QALY Difference: (A) [redacted] < (B) [redacted]	QALY Difference: (A) [redacted] < (B) [redacted]
Estimated parameters from survival analysis (OS) *B10 of ERG Clarification questions*	OS Survival Analysis	F45:N64; F71:N90	A change in these estimates affects the extrapolation of OS (proportion of patients in OS in each cycle) and, consequently, the costs, quality-life year gains and life-year gains of all health states.	This input is not currently used in the base case analysis but is considered in scenario analysis.	This input is not currently used in the base case analysis but is considered in scenario analysis.

2.2.2 Health-state unit costs and resource use

Differences between the updated model for the PD-L1 ≥50% subgroup from the economic model presenting the PD-L1 ≥1% population, in terms of costs and resource use, are highlighted throughout this section.

2.2.2.1 Disease-free survival

Treatment cost

Table 8 shows the TTOT data for the PD-L1 ≥50% subgroup in terms of the proportion of patients on atezolizumab in each cycle and Table 9 shows the cost of atezolizumab each month (11 months in total).

Table 8: TTOT (IMpower010, TTOT, Stage II–III, PD-L1 ≥50%, ATZ arm, 21 Jan 2021 data-cut)

Cycle	Proportion of patients on treatment
1	[redacted]
2	[redacted]
3	[redacted]
4	[redacted]
5	[redacted]
6	[redacted]
7	[redacted]
8	[redacted]
9	[redacted]
10	[redacted]
11	[redacted]
12	[redacted]
13	[redacted]
14	[redacted]
15	[redacted]
16	[redacted]

Adapted from Table 46, page 117 of company submission

Table 9: Treatment acquisition costs (IMpower010, TTOT, Stage II–III, PD-L1 ≥50%, ATZ arm, 21 Jan 2021 data-cut) – DFS health state

Month	Cost per month, PAS price (£)	Cost per month, list price (£)
0	[redacted]	£8,032.86
1	[redacted]	£3,816.52
2	[redacted]	£7,196.86
3	[redacted]	£3,562.08
4	[redacted]	£6,869.73
5	[redacted]	£3,380.34
6	[redacted]	£6,578.95
7	[redacted]	£3,198.61
8	[redacted]	£6,324.52
9	[redacted]	£3,125.91
10	[redacted]	£3,089.56

Adapted from Table 47, page 118 of company submission

2.2.2.2 First-line/second-line metastatic recurrence

Treatment cost

As mentioned in Section 2.2.1, following a 1:1 call with a UK clinical expert (in December 2021), changes to the metastatic recurrence health states were made.

The model used the four treatment options presented in Table 10 to define first-line metastatic treatment. The weighted average monthly treatment costs are presented in Table 11.

There are no changes to the market shares from what was presented in Table 53 of company submission document B.

Table 10: Treatment options (1L metastatic treatment)

Inputs	Option 1	Option 2	Option 3	Option 4
Drug 1	Pembrolizumab	Pemetrexed	Pembrolizumab	Pembrolizumab
Dose size	200mg/ fixed	500mg/m^2	200mg/ fixed	200mg/ fixed
Doses per cycle	1	1	1	1
Weeks btw. cycles	3	3	3	3
Drug 2	Pemetrexed	Carboplatin	n/a	Carboplatin
Dose size	500mg/m^2	150mg AUC	n/a	150mg AUC
Doses per cycle	1	1	n/a	1
Weeks btw. cycles	3	3	n/a	3
Estimated monthly cost	£9693.97	£2114.19	£8058.13	£8536.47

AUC: area under the curve

NB: These figures can be found in '1L Met. Recurrence Tx Schedule' tab of the model. The reported monthly cost accounts for administration costs.

Adapted from Table 52, page 122 of company submission

Table 11: Weighted average monthly treatment costs (1L Metastatic Treatment)

Arm	Overall weighted average monthly treatment cost (£)
Atezolizumab	£2,114.19
BSC	£7,225.59

Adapted from Table 54, page 123 of company submission

NB: the 1L metastatic treatment costs realised by BSC patients will also be realised by patients in the atezolizumab arm if they can re-challenge with immunotherapy.

For 2L metastatic recurrence, the model used the four treatment options presented in Table 12 to define second-line metastatic treatment. Compared to the company submission Document B, this contains no immunotherapy options. The market shares estimated by UK clinical oncologists are presented in Table 13.

NB: The proportions are calculated based on the results from the cost and resource use survey sent to UK clinical experts in August 2021.

Adapted from Table 56, page 124 of company submission

Table 14 presents the weighted average monthly treatment costs for the atezolizumab and BSC arms.

Table 12: Treatment options (2L metastatic treatment)

Inputs	Option 1	Option 2	Option 3	Option 4
Drug 1	Nintedanib	Pemetrexed	Docetaxel	Gemcitabine
Dose size	150mg/ fixed	500mg/ m^2	75mg/m^2 fixed*	1250mg/ m^2
Doses per cycle	2	1	1	2
Weeks btw. cycles	3	3	3	3
Drug 2	Docetaxel	Carboplatin	n/a	Carboplatin
Dose size	75mg/m^2 fixed*	150mg AUC	n/a	150mg AUC
Doses per cycle	1	1	n/a	1
Weeks btw. cycles	3	3	n/a	3
Estimated monthly cost	£6,716.29	£2,114.19	£456.01	£1,453.00

NB: These figures can be found in '2L Met. Recurrence Tx Schedule' tab of the model. The reported monthly cost accounts for administration costs.

Adapted from Table 55, page 124 of company submission

*An error was spotted in the model (file name: ID3852_Atezolizumab_eNSCLC_CE_Model_v2.1_ERG_clarifications) – Docetaxel should be 75 mg/m^2 fixed rather than 160 mg/m^2 fixed. This has been corrected in the updated model.

Table 13: Market shares of 2L treatment options

Atezolizumab arm		BSC arm	
Treatment options	**Proportion (%)**	**Treatment options**	**Proportion (%)**
Nintedanib + docetaxel	[redacted]	Nintedanib + docetaxel	[redacted]
Pemetrexed + carboplatin	[redacted]	Pemetrexed + carboplatin	[redacted]
Docetaxel	[redacted]	Docetaxel	[redacted]
Gemcitabine and carboplatin	[redacted]	Gemcitabine and carboplatin	[redacted]

NB: The proportions are calculated based on the results from the cost and resource use survey sent to UK clinical experts in August 2021.

Adapted from Table 56, page 124 of company submission

Table 14: Weighted average monthly treatment costs (2L metastatic treatment)

Arm	Overall weighted average monthly treatment cost (£)
Atezolizumab	£3723.73
BSC	£3723.73

Adapted from Table 57, page 124 of company submission

2.3 Summary of revised base-case analysis inputs and assumptions

2.3.1 Summary of base-case analysis inputs

Table 15 summarises all key variables applied in the base case of the economic model.

Table 15: Summary of variables applied in the base case setting of the economic model

Variable	Value	Measurement of uncertainty and distribution: CI (distribution)	Justification	Reference to section in submission Doc B and this document (where relevant)
General model parameters				
Time horizon	40 years	Fixed	Sufficiently long to capture all clinical and economic outcomes.	Section B.3.2 of Doc B
Discount rate – efficacy	3.5%	Fixed	As per reference case	
Discount – costs	3.5%	Fixed		
Population parameters				
Age	61.20 years	Fixed	As per IMpower010 trial	Baseline characteristics section 1.3.2
Body weight	73.00 kg	Fixed		
Height	170.00 cm	Fixed		
Body surface area	1.84 m^2	Fixed		
Proportion of males (%)	72.90%	Fixed		
Population in Analysis	PD-L1 ≥50% Stage II–IIIA	Fixed	[redacted]	
Efficacy inputs				
Disease-free survival				
Atezolizumab regimen	1,200 mg every 3 weeks	Fixed	As per IMpower010 trial	

Time to off treatment	Trial-observed	Fixed	As per IMpower010 trial	Section 2.2.2.1
Parametric distribution – atezolizumab arm	Log-logistic	Fixed	Clinically plausible option after considering statistical and visual fit, and clinical opinion	Section B.3.3.3 of Doc B (with changes to transition probabilities as described in Table 7)
Parametric distribution – BSC arm	Log-logistic	Fixed		
First event occurrence by type – trial data to use to inform recurrence type split	Separate by arm	Fixed	We have sufficient trial data to inform this type by arm	
First event occurrence by type – Atezo arm: proportion of patients with locoregional recurrence	[redacted]	Beta	As per IMpower010 trial	
First event occurrence by type – Atezo arm: proportion of patients with first line metastatic recurrence	[redacted]	Beta		
First event occurrence by type – Atezo arm: Transition probability to death (monthly)	[redacted]	Beta		
First event occurrence by type – BSC arm: proportion of patients with	[redacted]	Beta		

locoregional recurrence				
First event occurrence by type – Atezo arm: proportion of patients with first line metastatic recurrence	[redacted]	Beta		
First event occurrence by type – Atezo arm: Transition probability to death (monthly)	[redacted]	Beta		
Treatment effect – Duration of atezo treatment effect	Limited to 60 months	Fixed	A five-year treatment effect was chosen as this aligns with previous NSCLC appraisals (see company submission document B for further information)	
Cured patients – maximum proportion of cured patients	91.5 %	Fixed	Informed by Sonoda et al. 2019 (26). In the osimertinib appraisal, 95% of patients were assumed to be cured after 5 years (27).	Section B.3.3.4 of Doc B
Cured patients – cure proportion starts to increase	36 months	Fixed	Pignon et al. 2008 (14) and Clinical opinion	
Cured patients – cure proportion maximum reached	72 months	Fixed	Pignon et al. 2008 (14) and Clinical opinion	
Excess mortality of long-term survivors – standardised	1.25	Fixed	Based on Janssen-Heijnen et al. 2012 (28) and Clinical validation	

mortality ratio				
Cost-effectiveness analysis	Markov model	Fixed	As justified in response to B1 of ERG clarification response, A Markov model was also used in the osimertinib appraisal (ID3835) (27)	B1 of ERG clarification response document
Locoregional recurrence				
Treatment setting - % of patients by treatment intent: curative treatment	80%	Dirichlet	Informed by Sonoda et al. 2020 (29)	Section B.3.3.7 of Doc B
Treatment setting - % of patients by treatment intent: palliative treatment	20%	Dirichlet		
Treatment setting - % of patients by treatment intent: no treatment	0%	Dirichlet		
Treatment setting - Curative treatment regimen: include radiotherapy	Yes	Fixed	Clinical opinion	
Treatment setting - Curative treatment regimen: include chemotherapy	Yes	Fixed		
Treatment setting - Curative treatment regimen:	Cisplatin	Fixed		

treatment regimen drug 1				
Treatment setting - Curative treatment regimen: treatment regimen drug 2	Vinorelbine	Fixed		
Treatment setting - Palliative treatment regimen: include radiotherapy	No	Fixed		
Treatment setting - Palliative treatment regimen: include chemotherapy	No	Fixed		
Efficacy by treatment intent - use result from survival analysis or calculation (based on median)	Simple calculation	Fixed	Based on the median results from the Nakamichi et al. 2017 study (30) due to the uncertainty from using the analysis of the digitised Kaplan-Meier plot.	
Efficacy by treatment intent - Transition probability to first line metastatic recurrence: curative treatment	0.036	Beta		
Efficacy by treatment intent - % progression to first line	81%	Beta	Informed by NICE TA578 - committee papers (31), Table 9, page 57	

metastatic recurrence as first event: curative treatment				
Efficacy by treatment intent –Use result from survival analysis or calculation (based on median)	Simple calculation	Fixed	Based on the median results from the Kruser et al. 2014 study (32) due to the uncertainty from using the analysis of the digitised Kaplan-Meier plot.	
Efficacy by treatment intent – Transition probability to Death: palliative treatment and no treatment	0.136	Beta		
First-line metastatic recurrence				
Treatment setting - % of patients by treatment intent – with treatment	[redacted]	Beta	Informed by clinical opinion	Section B.3.3.8 of Doc B (with change from cisplatin to carboplatin following validation with a UK clinical expert in December 2021)
Treatment setting - % of patients by treatment intent – no treatment	[redacted]	Beta		
Treatment setting – limit treatment duration	Yes	Fixed	Informed by TA683 (33), TA600 (34), TA531 (35)	
Treatment setting – Treatment duration	24 months	Fixed		

Treatment setting – Treatment option 1	Pembrolizumab and pemetrexed	Fixed	Informed by clinical opinion. These market shares are not included in the PSA or deterministic analysis as patients cannot be rechallenged with immunotherapy, so 100% patients would receive treatment option 2 (pemetrexed and cisplatin)	
Treatment market shares – atezo arm – treatment option 1	[redacted]	Dirichlet		
Treatment setting – Treatment option 2	Pemetrexed and carbopltain	Fixed		
Treatment market shares – atezo arm – treatment option 2	[redacted]	Dirichlet		
Treatment setting – Treatment option 3	Pembrolizumab	Fixed		
Treatment market shares – atezo arm – treatment option 3	[redacted]	Dirichlet		
Treatment setting – Treatment option 4	Pembrolizumab and carboplatin	Fixed		
Treatment market shares – atezo arm – treatment option 4	[redacted]	Dirichlet		
Treatment setting – Re-challenging with immunotherapy allowed after	12 months	Fixed	Clinical opinion was that re-challenge with immunotherapy would be unlikely, this setting does not affect the model as 100% patients are assumed to receive pemetrexed and cisplatin	

treatment initiation				
Treatment setting – Re-challenging with immunotherapy: BSC arm, option 1 with pembrolizumab and pemetrexed	[redacted]	Dirichlet	Clinical opinion	
Treatment setting – Re-challenging with immunotherapy: BSC arm, option 2 with pemetrexed and cisplatin	[redacted]	Dirichlet		
Treatment setting – Re-challenging with immunotherapy: BSC arm, option 3 with pembrolizumab	[redacted]	Dirichlet		
Treatment setting – Re-challenging with immunotherapy: BSC arm, option 4 with pembrolizumab and carboplatin	[redacted]	Dirichlet		
Efficacy by treatment intent – Allow second line	Yes	Fixed	Validated by clinicians	

metastatic recurrence				
Efficacy by treatment intent – Survival analysis results	IMpower150 trial	Fixed		
Efficacy by treatment intent – Transition probability to second line metastatic recurrence - Treatment option 1	0.05	These are indirectly varied from the treatment market shares	Informed by IMpower150	
Efficacy by treatment intent – Transition probability to second line metastatic recurrence - Treatment option 2	0.11	These are indirectly varied from the treatment market shares		
Efficacy by treatment intent – Transition probability to second line metastatic recurrence - Treatment option 3	0.05	These are indirectly varied from the treatment market shares		
Efficacy by treatment intent – Transition probability to second line metastatic recurrence - Treatment option 4	0.05	These are indirectly varied from the treatment market shares		
Efficacy by treatment	0.11	These are indirectly		

intent – Transition probability to second line metastatic recurrence – Weighted average for atezo arm		varied from the treatment market shares	Clinical opinion on market shares	
Efficacy by treatment intent – Transition probability to second line metastatic recurrence – Weighted average for BSC arm	0.07	These are indirectly varied from the treatment market shares		
Efficacy by treatment intent – Transition probability to second line metastatic recurrence - % progression as first event	82.20%	Beta	Informed by IMpower150 (Table 22 from CSR, data on file)	
Efficacy by treatment intent –Use result from survival analysis or calculation (based on median)	Simple calculation	Fixed	Based on the median results from the Wong et al. 2016 study (36) due to the uncertainty from using the analysis of the digitised Kaplan-Meier plot.	
Efficacy by treatment intent – Transition probability to death: no treatment	0.23	Beta		
Second-line metastatic setting				
Treatment setting - %	[redacted]	Beta	Clinical opinion.	Section B.3.3.9 of

of patients by treatment intent – with treatment				Doc B (with change from cisplatin to carboplatin and changing Treatment 4 in 1L metastatic recurrence from atezolizumab monotherapy to gemcitabine and carboplatin following validation with a UK clinical expert in December 2021)
Treatment setting - % of patients by treatment intent – no treatment	[redacted]	Beta		
Treatment setting – Treatment option 1	Nintedanib and docetaxel	Fixed		
Treatment setting – Treatment option 2	Pemetrexed and carboplatin	Fixed		
Treatment setting – Treatment option 3	Docetaxel	Fixed		
Treatment setting – Treatment option 4	Gemcitabine and carboplatin	Fixed		
Treatment setting – Atezolizumab arm, option 1 with nintedanib and docetaxel	[redacted]	Dirichlet		
Treatment setting – Atezolizumab arm, option 2 with pemetrexed and carboplatin	[redacted]	Dirichlet		
Treatment setting – Atezolizumab arm, option 3 with docetaxel	[redacted]	Dirichlet		

Treatment setting – Atezolizumab arm, option 4 with Gemcitabine and carboplatin	[redacted]	Dirichlet		
Treatment setting – BSC arm, option 1 nintedanib and docetaxel	[redacted]	Dirichlet		
Treatment setting – BSC arm, option 2 with pemetrexed and cisplatin	[redacted]	Dirichlet		
Treatment setting – BSC arm, option 3 with docetaxel	[redacted]	Dirichlet		
Treatment setting – BSC arm, option 4 with atezolizumab	[redacted]	Dirichlet		
Efficacy by treatment intent – Transition probability to death, treatment option 1	0.07	These are indirectly varied from the treatment market shares	Informed by OAK	
Efficacy by treatment intent – Transition probability to death, treatment option 2	0.07	These are indirectly varied from the treatment market shares		

Efficacy by treatment intent – Transition probability to death, treatment option 3	0.07	These are indirectly varied from the treatment market shares		
Efficacy by treatment intent – Transition probability to death, treatment option 4	0.07	These are indirectly varied from the treatment market shares		
Efficacy by treatment intent – Transition probability to death, weighted average for atezo arm	[redacted]	These are indirectly varied from the treatment market shares	Clinical opinion on market shares	
Efficacy by treatment intent – Transition probability to death, weighted average for BSC arm	[redacted]	These are indirectly varied from the treatment market shares		
Efficacy by treatment intent –Use result from survival analysis or calculation (based on median)	Simple calculation	Fixed	Based on the median results from the Wong et al. 2016 study (36) due to the uncertainty from using the analysis of the digitised Kaplan-Meier plot.	
Efficacy by treatment intent – Transition probability to death: no treatment	0.23	Beta		

Cost inputs				
Drug costs				
Drug costs - Proportion of vials that are shared across different patients	100%	Fixed	As per previous appraisal (IMpower110 -TA705 (37)	Section B.3.5.1 of Doc B
Drug costs - Proportion of new vial that should be used to justify opening	2%	Fixed	Company assumption	
Drug costs – Atezolizumab: Composition (mg) = 840 – List Price (PAS price)	£2,665.38 [redacted])	Fixed	Sourced from BNF	
Drug costs – Atezolizumab: Composition (mg) = 1200 - List Price (PAS price)	£3,807 [redacted])	Fixed		
Radiotherapy – Cost per fraction	£144.54	Fixed	NHS reference costs 2019-2020, SC22Z	
CT scan	£119.01	Fixed	NHS Reference Costs 2019-2020, Diagnostic Imaging, Outpatient, HRG code RD24Z (two areas with contrast)	
Administration costs				
IV administration cost	£299.61	Gamma	Administration costs NHS Reference Costs 2019-2020, SB12Z, daycase and reg day/night	Section B.3.5.2 of Doc B
Disease-free survival cost and resource use				
Follow-up costs – CT scans:	24 months	Fixed	Clinical opinion	

change in scanning schedule				Section B.3.5.2 of Doc B
Follow-up costs – CT scans: Interval between scans in months (first 24 months)	6 months	Fixed		
Follow-up costs – CT scans: Interval between scans in months (after 24 months)	12 months	Fixed		
Follow-up costs – CT scans: Month at which CT scans cease	60 months	Fixed		
Follow-up costs – Include other healthcare resource costs	Yes	Fixed		
Follow-up costs – Duration of healthcare resource use	60 months	Fixed		
Follow-up costs – Healthcare resource use cost (monthly)	£53.19	This is indirectly varied as this is a weighted cost and individual costs are varied using Gamma)	Costs sourced from NHS reference costs and PSSRU, resource use from clinical opinion	

One-off AE management cost	£0	Fixed	All Grade 3+ AEs were below 2%, therefore AE management costs were not considered	Section B.3.5.5 of Doc B
Locoregional recurrence cost and resource use				
Curative treatment – Chemotherapy drug 1	Cisplatin, 80 mg/m^2, once every 3 weeks for 4 cycles	Fixed	Clinical opinion	Section B.3.5.2 of Doc B
Curative treatment – Chemotherapy drug 2	Vinorelbine, 60 mg/m^2, once every 3 weeks for 4 cycles	Fixed		
Curative treatment – Radiotherapy	Total treatment dose 66 Gy, 5 × 2Gy fractions per week	Fixed		
Curative treatment – AE cost (monthly)	£14.05	Gamma	TA578 committee papers (38), Table 49, costs updated to NHS reference costs 2019/2020	
Curative treatment – Follow-up costs – Include other healthcare resource costs	Yes	Fixed	Costs sourced from NHS reference costs and PSSRU, resource use from clinical opinion	
Curative treatment follow-up costs – Healthcare resource use cost (monthly)	£161.57	This is indirectly varied as this is a weighted cost and individual costs are varied using Gamma		
Palliative treatment – AE cost	£0	Fixed	No treatment, therefore no treatment-related AEs	Section B.3.5.5 of Doc B

Palliative treatment – Follow-up costs – Include other healthcare resource costs	Yes	Fixed	Costs sourced from NHS reference costs and PSSRU, resource use from clinical opinion	
Palliative treatment – Healthcare resource use cost (monthly)	£161.57	This is indirectly varied as this is a weighted cost and individual costs are varied using Gamma		
First-line metastatic recurrence cost and resource use				
Drug option 1	Pembrolizumab, 200mg every 3 weeks and pemetrexed 500 mg/m^2 every 3 weeks	Fixed	Clinical opinion	Section B.3.5.3 of Doc B
Drug option 2	Pemetrexed 500 mg/m^2 every 3 weeks and carboplatin 150 AUC every 3 weeks	Fixed		
Drug option 3	Pembrolizumab, 200mg every 3 weeks	Fixed		
Drug option 4	Pembrolizumab, 200mg every 3 weeks and carboplatin 150 AUC every 3 weeks	Fixed		

Overall weighted average costs – Atezo arm: Treatment cost (monthly)	£2,114.19	This is indirectly varied as this is a weighted cost and market shares are varied using dirichlet	Clinical opinion on market shares	
Overall weighted average costs – Atezo arm: AE cost (monthly)	£87.07	This is indirectly varied as this is a weighted cost and AE management costs are varied using Gamma	AE management costs from IMpower150 UK cost-effectiveness model [TA584] (39)	
Overall weighted average costs – BSC arm: Treatment cost (monthly)	£7,225.59	This is indirectly varied as this is a weighted cost and market shares are varied using dirichlet	Clinical opinion on market shares	
Overall weighted average costs – BSC arm: AE cost (monthly)	£93.45	This is indirectly varied as this is a weighted cost and AE management costs are varied using Gamma	AE management costs from IMpower150 UK cost-effectiveness model [TA584] (39)	
Follow-up care costs – Include other healthcare	Yes	Fixed	Costs sourced from NHS reference costs and PSSRU, resource use from clinical opinion	

resource costs				
Treatment follow-up – Healthcare resource use cost (monthly)	£352.11	This is indirectly varied as this is a weighted cost and individual costs are varied using Gamma)		
No treatment – Include other healthcare resource costs	Yes	Fixed		
No treatment follow-up – Healthcare resource use cost (monthly)	£352.11	This is indirectly varied as this is a weighted cost and individual costs are varied using Gamma)		
Second-line metastatic recurrence cost and resource use				
Drug option 1	Nintedanib 300 mg every 3 weeks and docetaxel 75 mg/m^2 every 3 weeks	Fixed	Clinical opinion	Section B.3.5.3 of Doc B
Drug option 2	Pemetrexed 500 mg/m^2 every 3 weeks and carboplatin 150 AUC every 3 weeks	Fixed		

Drug option 3	Docetaxel 75 mg/m^2 every 3 weeks	Fixed		
Drug option 4	Gemcitabine 1,250 mg/m^2 twice every 3 weeks and carboplatin 150 AUC every 3 weeks	Fixed		
Overall weighted average costs – Atezo arm: Treatment cost (monthly)	£3707.22	This is indirectly varied as this is a weighted cost and market shares are varied using dirichlet	Clinical opinion on market shares	
Overall weighted average costs – Atezo arm: AE cost (monthly)	£308.41	This is indirectly varied as this is a weighted cost and AE management costs are varied using Gamma	AE management costs from OAK UK cost-effectiveness model [TA520] (40)	
Overall weighted average costs – BSC arm: Treatment cost (monthly)	£3707.22	This is indirectly varied as this is a weighted cost and market shares are varied using dirichlet	Clinical opinion on market shares	
Overall weighted average costs – BSC arm: AE	£308.41	This is indirectly varied as this is a weighted	AE management costs from OAK UK cost-effectiveness model [TA520] (40)	

cost (monthly)		cost and AE management costs are varied using Gamma)		
Follow-up care costs – Include other healthcare resource costs	Yes	Fixed	Costs sourced from NHS reference costs and PSSRU, resource use from clinical opinion	
Treatment follow-up – Healthcare resource use cost (monthly)	£608.34	This is indirectly varied as this is a weighted cost and individual costs are varied using Gamma)		
No treatment – Include other healthcare resource costs	Yes	Fixed		
No treatment follow-up – Healthcare resource use cost (monthly)	£608.34	This is indirectly varied as this is a weighted cost and individual costs are varied using Gamma)		
End of life costs				
Disease-related death	£4598.01	Gamma	Informed by NICE TA705 (37) (IMpower110), page 123	Section B.3.5.7 of Doc B
Utilities – base case				
Disease-free survival				

Utility calculation method	Calculated disutilities	Fixed	This approach ensured that all health state utility values remained below the general population utility and the progressed states aligned over time (see Section B.3.4.3.1)	
Literature source	Jang et al. 2010	Fixed	Jang et al. 2010 (41) as it provided the most clinically plausible values (see Section B.3.4.3.2)	Section B.3.4.3 of Doc B
On treatment disutility	0.03	Beta		
Off treatment disutility	0.03	Beta		
AE total disutility	0	Beta	All Grade 3+ AEs were below 2%, therefore AE disutilities were not considered	
Locoregional recurrence				
Literature source	Chouaid et al. 2013	Fixed	Chouaid et al. 2013 (42) was the only source available to inform the utility of patients within the locoregional recurrence health state	Section B.3.4.3 of Doc B
Curative treatment disutility	0.08	Beta		
Palliative treatment – no treatment disutility	0.17	Beta		
First-line metastatic recurrence				
Literature source	IMpower150	Fixed	IMpower150 was the source used due to the trial population aligning with the population of interest, first-line metastatic. Also it is more conservative than the other sources.	Section B.3.4.3 of Doc B
Treatment disutility	0.11	Beta		
No treatment disutility	0.17	Beta		
Second-line metastatic recurrence				
Literature source	IMpower150	Fixed	IMpower150 was the source used due to the trial population aligning with the population of interest, first-line metastatic. Also it is more conservative than the other sources.	Section B.3.4.3 of Doc B
Treatment disutility	0.13	Beta		
No treatment disutility	0.17	Beta		

Abbreviations: CI, confidence interval

2.3.2 Additional changes to the economic model post-ERG clarification response

Probability of death

As addressed in question B29 of the ERG clarification questions, in the updated economic model for the PD-L1 ≥50% subgroup, the probability of death is similarly adjusted for both the DFS health state and the post-DFS health states (i.e., replacing "t_mort" to "t_mort_dfs").

FIXED function

In response to ERG clarification question B20, the FIXED function was removed from the economic model.

Treatment regimen

In the "2L Met. Recurrence Tx Schedule" sheet, row 85, the dose size for docetaxel should be 75 mg/m^2, rather than 160 mg/m^2. This error has been addressed in the updated economic model.

2.3.3 Additional data in response to the ERG clarification questions for the PD-L1 ≥50% subgroup

For the ERG clarification questions, the company response sent on 7th December 2021 included additional data. The equivalent data for the PD-L1 ≥50% subgroup is provided in the appendices. Below is a description of what is included:

- Appendix A – DFS comparisons of model versus IMpower010 KM data
    - In response to B6 of clarification questions to provide DFS% and OS% comparisons, every 3 months (cycles), model vs IMpower10 (KM), up to the end of the available KM data
- Appendix B – Cumulative hazard plots
    - In response to B7 of clarification questions to provide estimated hazards over time
- Appendix C – Q-Q plots

- In response to B7 of clarification questions to provide Q-Q plots for the IMpower010 DFS KM data

- Appendix D – Parametric survival analysis of the IMpower010 OS KM data
    - In response to B8 of clarification questions to provide parametric survival analysis of the IMpower010 OS KM data

- Appendix E – Summary of OS and DFS parametric models and IMpower010 KM data
    - In response to B9 of clarification questions to present all the IMpower010 DFS and OS KM data overlayed with the unadjusted log-logistic model fit to each KM curve and the company base case projection for each endpoint

- Appendix F – Comparison of DFS events between the atezolizumab and BSC arms
    - In response to B11 of clarification questions to analyse whether type of DFS event was significantly associated with treatment arm amongst patients in the IMpower010 trial

- Appendix G – Comparison of cause of death between the atezolizumab and BSC arms
    - In response to B16 of clarification questions to analyse whether cause of death (all-cause versus disease-related) was significantly associated with treatment arm amongst patients in the IMpower010 trial

2.4 Base-case results (PD-L1 ≥50% subgroup)

Summary of base-case cost-effectiveness results

- **Cost-effectiveness results are presented with and without confidential PAS for atezolizumab (list price for all other drugs) for the following population:**
    - **Adult patients with Stage II to IIIA with NSCLC whose tumours have PD-L1 expression on ≥50% of TCs and whose disease has not progressed following platinum-based adjuvant chemotherapy, including the EGFR mutation or ALK-positive population**

- **In this population, the resulting base case incremental cost-effectiveness ratio (ICER) when comparing atezolizumab to BSC was:**
  - [redacted] **at PAS price**
  - **£18,627 per QALY gained at list price**
- **Compared with the PD-L1 ≥1% stage II to IIIA population presented in the company submission document B, atezolizumab is more cost-effective in the PD-L1 ≥50% stage II to IIIA subgroup, as this is where the greatest benefit is observed**
- **A limitation of the with-PAS analysis is that confidential discounts are in place for other therapies in the pathway which Roche are unable to account for. This analysis is also limited by the availability of relevant data which introduces a degree of uncertainty into the analysis**

2.4.1 Base-case incremental cost-effectiveness analysis results

Base case results of the economic model are presented in Table 16 (list price) and Table 17 (PAS price; [redacted] discount) for the Stage II–IIIA patients with NSCLC whose tumours have PD-L1 expression on ≥ 50% TC. In these comparisons, all comparators (and therapies included in the treatment pathway) are at list price.

Since osimertinib has recently been approved for the CDF for adjuvant treatment of EGFR mutation-positive non-small-cell lung cancer after complete tumour resection (3), results for the Stage II-IIIA patients following resection and platinum-based chemotherapy with NSCLC whose tumours have PD-L1 expression on ≥ 50% TC, excluding EGFR mutant or ALK-positive population have also been included (see Section 2.6).

Table 16: Base case cost-effectiveness results – PD-L1 ≥50% Stage II–IIIA population – list price

Technologies	Total costs	Total LYG	Total QALYs	Incremental costs	Incremental LYG	Incremental QALYs	ICER incremental (£/QALY)	NMB (WTP £30,000)
Atezolizumab	[redacted]	10.02	[redacted]	[redacted]	2.57	[redacted]	£18,627	£21,944
BSC	[redacted]	7.45	[redacted]					

NMB is calculated as: (incremental gain in QALYs x threshold) – incremental cost. A positive incremental NMB indicates that the intervention is cost-effective compared with the alternative at the given willingness-to-pay threshold.

LYs, life years; NMB, net monetary benefit; QALYs, quality-adjusted life years

Table 17: Base case cost-effectiveness results – PD-L1 ≥50% Stage II–IIIA population – PAS price

Technologies	Total costs	Total LYG	Total QALYs	Incremental costs	Incremental LYG	Incremental QALYs	ICER incremental (£/QALY)	NMB (WTP £30,000)
Atezolizumab	[redacted]	10.02	[redacted]	[redacted]	2.57	[redacted]	[redacted]	[redacted]
BSC	[redacted]	7.45	[redacted]					

NMB is calculated as: (incremental gain in QALYs x threshold) – incremental cost. A positive incremental NMB indicates that the intervention is cost-effective compared with the alternative at the given willingness-to-pay threshold.

LYs, life years; NMB, net monetary benefit; QALYs, quality-adjusted life years

In the Stage II–IIIA population at list price, atezolizumab provided [redacted] QALYs and 10.02 life years at a total overall cost of [redacted]. In contrast, BSC provided [redacted] QALYs and 7.45 life years, at a total cost of [redacted]. The resulting base ICER when comparing atezolizumab to BSC was £18,627 per QALY gained, showing that atezolizumab is cost-effective at list price.

Results of the with-PAS analysis showed that adjuvant atezolizumab treatment resulted in reduced total costs in the atezolizumab arm of [redacted] and no change to the total costs in the BSC arm, as no atezolizumab is used in the metastatic states. This resulted atezolizumab [redacted] versus BSC, for the PD-L1 ≥50% stage II-IIIA population. The Net Monetary Benefit (NMB) approach was also included to aid interpretation of negative ICERs. A positive incremental NMB, as seen in Table 17, indicates that atezolizumab is cost-effective compared with BSC at the given willingness-to-pay threshold of £30,000.

2.5 Sensitivity analyses

Summary of sensitivity analyses results

- **Extensive sensitivity and scenario analyses were conducted in the economic model to demonstrate the uncertainty around the parameters used, assess the plausibility of different scenarios and approaches, and help understand what key variables and assumptions potentially have a major impact on cost-effectiveness results**
- **The PSA ICER results when comparing atezolizumab with PAS to BSC, was consistent with the deterministic base case (both dominant)**
- **The one-way sensitivity analyses showed that the proportion of patients in the 1L metastatic state who receive treatment, the proportion of patients who have metastatic recurrence in the atezolizumab arm, the proportion of patients who have metastatic recurrence in the BSC arm, and the market share of pemetrexed and carboplatin in 1L metastatic treatment for the BSC arm were the most influential parameters on the ICER**
- **In the scenario analyses, all scenarios show atezolizumab is cost-effective and mostly dominant.**
- **These results help to quantify and understand the impact of the uncertainty in the analysis on cost-effectiveness and decision-making. Overall. The**

results show that the model results are robust for decision making and at PAS price, atezolizumab is dominant in the majority of scenarios presented

2.5.1 Probabilistic sensitivity analysis

To assess the uncertainty surrounding the variables included in the cost-effectiveness model, a PSA was undertaken using 5,000 iterations to ensure results had converged. Results of the PSA compared to deterministic results at list price are presented in Table 18. The with-PAS equivalent comparison is presented in Table 19. Deterministic and probabilistic results are similar, therefore not indicating any signs of non-linearity in the model.

Table 18: PSA results compared to base-case (list price)

	Costs		QALYs		ICERs	
	Deterministic base case	PSA	Deterministic base case	PSA	Deterministic base case	PSA
Stage II-IIIA population						
Atezolizumab	[redacted]	[redacted]	[redacted]	[redacted]	£18,627	£19,334
BSC	[redacted]	[redacted]	[redacted]	[redacted]	-	-

Table 19: PSA results compared to base-case (with PAS)

	Costs		QALYs		ICERs	
	Deterministic base case	PSA	Deterministic base case	PSA	Deterministic base case	PSA
Stage II-IIIA population						
Atezolizumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
BSC	[redacted]	[redacted]	[redacted]	[redacted]	-	-

The incremental cost-effectiveness planes in Figure 6 and Figure 7 show the individual PSA iterations for the comparisons of atezolizumab to BSC in the Stage II–IIIA populations at list and PAS price, respectively. At PAS price, atezolizumab was dominant in 57.8% of the simulations; demonstrating that atezolizumab is a cost-effective option for the NHS in patients with Stage II–IIIA NSCLC. Cost-effectiveness acceptability curves for the comparisons of atezolizumab to BSC in the Stage II–IIIA populations at list and PAS price are presented in Figure 8 and Figure 9. At a £20,000 and £30,000 WTP, the likelihood of atezolizumab being the most cost-effective treatment option is 98% and 99%, respectively.

Figure 6: Incremental cost-effectiveness plane – atezolizumab vs BSC in Stage II–IIIA NSCLC, list price

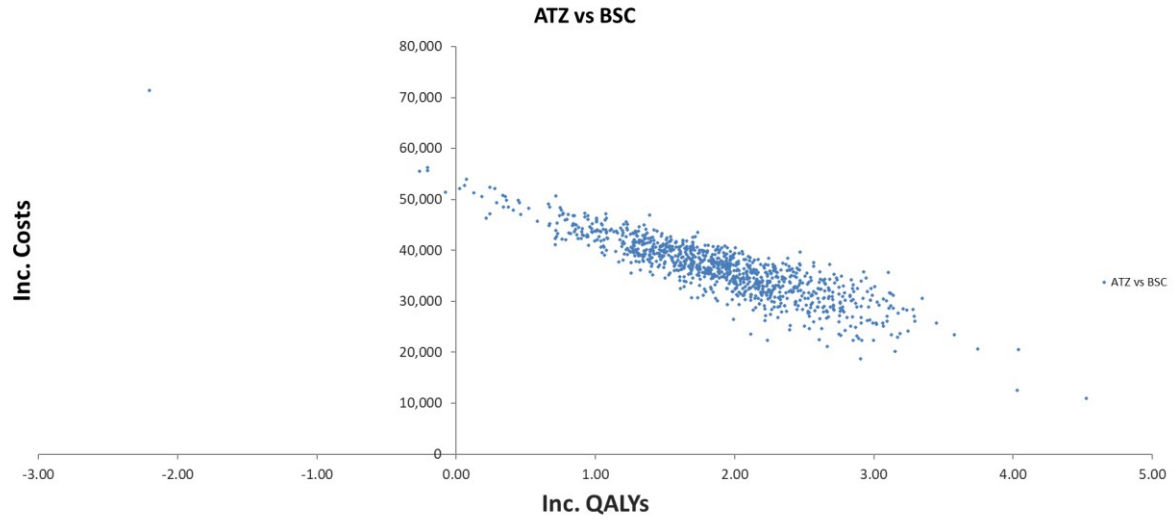


Figure 7: Incremental cost-effectiveness plane – atezolizumab vs BSC in Stage II–IIIA NSCLC, PAS price

[redacted]

Figure 8: Cost-effectiveness acceptability curve – atezolizumab vs BSC in Stage II–IIIA NSCLC, list price

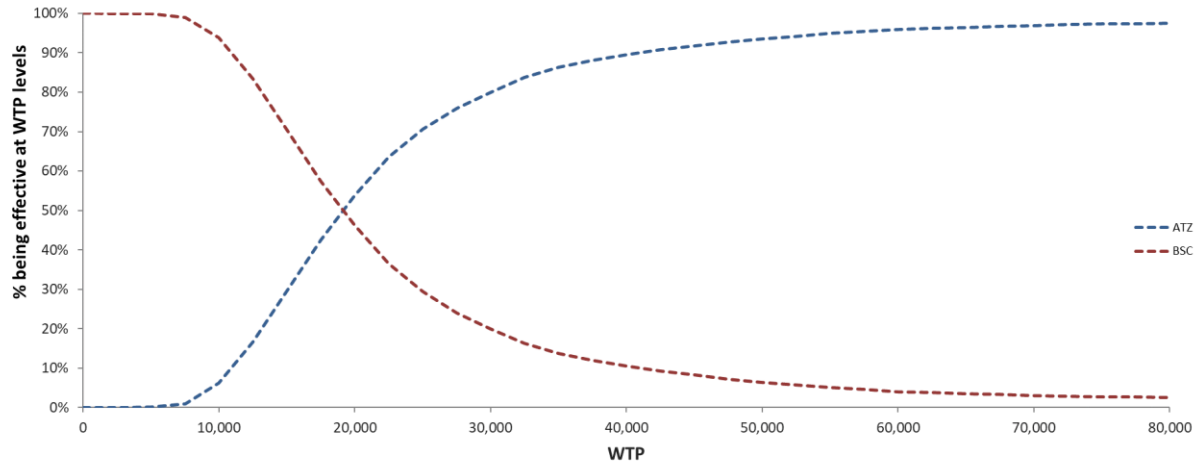


Figure 9: Cost-effectiveness acceptability curve – atezolizumab vs BSC in Stage II–IIIA NSCLC, PAS price

[redacted]

2.5.2 Deterministic sensitivity analysis

The parameter values used in the deterministic sensitivity analysis are presented in Table 20 below. The base case values of most parameters were varied using upper and lower limits of 95% confidence intervals for the variables, with the exception of discount rates, which were varied from 1.5% to 5.0%. Key remaining model parameters are tested in scenario analyses (see Section 2.5.3).

Table 20: Parameter values for univariate sensitivity analysis

Parameter	Base case value	PAS price		List price	
		Lower value	Higher value	Lower value	Higher value
Proportion of patients who have metastatic recurrence as recurrence - ATZ Arm	[redacted]	0.24	0.57	0.24	0.57
Proportion of patients who have metastatic recurrence as recurrence - BSC Arm	[redacted]	0.52	0.75	0.52	0.75
Proportion of patients with Locoregional Recurrence - ATZ arm	[redacted]	0.43	0.76	0.43	0.76

Proportion of patients with Locoregional Recurrence - BSC arm	[redacted]	0.25	0.48	0.25	0.48
Transition probability to death from DFS health state - ATZ Arm	[redacted]	0.0006	0.0009	0.0006	0.0009
Transition probability to death from DFS health state - BSC Arm	[redacted]	0.0004	0.0006	0.0004	0.0006
% on Curative Treatment - Locoregional Recurrence	0.80	0.72	0.85	0.72	0.85
% on Palliative Treatment - Locoregional Recurrence	0.20	0.14	0.27	0.14	0.27
Transition probability (PFS - LR CT)	0.04	0.03	0.04	0.03	0.04
% have Progression as first Event - Locoregional Recurrence	0.81	0.66	0.93	0.67	0.92
Transition probability (OS - LR PT)	0.14	0.11	0.16	0.11	0.16
% on 1L metastatic Treatment - 1L Metastatic	[redacted]	0.56	0.79	0.56	0.79
Treatment Option 1 - Market Share - 1L Metastatic Treatment - BSC Arm	[redacted]	0.21	0.35	0.21	0.35
Treatment Option 2 - Market Share - 1L Metastatic Treatment - BSC Arm	[redacted]	0.17	0.30	0.17	0.30
Treatment Option 3 - Market Share - 1L Metastatic Treatment - BSC Arm	[redacted]	0.25	0.40	0.25	0.40
% have Progression as first Event - 1L Metastatic Recurrence	[redacted]	0.68	0.94	0.66	0.94
Transition probability (1LMNTx)	0.23	0.19	0.27	0.19	0.27
% on 2L metastatic Treatment - 2L Metastatic	[redacted]	0.42	0.58	0.42	0.58
Treatment Option 1 - Market Share - 2L Metastatic Treatment - Atezolizumab Arm	[redacted]	0.35	0.52	0.35	0.51
Treatment Option 2 - Market Share - 2L Metastatic Treatment - Atezolizumab Arm	[redacted]	0.20	0.34	0.20	0.35

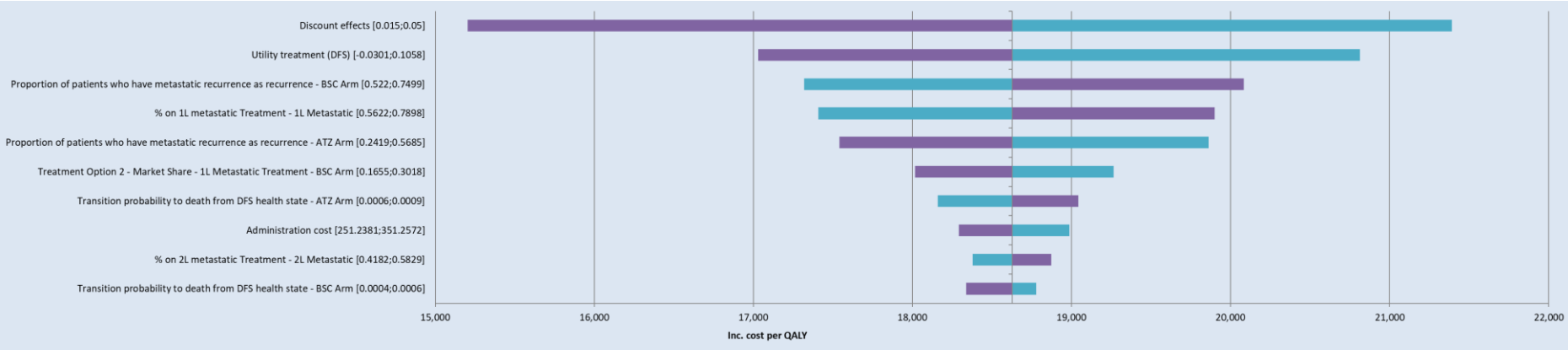
Treatment Option 3 - Market Share - 2L Metastatic Treatment - Atezolizumab Arm	[redacted]	0.16	0.30	0.17	0.30
Treatment Option 1 - Market Share - 2L Metastatic Treatment - BSC Arm	[redacted]	0.35	0.51	0.35	0.51
Treatment Option 2 - Market Share - 2L Metastatic Treatment - BSC Arm	[redacted]	0.20	0.34	0.20	0.34
Treatment Option 3 - Market Share - 2L Metastatic Treatment - BSC Arm	[redacted]	0.17	0.30	0.17	0.30
Transition probability (2LMNTx)	0.23	0.19	0.27	0.19	0.27
Discount costs	0.04	0.02	0.05	0.02	0.05
Discount effects	0.04	0.02	0.05	0.02	0.05
Administration cost	299.61	252.52	351.09	251.24	351.26
Other healthcare resource use (DFS)	53.19	48.74	57.84	48.73	57.67
Total AE management cost - LRR	14.05	11.84	16.49	11.83	16.47
Other healthcare resource use (LR - CT)	161.57	146.06	178.21	146.16	177.75
Other healthcare resource use (LR - PT)	161.57	146.09	178.25	145.80	177.99
Total AE management cost - 1L Met Atezo	87.07	73.86	101.09	73.79	101.85
Total AE management cost - 1L Met BSC	93.45	85.34	101.92	85.42	101.88
Other healthcare resource use (1LM - Tx)	352.11	321.20	383.22	322.95	383.60
Other healthcare resource use (1LM - NTx)	352.11	322.58	383.43	322.22	383.67
Total AE management cost - 2L Met Atezo	308.41	279.68	337.71	279.46	338.04
Total AE management cost - 2L Met BSC	308.41	279.66	337.46	279.61	337.45
Other healthcare resource use (2LM - Tx)	608.34	561.23	657.83	562.14	656.78
Other healthcare resource use (2LM - NTx)	608.34	561.19	656.53	562.06	656.61
End of life cost - disease death	4598.01	3853.59	5381.79	3864.19	5376.15
Utility treatment (DFS)	0.03	-0.03	0.11	-0.03	0.11

Utility no treatment (DFS)	0.03	-0.03	0.11	-0.03	0.11
Utility treatment (LR - CT)	0.08	0.01	0.16	0.01	0.16
Utility treatment (LR - PT)	0.17	0.12	0.22	0.13	0.22
Utility treatment (1LM)	0.11	0.10	0.12	0.10	0.12
Utility no treatment (1LM)	0.17	0.12	0.22	0.13	0.22
Utility treatment (2LM)	0.13	0.10	0.15	0.10	0.15
Utility no treatment (2LM)	0.17	0.12	0.22	0.13	0.22

Deterministic sensitivity analyses at list price and PAS price results for the PD-L1 ≥50% stage II–IIIA population are presented in Figure 10 and Figure 11.

Based on the deterministic sensitivity analyses at list price, the most influential parameters appear to be discount effects, utility in DFS state (on treatment), proportion of patients who have 1L metastatic recurrence in the BSC arm, and proportion of patients on 1L metastatic treatment. 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. This is further evidenced by discount rates being the most sensitive input, as discount rates impact results more broadly throughout the model than any other input.

Figure 10: Tornado diagram – Stage II–IIIA, PD-L1 ≥50% subgroup, list price



With the deterministic sensitivity analyses at PAS price, the most influential parameters appear to be the proportion of patients in the 1L metastatic state who receive treatment, the proportion of patients who have metastatic recurrence in the atezolizumab arm, the proportion of patients who have metastatic recurrence in the BSC arm, and the market share of pemetrexed and carboplatin in 1L metastatic treatment for the BSC arm. The tornado diagram of atezolizumab at PAS price differs from atezolizumab at list price as the driver of the ICER is no longer discount effects, but instead the proportion of patients receiving metastatic treatment and who experience metastatic recurrence, where the associated costs and effects from metastatic treatment is having the biggest impact.

Figure 11: Tornado diagram – Stage II–IIIA, PD-L1 ≥50% subgroup, PAS price

2.5.3 Scenario analysis

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

Model settings

- Time horizon

Clinical inputs

- Alternative plausible DFS extrapolations
- Trial data to inform recurrence types and death
- Treatment effect duration
- Cure proportion
- Standardised mortality rate
- Transition probability calculation method
- Allow second-line metastatic recurrence
- Month at which there is a change to CT scanning schedule
- Time to off treatment

Health state utilities

- Health state utility calculation method
- Source of utility inputs for disease-free survival

Costs and resource use

- Atezolizumab treatment schedule

Additional scenarios from the ERG clarification questions

- DFS and OS projections across model arms are used for survival analysis (ERG clarification question B10)
- ERG estimated administration costs (ERG clarification question B13)
- AE management costs to incorporate costs for all observed treatment-related Grade 2+ AEs in IMpower010 (ERG clarification question B14)

- Incorporate expected utility impact of all observed treatment-related Grade 2+ AEs in IMpower010 (ERG clarification question B15)

Results of the scenario analyses are presented in Table 21 and Table 22 for the PD-L1 ≥50% stage II–IIIA population at PAS price and list price for atezolizumab.

All scenario results remain cost-effective and atezolizumab is dominant at PAS price for the majority of scenarios, and the most sensitive scenarios based on the DFS distribution selection and using the OS extrapolated data were [redacted] cost per QALY gained. Sensitivity to the DFS distribution scenarios are expected as they determine early movements from the DFS health state, impacting downstream costs and outcomes in progressive states. The IMpower010 OS data are extremely immature and there is uncertainty around the results of this scenario. It should be noted that, whilst sensitive to DFS distribution choice, all distributions explored were judged to be conservative during validation with UK clinical experts.

Table 21: Results from scenario analyses – Stage II–IIIA, PD-L1 ≥50% subgroup (PAS price for atezolizumab)

Parameter	Value	Atezolizumab			Best Supportive Care			ATZ vs. BSC		
		Life Years	QALYS	Costs	Life Years	QALYS	Costs	Inc. costs per LY gained	Inc. costs per QALY gained	NMB (WTP £30k)
Base case		10.02	[redacted]	[redacted]	7.45	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
DFS distributions	Exponential	9.85	[redacted]	[redacted]	6.90	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Weibull	9.48	[redacted]	[redacted]	7.08	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Log-normal	10.26	[redacted]	[redacted]	7.54	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Generalized Gamma	9.75	[redacted]	[redacted]	8.08	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Gompertz	9.47	[redacted]	[redacted]	7.85	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Gamma	9.52	[redacted]	[redacted]	6.98	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Trial data used to inform recurrence type split	Pool across Arms	9.91	[redacted]	[redacted]	7.54	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Treatment effect	Maintained over Time	9.95	[redacted]	[redacted]	7.45	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Standardised mortality rate	1.50	9.63	[redacted]	[redacted]	7.20	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

	2.00	8.99	[redacted]	[redacted]	6.77	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Atezolizumab treatment schedule	1, 680mg/ every 4 weeks	10.02	[redacted]	[redacted]	7.45	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
LRR: Efficacy by treatment intent	Digitised Data	10.37	[redacted]	[redacted]	7.77	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Metastatic recurrence 1L: Efficacy by treatment intent	Digitised Data	10.06	[redacted]	[redacted]	7.52	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Metastatic recurrence 1L: allow metastatic recurrence 2L	No	10.28	[redacted]	[redacted]	7.89	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Metastatic recurrence 1L - Efficacy source	IMpower110	10.00	[redacted]	[redacted]	7.42	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Metastatic recurrence 2L - Efficacy by treatment intent	Digitised Data	10.06	[redacted]	[redacted]	7.51	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
DFS cost inputs: scanning schedule	36.00	10.02	[redacted]	[redacted]	7.45	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Time-to-off treatment	Until Progression or Death	10.02	[redacted]	[redacted]	7.45	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Utility method	Source utilities	10.02	[redacted]	[redacted]	7.45	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
DFS utility source input	Manser et al. (2006)	10.02	[redacted]	[redacted]	7.45	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Grutters et al. (2010)	10.02	[redacted]	[redacted]	7.45	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

	Black, Keeler and Soneji (2014)	10.02	[redacted]	[redacted]	7.45	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Yang et al. (2014)	10.02	[redacted]	[redacted]	7.45	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Metastatic recurrence 1L utility source input	IMpower110	10.02	[redacted]	[redacted]	7.45	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Chouaid et al. (2013)	10.02	[redacted]	[redacted]	7.45	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Metastatic recurrence 2L utility source input	IMpower110	10.02	[redacted]	[redacted]	7.45	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Chouaid et al. (2013)	10.02	[redacted]	[redacted]	7.45	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Nafees et al. (2008)	10.02	[redacted]	[redacted]	7.45	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Allow vial sharing	No	10.02	[redacted]	[redacted]	7.45	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
OS based entirely on extrapolated 010 results	010 OS throughout model	7.17	[redacted]	[redacted]	7.31	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
End of Life costs	Exclude	10.02	[redacted]	[redacted]	7.45	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Time horizon	10.00	6.55	[redacted]	[redacted]	5.19	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	20.00	9.13	[redacted]	[redacted]	6.87	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	30.00	9.95	[redacted]	[redacted]	7.41	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

"Cure" proportion implementation	5 years	9.75	[redacted]	[redacted]	7.24	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	6 years	9.30	[redacted]	[redacted]	6.94	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Ramp up 2–8 years	9.83	[redacted]	[redacted]	7.35	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Ramp up 3–8 years	9.56	[redacted]	[redacted]	7.13	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Maximum "cure" proportion	20%	8.31	[redacted]	[redacted]	6.26	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	40%	8.67	[redacted]	[redacted]	6.52	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	60%	9.11	[redacted]	[redacted]	6.82	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	80%	9.65	[redacted]	[redacted]	7.20	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Additional admin costs	Add £192.90 and £2.58	10.02	[redacted]	[redacted]	7.45	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Grade 2+ AE management costs	AE cost from PACIFIC (TA578)	10.02	[redacted]	[redacted]	7.45	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	AE cost from IMpower150 (TA584)	10.02	[redacted]	[redacted]	7.45	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	AE cost from OAK (TA520)	10.02	[redacted]	[redacted]	7.45	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Grade 2+ disutilities	disutility from PACIFIC (TA578, pg 334 of Committee papers)	10.02	[redacted]	[redacted]	7.45	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

	disutility from Nafees et al. 2008 (Table 2, febrile neutropenia)	10.02	[redacted]	[redacted]	7.45	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

NMB, net monetary benefit, NMB is calculated as: (incremental gain in QALYs x threshold) – incremental cost. A positive incremental NMB indicates that the intervention is cost-effective compared with the alternative at the given willingness-to-pay threshold.

LYs, life years; QALYs, quality-adjusted life years;

Table 22: Results from scenario analyses – Stage II–IIIA, PD-L1 ≥50% NSCLC population (list price for atezolizumab)

Parameter	Value	Atezolizumab			Best Supportive Care			ATZ vs. BSC		
		Life Years	QALYS	Costs	Life Years	QALYS	Costs	Inc. costs per LY gained	Inc. costs per QALY gained	NMB (WTP £30k)
Base case		10.02	[redacted]	[redacted]	7.45	[redacted]	[redacted]	£13,995	£18,627	[redacted]
DFS distributions	Exponential	9.85	[redacted]	[redacted]	6.90	[redacted]	[redacted]	£11,067	£14,758	[redacted]
	Weibull	9.48	[redacted]	[redacted]	7.08	[redacted]	[redacted]	£15,451	£20,540	[redacted]
	Log-normal	10.26	[redacted]	[redacted]	7.54	[redacted]	[redacted]	£12,779	£17,027	[redacted]
	Generalized Gamma	9.75	[redacted]	[redacted]	8.08	[redacted]	[redacted]	£25,511	£33,680	[redacted]
	Gompertz	9.47	[redacted]	[redacted]	7.85	[redacted]	[redacted]	£26,127	£34,490	[redacted]
	Gamma	9.52	[redacted]	[redacted]	6.98	[redacted]	[redacted]	£14,271	£18,985	[redacted]
Trial data used to inform recurrence type split	Pool across Arms	9.91	[redacted]	[redacted]	7.54	[redacted]	[redacted]	£16,150	£21,463	[redacted]

Treatment effect	Maintained over Time	9.95	[redacted]	[redacted]	7.45	[redacted]	[redacted]	£14,667	£19,499	[redacted]
Standardised mortality rate	1.50	9.63	[redacted]	[redacted]	7.20	[redacted]	[redacted]	£14,765	£19,577	[redacted]
	2.00	8.99	[redacted]	[redacted]	6.77	[redacted]	[redacted]	£16,220	£21,373	[redacted]
Atezolizumab treatment schedule	1, 680mg/ every 4 weeks	10.02	[redacted]	[redacted]	7.45	[redacted]	[redacted]	£15,269	£20,322	[redacted]
LRR: Efficacy by treatment intent	Digitised Data	10.37	[redacted]	[redacted]	7.77	[redacted]	[redacted]	£13,859	£18,476	[redacted]
Metastatic recurrence 1L: Efficacy by treatment intent	Digitised Data	10.06	[redacted]	[redacted]	7.52	[redacted]	[redacted]	£14,109	£18,750	[redacted]
Metastatic recurrence 1L: allow metastatic recurrence 2L	No	10.28	[redacted]	[redacted]	7.89	[redacted]	[redacted]	£12,720	£16,845	[redacted]
Metastatic recurrence 1L - Efficacy source	IMpower110	10.00	[redacted]	[redacted]	7.42	[redacted]	[redacted]	£14,176	£18,873	[redacted]
Metastatic recurrence 2L - Efficacy by treatment intent	Digitised Data	10.06	[redacted]	[redacted]	7.51	[redacted]	[redacted]	£14,055	£18,682	[redacted]
DFS cost inputs: scanning schedule	36.00	10.02	[redacted]	[redacted]	7.45	[redacted]	[redacted]	£14,006	£18,641	[redacted]
Time-to-off treatment	Until Progression or Death	10.02	[redacted]	[redacted]	7.45	[redacted]	[redacted]	£17,538	£23,342	[redacted]
Utility method	Source utilities	10.02	[redacted]	[redacted]	7.45	[redacted]	[redacted]	£13,995	£18,814	[redacted]
DFS utility source input	Manser et al. (2006)	10.02	[redacted]	[redacted]	7.45	[redacted]	[redacted]	£13,995	£27,175	[redacted]

	Grutters et al. (2010)	10.02	[redacted]	[redacted]	7.45	[redacted]	[redacted]	£13,995	£19,540	[redacted]
	Black, Keeler and Soneji (2014)	10.02	[redacted]	[redacted]	7.45	[redacted]	[redacted]	£13,995	£21,674	[redacted]
	Yang et al. (2014)	10.02	[redacted]	[redacted]	7.45	[redacted]	[redacted]	£13,995	£17,364	[redacted]
Metastatic recurrence 1L utility source input	IMpower110	10.02	[redacted]	[redacted]	7.45	[redacted]	[redacted]	£13,995	£18,726	[redacted]
	Chouaid et al. (2013)	10.02	[redacted]	[redacted]	7.45	[redacted]	[redacted]	£13,995	£18,628	[redacted]
Metastatic recurrence 2L utility source input	IMpower110	10.02	[redacted]	[redacted]	7.45	[redacted]	[redacted]	£13,995	£18,636	[redacted]
	Chouaid et al. (2013)	10.02	[redacted]	[redacted]	7.45	[redacted]	[redacted]	£13,995	£18,572	[redacted]
	Nafees et al. (2008)	10.02	[redacted]	[redacted]	7.45	[redacted]	[redacted]	£13,995	£18,564	[redacted]
Allow vial sharing	No	10.02	[redacted]	[redacted]	7.45	[redacted]	[redacted]	£13,950	£18,568	[redacted]
OS based entirely on extrapolated 010 results	010 OS throughout model	7.17	[redacted]	[redacted]	7.31	[redacted]	[redacted]	-£195,166	£271,750	[redacted]
End of Life costs	Exclude	10.02	[redacted]	[redacted]	7.45	[redacted]	[redacted]	£14,721	£19,593	[redacted]
Time horizon	10.00	6.55	[redacted]	[redacted]	5.19	[redacted]	[redacted]	£25,863	£32,820	[redacted]
	20.00	9.13	[redacted]	[redacted]	6.87	[redacted]	[redacted]	£15,872	£20,811	[redacted]
	30.00	9.95	[redacted]	[redacted]	7.41	[redacted]	[redacted]	£14,129	£18,773	[redacted]
“Cure” proportion implementation	5 years	9.75	[redacted]	[redacted]	7.24	[redacted]	[redacted]	£14,495	£19,286	[redacted]
	6 years	9.30	[redacted]	[redacted]	6.94	[redacted]	[redacted]	£15,739	£20,917	[redacted]

	Ramp up 2–8 years	9.83	[redacted]	[redacted]	7.35	[redacted]	[redacted]	£14,742	£19,606	[redacted]
	Ramp up 3–8 years	9.56	[redacted]	[redacted]	7.13	[redacted]	[redacted]	£15,153	£20,146	[redacted]
Maximum "cure" proportion	20%	8.31	[redacted]	[redacted]	6.26	[redacted]	[redacted]	£19,416	£25,661	[redacted]
	40%	8.67	[redacted]	[redacted]	6.52	[redacted]	[redacted]	£18,096	£23,954	[redacted]
	60%	9.11	[redacted]	[redacted]	6.82	[redacted]	[redacted]	£16,630	£22,055	[redacted]
	80%	9.65	[redacted]	[redacted]	7.20	[redacted]	[redacted]	£15,005	£19,944	[redacted]
Additional admin costs	Add £192.90 and £2.58	10.02	[redacted]	[redacted]	7.45	[redacted]	[redacted]	£15,018	£19,988	[redacted]
Grade 2+ AE management costs	AE cost from PACIFIC (TA578)	10.02	[redacted]	[redacted]	7.45	[redacted]	[redacted]	£14,141	£18,822	[redacted]
	AE cost from IMpower150 (TA584)	10.02	[redacted]	[redacted]	7.45	[redacted]	[redacted]	£15,185	£20,211	[redacted]
	AE cost from OAK (TA520)	10.02	[redacted]	[redacted]	7.45	[redacted]	[redacted]	£14,885	£19,812	[redacted]
Grade 2+ disutilities	disutility from PACIFIC (TA578, pg 334 of Committee papers)	10.02	[redacted]	[redacted]	7.45	[redacted]	[redacted]	£13,995	£19,070	[redacted]
	disutility from Nafees et al. 2008 (Table 2, febrile neutropenia)	10.02	[redacted]	[redacted]	7.45	[redacted]	[redacted]	£13,995	£18,988	[redacted]

NMB, net monetary benefit, NMB is calculated as: (incremental gain in QALYs x threshold) – incremental cost. A positive incremental NMB indicates that the intervention is cost-effective compared with the alternative at the given willingness-to-pay threshold.

LYs, life years; QALYs, quality-adjusted life years;

2.5.4 Summary of sensitivity analyses results

PSA, DSA and scenario analysis have been conducted to investigate the uncertainty around the economic model.

PSA results at PAS price were compared to the base case in Table 19. The PSA simulations showed that atezolizumab was dominant and ICER results were similar to the deterministic results. Atezolizumab was dominant in [redacted] of the simulations. Furthermore, the cost-effectiveness acceptability curve showed that the atezolizumab arm had a [redacted] probability of being the most cost-effective treatment at the £30,000 willingness-to pay-threshold at PAS price.

The results of the DSA (at PAS price for atezolizumab) showed that the model drivers were the proportion of patients in the 1L metastatic state who receive treatment, the proportion of patients who have metastatic recurrence in the atezolizumab arm, the proportion of patients who have metastatic recurrence in the BSC arm, and the market share of pemetrexed and carboplatin in 1L metastatic treatment for the BSC arm. The lowest and highest ICER at [redacted] and [redacted] per QALY gained was produced using the upper and lower value of the proportion of patients on 1L metastatic treatment in the 1L metastatic health state (0.79 and 0.56).

A number of scenario analyses were conducted as part of this submission and at PAS price for atezolizumab, all scenarios show atezolizumab is cost-effective and mostly dominant.

This analysis was limited by the availability of relevant data. To compensate for the shortfall in data, assumptions and expert opinion were utilised. These factors introduced a degree of uncertainty into the analysis. The extensive sensitivity analysis aimed to quantify and understand the impact of this uncertainty on cost-effectiveness and decision making.

2.6 Subgroup analysis (PD-L1 ≥50% subgroup excluding EGFR/ALK+ mutations)

Summary of cost-effectiveness results for the PD-L1 ≥50% stage II–IIIA population, excluding EGFR/ALK+:

- **Cost-effectiveness results are presented with and without confidential PAS for atezolizumab (list price for all other drugs)**
- **In this population, the resulting incremental cost-effectiveness ratio (ICER) when comparing atezolizumab to BSC was:**
  - [redacted] **at PAS price**
  - **£17,403 per QALY gained at list price**
- **In the PSA, atezolizumab at PAS price is dominant versus BSC**
- **The one-way sensitivity analyses showed that the transition probability to first-line metastatic health state in the BSC arm, discount costs, administration costs, and proportion who have progression as first event to first-line metastatic health state, are the most influential parameters on the ICER. However, no individual input had a significantly large impact**
- **In the scenario analyses, all scenarios show atezolizumab is cost-effective and mostly dominant.**
- **A limitation of the with-PAS analysis is that confidential discounts are in place for other therapies in the pathway which Roche are unable to account for. This analysis is also limited by the availability of relevant data which introduces a degree of uncertainty into the analysis**

2.6.1 Deterministic analysis (subgroup)

Subgroup results of the economic model are presented in Table 23 (list price) and LYs, life years; NMB, net monetary benefit; QALYs, quality-adjusted life years

Table 24 (PAS price; [redacted] discount) for the PD-L1 ≥50% stage II–IIIA patients, excluding EGFR mutant or ALK-positive. In these comparisons, all comparators (and therapies included in the treatment pathway) are at list price.

Table 23: Subgroup cost-effectiveness results – PD-L1 ≥ 50% subgroup Stage I – IIA NSCLC, excluding EGFR mutant or ALK-positive - list price

Technologies	Total costs	Total LYG	Total QALYs	Incremental costs	Incremental LYG	Incremental QALYs	ICER incremental (£/QALY)	NMB (WTP £30k)
Atezolizumab	[redacted]	10.32	[redacted]	[redacted]	2.58	[redacted]	£17,403	£24,421
BSC	[redacted]	7.74	[redacted]					

NMB is calculated as: (incremental gain in QALYs x threshold) – incremental cost. A positive incremental NMB indicates that the intervention is cost-effective compared with the alternative at the given willingness-to-pay threshold.

LYs, life years; NMB, net monetary benefit; QALYs, quality-adjusted life years

Table 24: Deterministic cost-effectiveness results – Stage II–IIIA, PD-L1 ≥ 50% subgroup, excluding EGFR mutant or ALK-positive – PAS price

Technologies	Total costs	Total LYG	Total QALYs	Incremental costs	Incremental LYG	Incremental QALYs	ICER incremental (£/QALY)	NMB (WTP £30k)
Atezolizumab	[redacted]	10.32	[redacted]	[redacted]	2.58	[redacted]	[redacted]	[redacted]
BSC	[redacted]	7.74	[redacted]					

NMB is calculated as: (incremental gain in QALYs x threshold) – incremental cost. A positive incremental NMB indicates that the intervention is cost-effective compared with the alternative at the given willingness-to-pay threshold.

LYs, life years; NMB, net monetary benefit; QALYs, quality-adjusted life years

In the Stage II–IIIA population, PD-L1 ≥ 50% excluding EGFR/ALK+ and at PAS price for atezolizumab and all comparators:

- Atezolizumab provided [redacted] QALYs and 10.32 life years at a total overall cost of [redacted]. In contrast, BSC provided [redacted] QALYs and 7.74 life years, at a total cost of [redacted]. Atezolizumab at PAS price is [redacted] versus BSC for the PD-L1 ≥ 50% stage II–IIIA, excluding EGFR/ALK+ population.

2.6.2 Probabilistic sensitivity analysis (subgroup)

To assess the uncertainty surrounding the variables included in the cost-effectiveness model, a probability sensitivity analysis PSA was undertaken using 5,000 iterations. Results of the PSA compared to deterministic results at list price and PAS price are presented in Table 25 and Table 26. Deterministic and probabilistic results are similar, therefore not indicating any signs of non-linearity in the model.

Table 25: Subgroup PSA results compared to DSA, PD-L1 ≥ 50% Stage II – IIIA NSCLC, excluding EGFR mutant or ALK-positive (list price)

	Costs		QALYs		ICERs	
	Deterministic	PSA	Deterministic base case	PSA	Deterministic	PSA
PD-L1 ≥ 50% Stage II–IIIA NSCLC, excluding EGFR mutant or ALK-positive						
Atezolizumab	[redacted]	[redacted]	[redacted]	[redacted]	£17,403	£17,869
BSC	[redacted]	[redacted]	[redacted]	[redacted]	-	-

Table 26: Subgroup PSA results compared to DSA, PD-L1 ≥50% Stage II – IIIA NSCLC, excluding EGFR mutant or ALK-positive (PAS price)

	Costs		QALYs		ICERs	
	Deterministic	PSA	Deterministic	PSA	Deterministic	PSA
PD-L1 ≥ 50% Stage II–IIIA NSCLC Stage II–IIIA population, excluding EGFR/ALK+						
Atezolizumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
BSC	[redacted]	[redacted]	[redacted]	[redacted]	-	-

The incremental cost-effectiveness plane in Figure 12 and Figure 13 show the PSA iterations for the comparison of atezolizumab to BSC in the PD-L1 ≥50% stage II–IIIA populations without EGFR/ALK+ mutations, at list and PAS price. In addition, the cost-effectiveness acceptability curves for the comparisons of atezolizumab to BSC, at list and PAS price are shown in Figure 14 and Figure 15. At PAS price, atezolizumab is dominant in [redacted] of the simulations. At a £20,000 and £30,000 WTP, the likelihood of atezolizumab being the most cost-effective treatment option is [redacted], respectively.

Figure 12: Incremental cost-effectiveness plane – atezolizumab vs BSC in PD-L1 ≥ 50% Stage II – IIIA NSCLC, excluding EGFR mutant or ALK-positive, list price

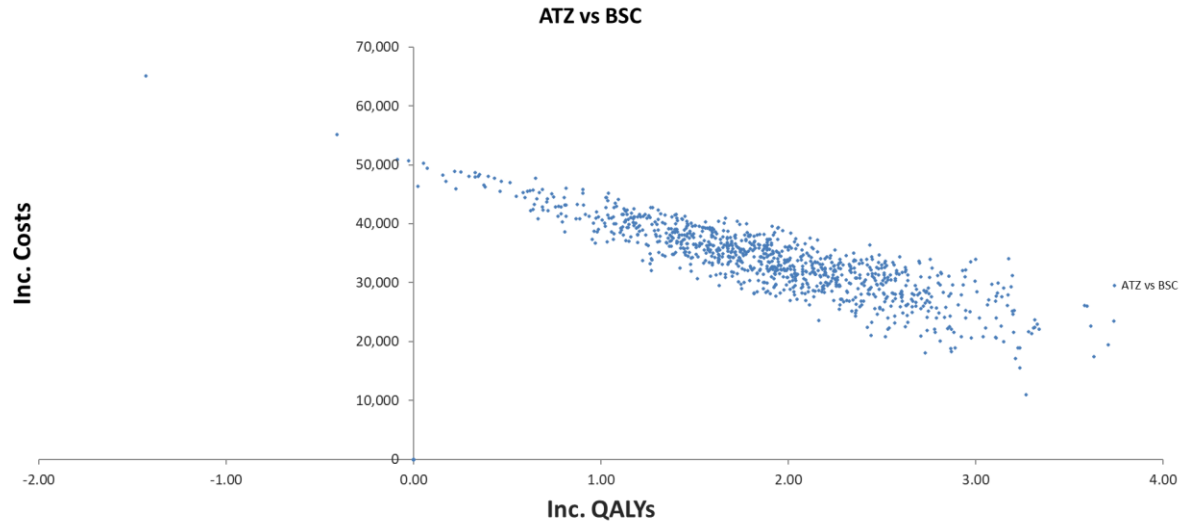


Figure 13: Incremental cost-effectiveness plane – atezolizumab vs BSC in Stage II – IIIA, PD-L1 ≥ 50% NSCLC, excluding EGFR mutant or ALK-positive (PAS price)

[redacted]

Figure 14: Cost-effectiveness acceptability curve – atezolizumab vs BSC in PD-L1 ≥ 50% Stage II – IIIA NSCLC, excluding EGFR mutant or ALK-positive, list price

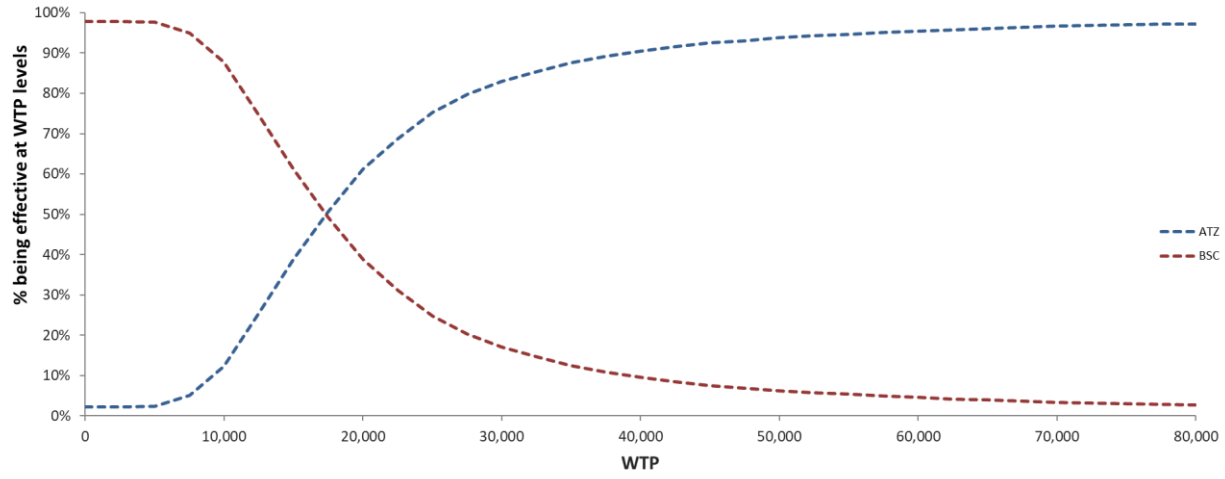


Figure 15: Cost-effectiveness acceptability curve – atezolizumab vs BSC in Stage II–IIIA, PD-L1 ≥ 50% NSCLC, excluding EGFR mutant or ALK-positive (PAS price)[redacted]

2.6.3 Deterministic sensitivity analysis (subgroup)

The parameter values used in the deterministic sensitivity analysis are presented in Table 27 below.

The base case values of most parameters were varied using upper and lower limits of 95% confidence intervals for the variables, with the exception of discount rates, which were varied from 1.5% to 5.0%. Key remaining model parameters are tested in scenario analyses (see Section 2.6.3).

Table 27: Parameter values for univariate sensitivity analysis, in patients with PD-L1 ≥ 50% Stage II – IIIA NSCLC, excluding EGFR mutant or ALK-positive

Parameter	Base case value	PAS price		List price	
		Lower value	Higher value	Lower value	Higher value
Proportion of patients who have metastatic recurrence as recurrence - ATZ Arm	[redacted]	0.20	0.57	0.19	0.56
Proportion of patients who have metastatic recurrence as recurrence - BSC Arm	[redacted]	0.50	0.77	0.50	0.77
Proportion of patients with Locoregional Recurrence - ATZ arm	[redacted]	0.41	0.78	0.42	0.79

Proportion of patients with Locoregional Recurrence - BSC arm	[redacted]	0.22	0.48	0.21	0.47
Transition probability to death from DFS health state - ATZ Arm	[redacted]	0.0007	0.0009	0.0007	0.0009
Transition probability to death from DFS health state - BSC Arm	[redacted]	0.0005	0.0007	0.0005	0.0007
% on Curative Treatment - Locoregional Recurrence	0.80	0.71	0.85	0.71	0.85
% on Palliative Treatment - Locoregional Recurrence	0.20	0.14	0.27	0.14	0.27
Transition probability (PFS - LR CT)	0.04	0.03	0.04	0.03	0.04
% have Progression as first Event - Locoregional Recurrence	0.81	0.64	0.93	0.64	0.92
Transition probability (OS - LR PT)	0.14	0.11	0.16	0.11	0.16
% on 1L metastatic Treatment - 1L Metastatic	[redacted]	0.55	0.79	0.54	0.79
Treatment Option 1 - Market Share - 1L Metastatic Treatment - BSC Arm	[redacted]	0.20	0.35	0.20	0.35
Treatment Option 2 - Market Share - 1L Metastatic Treatment - BSC Arm	[redacted]	0.16	0.30	0.16	0.30
Treatment Option 3 - Market Share - 1L Metastatic Treatment - BSC Arm	[redacted]	0.24	0.40	0.25	0.40
% have Progression as first Event - 1L Metastatic Recurrence	[redacted]	0.64	0.94	0.65	0.94
Transition probability (1LMNTx)	0.23	0.19	0.27	0.19	0.27
% on 2L metastatic Treatment - 2L Metastatic	[redacted]	0.41	0.58	0.41	0.58
Treatment Option 1 - Market Share - 2L Metastatic Treatment - Atezolizumab Arm	[redacted]	0.35	0.51	0.34	0.51
Treatment Option 2 - Market Share - 2L Metastatic Treatment - Atezolizumab Arm	[redacted]	0.19	0.34	0.19	0.34

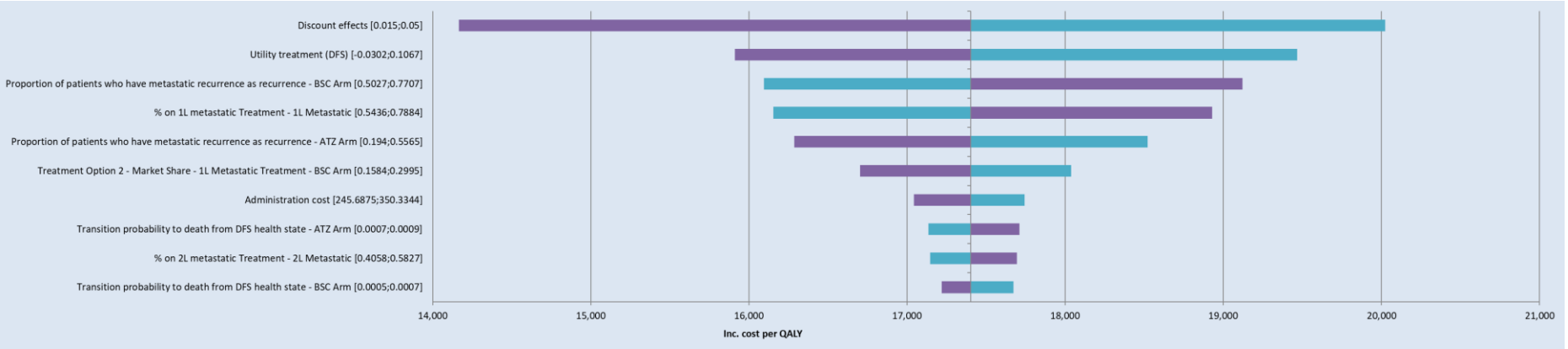
Treatment Option 3 - Market Share - 2L Metastatic Treatment - Atezolizumab Arm	[redacted]	0.16	0.30	0.16	0.30
Treatment Option 1 - Market Share - 2L Metastatic Treatment - BSC Arm	[redacted]	0.35	0.51	0.34	0.51
Treatment Option 2 - Market Share - 2L Metastatic Treatment - BSC Arm	[redacted]	0.19	0.34	0.19	0.34
Treatment Option 3 - Market Share - 2L Metastatic Treatment - BSC Arm	[redacted]	0.16	0.30	0.16	0.30
Transition probability (2LMNTx)	0.23	0.19	0.27	0.19	0.27
Discount costs	0.04	0.02	0.05	0.02	0.05
Discount effects	0.04	0.02	0.05	0.02	0.05
Administration cost	299.61	248.16	349.90	245.69	350.33
Other healthcare resource use (DFS)	53.19	48.21	57.67	48.25	57.85
Total AE management cost - LRR	14.05	11.65	16.44	11.47	16.44
Other healthcare resource use (LR - CT)	161.57	144.64	177.81	144.01	177.73
Other healthcare resource use (LR - PT)	161.57	144.51	177.73	143.83	177.82
Total AE management cost - 1L Met Atezo	87.07	72.23	101.38	71.85	101.35
Total AE management cost - 1L Met BSC	93.45	84.54	101.61	84.12	101.65
Other healthcare resource use (1LM - Tx)	352.11	318.89	382.52	317.53	383.79
Other healthcare resource use (1LM - NTx)	352.11	318.97	383.37	318.56	382.98
Total AE management cost - 2L Met Atezo	308.41	276.36	337.90	276.61	337.72
Total AE management cost - 2L Met BSC	308.41	276.20	338.21	276.12	338.04
Other healthcare resource use (2LM - Tx)	608.34	555.77	657.58	555.49	656.21
Other healthcare resource use (2LM - NTx)	608.34	554.36	657.31	553.99	657.37
End of life cost - disease death	4598.01	3776.48	5344.17	3748.29	5380.67
Utility treatment (DFS)	0.03	-0.03	0.11	-0.03	0.11

Utility no treatment (DFS)	0.03	-0.03	0.11	-0.03	0.11
Utility treatment (LR - CT)	0.08	0.00	0.16	0.00	0.16
Utility treatment (LR - PT)	0.17	0.12	0.22	0.12	0.22
Utility treatment (1LM)	0.11	0.10	0.12	0.10	0.12
Utility no treatment (1LM)	0.17	0.12	0.22	0.12	0.22
Utility treatment (2LM)	0.13	0.10	0.15	0.10	0.15
Utility no treatment (2LM)	0.17	0.12	0.22	0.12	0.22

Deterministic sensitivity analyses results at list and PAS price for atezolizumab for the PD-L1 ≥50% stage II–IIIA population, excluding EGFR/ALK+ subgroup are presented in Figure 16 and Figure 17.

Based on the deterministic sensitivity analyses at list price, the most influential parameters appear to be discount effects, utility in DFS state (on treatment), proportion of patients who have 1L metastatic recurrence in the BSC arm, and proportion of patients on 1L metastatic treatment. 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. This is further evidenced by discount rates being the most sensitive input, as discount rates impact results more broadly throughout the model than any other input.

Figure 16: Tornado diagram – in patients with PD-L1 ≥ 50% Stage II – IIIA NSCLC, excluding EGFR mutant or ALK-positive, list price



Based on the deterministic sensitivity analyses at PAS price, the most influential parameters appear to be the proportion of patients on 1L metastatic treatment in the 1L metastatic health state, the proportion of patients who have metastatic recurrence in the BSC arm, the market share of pemetrexed and carboplatin in 1L metastatic treatment for the BSC arm, and the proportion of patients who have metastatic recurrence in the atezolizumab arm. The tornado diagram of atezolizumab at PAS price differs from atezolizumab at list price as the driver of the ICER is no longer discount effects, but instead the proportion of patients receiving metastatic treatment and who experience metastatic recurrence, where the associated costs and effects from metastatic treatment is having the biggest impact.

Figure 17: Tornado diagram – atezolizumab vs BSC in Stage II–IIIA, PD-L1 ≥ 50% NSCLC, excluding EGFR mutant or ALK-positive, PAS price

2.6.4 Scenario analysis (subgroup)

Scenario analyses (with PAS and at list price) were conducted to assess uncertainty around remaining parameter inputs and structural assumptions in the model for the PD-L1 ≥50% stage II-IIIA population, excluding EGFR/ALK+ mutations (Table 28 and Table 29). This was carried out as described in Section 2.5.3.

All scenario analyses results with atezolizumab at PAS and list price, remain cost-effective. The majority of scenarios with atezolizumab at PAS price show that atezolizumab is dominant versus BSC.

Table 28: Results from scenario analyses – Stage II-IIIA, PD-L1 >50% NSCLC, excluding EGFR mutant or ALK-positive (PAS price for atezolizumab)

Parameter	Value	Atezolizumab			Best Supportive Care			ATZ vs. BSC		
		Life Years	QALYS	Costs	Life Years	QALYS	Costs	Inc. costs per LY gained	Inc. costs per QALY gained	NMB (WTP £30k)
Base case		10.32	[redacted]	[redacted]	7.74	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
DFS distributions	Exponential	10.07	[redacted]	[redacted]	7.16	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Weibull	9.85	[redacted]	[redacted]	7.40	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Log-normal	10.53	[redacted]	[redacted]	7.83	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Generalized Gamma	10.16	[redacted]	[redacted]	8.37	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Gompertz	10.00	[redacted]	[redacted]	8.17	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Gamma	9.85	[redacted]	[redacted]	7.30	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Trial data used to inform recurrence type split	Pool across Arms	10.21	[redacted]	[redacted]	7.84	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Treatment effect	Maintained over Time	10.29	[redacted]	[redacted]	7.74	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Standardised mortality rate	1.50	9.91	[redacted]	[redacted]	7.46	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	2.00	9.23	[redacted]	[redacted]	7.01	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Atezolizumab treatment schedule	1, 680mg/ every 4 weeks	10.32	[redacted]	[redacted]	7.74	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
LRR: Efficacy by treatment intent	Digitised Data	10.65	[redacted]	[redacted]	8.04	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Metastatic recurrence 1L: Allow metastatic recurrence 2L	No	10.56	[redacted]	[redacted]	8.16	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Metastatic recurrence 1L - Efficacy source	IMpower110	10.31	[redacted]	[redacted]	7.71	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Metastatic recurrence 2L - Efficacy by treatment intent	Digitised Data	10.35	[redacted]	[redacted]	7.80	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
DFS cost inputs: scanning schedule	36.00	10.32	[redacted]	[redacted]	7.74	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Time-to-off treatment	Until Progression or Death	10.32	[redacted]	[redacted]	7.74	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Utility method	Source utilities	10.32	[redacted]	[redacted]	7.74	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
DFS utility source input	Manser et al. (2006)	10.32	[redacted]	[redacted]	7.74	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Grutters et al. (2010)	10.32	[redacted]	[redacted]	7.74	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Black, Keeler and Soneji (2014)	10.32	[redacted]	[redacted]	7.74	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Yang et al. (2014)	10.32	[redacted]	[redacted]	7.74	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Metastatic recurrence 1L utility source input	IMpower110	10.32	[redacted]	[redacted]	7.74	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Chouaid et al. (2013)	10.32	[redacted]	[redacted]	7.74	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Metastatic recurrence 2L utility source input	IMpower110	10.32	[redacted]	[redacted]	7.74	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Chouaid et al. (2013)	10.32	[redacted]	[redacted]	7.74	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Nafees et al. (2008)	10.32	[redacted]	[redacted]	7.74	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Allow vial sharing	0.00	10.32	[redacted]	[redacted]	7.74	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
End of Life costs	Exclude	10.32	[redacted]	[redacted]	7.74	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Time horizon	10.00	6.66	[redacted]	[redacted]	5.32	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	20.00	9.37	[redacted]	[redacted]	7.11	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	30.00	10.25	[redacted]	[redacted]	7.69	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
"Cure" proportion implementation	5 years	10.09	[redacted]	[redacted]	7.54	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	6 years	9.65	[redacted]	[redacted]	7.23	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Ramp up 2–8 years	10.13	[redacted]	[redacted]	7.63	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Ramp up 3–8 years	9.88	[redacted]	[redacted]	7.42	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Maximum "cure" proportion	20%	8.65	[redacted]	[redacted]	6.54	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	40%	9.01	[redacted]	[redacted]	6.80	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	60%	9.44	[redacted]	[redacted]	7.11	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	80%	9.97	[redacted]	[redacted]	7.49	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Additional admin costs	Add £192.90 and £2.58	10.32	[redacted]	[redacted]	7.74	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Table 29: Subgroup results from scenario analyses – PD-L1 ≥ 50% Stage II – IIIA NSCLC, excluding EGFR mutant or ALK-positive population (list price for atezolizumab)

Parameter	Value	Atezolizumab			Best Supportive Care			ATZ vs. BSC		
		Life Years	QALYS	Costs	Life Years	QALYS	Costs	Inc. costs per LY gained	Inc. costs per QALY gained	NMB (WTP £30k)
Base case		10.32	[redacted]	[redacted]	7.74	[redacted]	[redacted]	£13,078	£17,403	£24,421
DFS distributions	Exponential	10.07	[redacted]	[redacted]	7.16	[redacted]	[redacted]	£10,628	£14,165	£34,570
	Weibull	9.85	[redacted]	[redacted]	7.40	[redacted]	[redacted]	£14,114	£18,766	£20,728
	Log-normal	10.53	[redacted]	[redacted]	7.83	[redacted]	[redacted]	£12,121	£16,143	£28,151
	Generalized Gamma	10.16	[redacted]	[redacted]	8.37	[redacted]	[redacted]	£22,149	£29,285	£965
	Gompertz	10.00	[redacted]	[redacted]	8.17	[redacted]	[redacted]	£21,203	£28,067	£2,676
	Gamma	9.85	[redacted]	[redacted]	7.30	[redacted]	[redacted]	£13,352	£17,761	£23,432
Trial data used to inform recurrence type split	Pool across Arms	10.21	[redacted]	[redacted]	7.84	[redacted]	[redacted]	£15,302	£20,330	£17,249
Treatment effect	Maintained over Time	10.29	[redacted]	[redacted]	7.74	[redacted]	[redacted]	£13,389	£17,806	£23,371
Standardised mortality rate	1.50	9.91	[redacted]	[redacted]	7.46	[redacted]	[redacted]	£13,813	£18,310	£21,535
	2.00	9.23	[redacted]	[redacted]	7.01	[redacted]	[redacted]	£15,208	£20,035	£16,777
Atezolizumab treatment schedule	1, 680mg/ every 4 weeks	10.32	[redacted]	[redacted]	7.74	[redacted]	[redacted]	£14,606	£19,437	£20,479
LRR: Efficacy by treatment intent	Digitised Data	10.65	[redacted]	[redacted]	8.04	[redacted]	[redacted]	£12,911	£17,210	£25,120

Metastatic recurrence 1L: Allow metastatic recurrence 2L	No	10.36	[redacted]	[redacted]	7.81	[redacted]	[redacted]	£13,182	£17,515	£23,967
Metastatic recurrence 1L - Efficacy source	IMpower110	10.56	[redacted]	[redacted]	8.16	[redacted]	[redacted]	£11,708	£15,500	£26,237
Metastatic recurrence 2L - Efficacy by treatment intent	Digitised Data	10.31	[redacted]	[redacted]	7.71	[redacted]	[redacted]	£13,267	£17,659	£24,039
DFS cost inputs: scanning schedule	36.00	10.35	[redacted]	[redacted]	7.80	[redacted]	[redacted]	£13,130	£17,448	£24,137
Time-to-off treatment	Until Progression or Death	10.32	[redacted]	[redacted]	7.74	[redacted]	[redacted]	£13,088	£17,416	£24,396
Utility method	Source utilities	10.32	[redacted]	[redacted]	7.74	[redacted]	[redacted]	£17,276	£22,989	£13,592
DFS utility source input	Manser et al. (2006)	10.32	[redacted]	[redacted]	7.74	[redacted]	[redacted]	£13,078	£17,581	£23,834
	Grutters et al. (2010)	10.32	[redacted]	[redacted]	7.74	[redacted]	[redacted]	£13,078	£25,361	£6,171
	Black, Keeler and Soneji (2014)	10.32	[redacted]	[redacted]	7.74	[redacted]	[redacted]	£13,078	£18,254	£21,710
	Yang et al. (2014)	10.32	[redacted]	[redacted]	7.74	[redacted]	[redacted]	£13,078	£20,242	£16,265
Metastatic recurrence 1L utility source input	IMpower110	10.32	[redacted]	[redacted]	7.74	[redacted]	[redacted]	£13,078	£16,225	£28,644
	Chouaid et al. (2013)	10.32	[redacted]	[redacted]	7.74	[redacted]	[redacted]	£13,078	£17,497	£24,109

Metastatic recurrence 2L utility source input	IMpower110	10.32	[redacted]	[redacted]	7.74	[redacted]	[redacted]	£13,078	£17,411	£24,394
	Chouaid et al. (2013)	10.32	[redacted]	[redacted]	7.74	[redacted]	[redacted]	£13,078	£17,350	£24,599
	Nafees et al. (2008)	10.32	[redacted]	[redacted]	7.74	[redacted]	[redacted]	£13,078	£17,343	£24,624
Allow vial sharing	0.00	10.32	[redacted]	[redacted]	7.74	[redacted]	[redacted]	£13,034	£17,345	£24,534
End of Life costs	Exclude	10.32	[redacted]	[redacted]	7.74	[redacted]	[redacted]	£13,781	£18,338	£22,608
Time horizon	10.00	6.66	[redacted]	[redacted]	5.32	[redacted]	[redacted]	£24,580	£31,159	-£1,230
	20.00	9.37	[redacted]	[redacted]	7.11	[redacted]	[redacted]	£14,880	£19,501	£18,106
	30.00	10.25	[redacted]	[redacted]	7.69	[redacted]	[redacted]	£13,207	£17,544	£23,948
"Cure" proportion implementation	5 years	10.09	[redacted]	[redacted]	7.54	[redacted]	[redacted]	£13,239	£17,616	£23,760
	6 years	9.65	[redacted]	[redacted]	7.23	[redacted]	[redacted]	£14,296	£19,003	£20,015
	Ramp up 2–8 years	10.13	[redacted]	[redacted]	7.63	[redacted]	[redacted]	£13,765	£18,304	£21,924
	Ramp up 3–8 years	9.88	[redacted]	[redacted]	7.42	[redacted]	[redacted]	£13,971	£18,574	£21,166
Maximum "cure" proportion	20%	8.65	[redacted]	[redacted]	6.54	[redacted]	[redacted]	£17,539	£23,200	£10,864
	40%	9.01	[redacted]	[redacted]	6.80	[redacted]	[redacted]	£16,475	£21,822	£13,650
	60%	9.44	[redacted]	[redacted]	7.11	[redacted]	[redacted]	£15,276	£20,266	£17,097
	80%	9.97	[redacted]	[redacted]	7.49	[redacted]	[redacted]	£13,927	£18,511	£21,422
Additional admin costs	Add £192.90 and £2.58	10.32	[redacted]	[redacted]	7.74	[redacted]	[redacted]	£14,062	£18,712	£21,884

2.7 *Interpretation and conclusions of economic evidence*

Conclusions of economic results evidence

- **Extensive scenario and sensitivity analyses show that atezolizumab at PAS price is cost-effective in all scenarios presented**
- **Scenario analyses explored in response to ERG Clarification questions also show that atezolizumab at PAS price remains cost-effective**
- **In a potentially curative setting, preventing early lung cancer recurrence or progression to metastatic disease has significant benefits for both patients and society**

2.7.1 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 anticipated licence.

A UK clinical expert was consulted on the differences in treatment pathway and resource use for the PD-L1 ≥50% Stage II – IIIA population compared to the PD-L1 ≥1% Stage II – IIIA population and the economic evaluation fully incorporates these changes.

2.7.2 Conclusions

Atezolizumab reduced the risk of recurrence, new primary NSCLC formation, or death by 34% (DFS HR 0.66 [95% CI: 0.50–0.88]) compared to BSC, in the PD-L1 ≥ 1% Stage II–IIIA population and by 57% (DFS HR 0.43 [95% CI: 0.27, 0.68]), in the PD-L1 ≥ 50% Stage II–IIIA population. In addition, there were no new safety signals demonstrated in IMpower010 and the safety profile for adjuvant atezolizumab is consistent with that established for atezolizumab monotherapy across multiple indications and lines of therapy.

The economic analysis for the PD-L1 ≥ 50% Stage II–IIIA population shows that atezolizumab in the adjuvant setting offers an incremental QALY gain at a modest increase in cost to the healthcare system. The deterministic and probabilistic results gives confidence in decision making and supports the view that atezolizumab is a cost-effective use of NHS resources. The economic evaluation for the PD-L1 ≥ 50% Stage II–IIIA population is more favourable than for the PD-L1 ≥ 1% Stage II–IIIA population as it shows that atezolizumab

(at PAS price) is dominant compared to BSC, as well as being dominant in the majority of scenarios tested.

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 offers an innovative approach to adjuvant therapy which can lead to better outcomes for patients compared to the current standard of care (active monitoring).

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Appendix A – DFS and OS comparisons of model versus IMpower010 (KM)

In IMpower010, the tumour assessment schedule was every 4 months during the first year, every six months from the second year until year 5 and annually afterwards until disease recurrence, death, loss to follow-up, consent withdrawal, or study termination by the Sponsor, whichever occurs first. Therefore, the DFS% below is every 4 months in the first year and every 6 months thereafter.

Please see Table 30 and Table 31 for the DFS comparisons between model vs. the IMpower010 (KM) data.

Table 30: DFS from the model versus clinical trial - atezolizumab, PD-L1 ≥ 50% Stage II–IIIA NSCLC

Months	Model results	IMpower010, PD-L1 ≥ 50% Stage II–IIIA NSCLC, including EGFR mutant or ALK-positive KM estimates
0	[redacted]	[redacted]
4	[redacted]	[redacted]
8	[redacted]	[redacted]
12	[redacted]	[redacted]
18	[redacted]	[redacted]
24	[redacted]	[redacted]
30	[redacted]	[redacted]
36	[redacted]	[redacted]

NB: There are few patients at risk after 36 months, hence the data are not presented (i.e., [redacted] patients at risk at 42 months)

Table 31: DFS from the model versus clinical trial - BSC, PD-L1 ≥ 1% Stage II–IIIA NSCLC

Months	Model results	IMpower010, PD-L1 ≥ 50% Stage II–IIIA NSCLC , including EGFR mutant or ALK-positive KM estimates
0	[redacted]	[redacted]
4	[redacted]	[redacted]
8	[redacted]	[redacted]
12	[redacted]	[redacted]
18	[redacted]	[redacted]
24	[redacted]	[redacted]
30	[redacted]	[redacted]

36	[redacted]	[redacted]

NB: There are few patients at risk after 36 months, hence the data are not presented (i.e., [redacted] patients at risk at 42 months)

Similarly, for OS, OS% is provided every 4 months in the first year and every 6 months thereafter. Please see Table 32 and Table 33 for the OS comparisons between model vs. IMpower010 (KM) data. Note that after month 36, there is high uncertainty given the small number of patients at risk and the small number of events occurring after then.

Table 32: OS from the model versus clinical trial - atezolizumab, PD-L1 ≥ 50% Stage II–IIIA NSCLC

Months	Model results	IMpower010, PD-L1 ≥ 50% Stage II–IIIA NSCLC, including EGFR mutant or ALK-positive KM estimates
0	[redacted]	[redacted]
4	[redacted]	[redacted]
8	[redacted]	[redacted]
12	[redacted]	[redacted]
18	[redacted]	[redacted]
24	[redacted]	[redacted]
30	[redacted]	[redacted]
36	[redacted]	[redacted]

NB: There are few patients at risk after 36 months, hence the data are not presented (i.e., [redacted] patients at risk at 42 months)

Table 33: OS from the model versus clinical trial - BSC, PD-L1 ≥ 50% Stage II–IIIA NSCLC

Months	Model results	IMpower010, PD-L1 ≥ 50% Stage II–IIIA NSCLC, including EGFR mutant or ALK-positive KM estimates
0	[redacted]	[redacted]
4	[redacted]	[redacted]
8	[redacted]	[redacted]
12	[redacted]	[redacted]
18	[redacted]	[redacted]
24	[redacted]	[redacted]
30	[redacted]	[redacted]
36	[redacted]	[redacted]

NB: There are few patients at risk after 36 months, hence the data are not presented (i.e., [redacted] patients at risk at 42 months)

Appendix B – Cumulative hazard plots

The plot of KM cumulative hazard vs time is provided in Figure 18 and Figure 19 for the atezolizumab and BSC arms, respectively. These plots can be useful to assess the fitting of the parametric function to the observed survival data, although after month 36 there is high uncertainty, given the small number of patients at risk and the small number of events occurring after then.

Figure 18: Cumulative Hazard Plot (IMpower010, DFS, Stage II-IIIA, PD-L1 ≥50%, 21 Jan 2021 Data-Cut, Atezolizumab Arm)

Figure 19: Cumulative Hazard Plot (IMpower010, DFS, Stage II-IIIA, PD-L1 ≥50%, 21 Jan 2021 Data-Cut, BSC Arm)

In Figure 20 and Figure 21, the cumulative hazard estimated with each parametric function is overlayed with the KM cumulative hazard in one plot. The cumulative hazard plots for each parametric model fitted to the DFS data are also provided in separate plots in Figure 22–Figure 35. These cumulative hazard plots show the probability of experiencing DFS events until time t and its 95% confidence interval (shaded area/dotted lines).

Figure 20: DFS – KM cumulative hazard and parametric fits (IMpower010, DFS, Stage II-IIIA, PD-L1 ≥50%, 21 Jan 2021 Data-Cut, Atezolizumab Arm)

Figure 21: DFS – KM cumulative hazard and parametric fits (IMpower010, DFS, Stage II-IIIA, PD-L1 ≥50%, 21 Jan 2021 Data-Cut, BSC Arm)

Figure 22: DFS – KM cumulative hazard and Exponential fit (IMpower010, DFS, Stage II-IIIA, PD-L1 ≥50%, 21 Jan 2021 Data-Cut, atezolizumab Arm)

Figure 23: DFS – KM cumulative hazard and Weibull fit (IMpower010, DFS, Stage II-IIIA, PD-L1 ≥50%, 21 Jan 2021 Data-Cut, Atezolizumab Arm)

Figure 24: DFS – KM cumulative hazard and Log-Normal fit (IMpower010, DFS, Stage II-IIIA, PD-L1 ≥50%, 21 Jan 2021 Data-Cut, Atezolizumab Arm)

Figure 25: DFS – KM cumulative hazard and Generalised Gamma fit (IMpower010, DFS, Stage II-IIIA, PD-L1 ≥50%, 21 Jan 2021 Data-Cut, Atezolizumab Arm)

Figure 26: DFS – KM cumulative hazard and Log-Logistic fit (IMpower010, DFS, Stage II-IIIA, PD-L1 ≥50%, 21 Jan 2021 Data-Cut, Atezolizumab Arm)

Figure 27: DFS – KM cumulative hazard and Gompertz fit (IMpower010, DFS, Stage II-IIIA, PD-L1 ≥50%, 21 Jan 2021 Data-Cut, Atezolizumab Arm)

Figure 28: DFS – KM cumulative hazard and Gamma fit (IMpower010, DFS, Stage II-IIIA, PD-L1 ≥50%, 21 Jan 2021 Data-Cut, Atezolizumab Arm)

Figure 29: DFS – KM cumulative hazard and Exponential fit (IMpower010, DFS, Stage II-IIIA, PD-L1 ≥50%, 21 Jan 2021 Data-Cut, BSC Arm)

Figure 30: DFS – KM cumulative hazard and Weibull fit (IMpower010, DFS, Stage II-IIIA, PD-L1 ≥50%, 21 Jan 2021 Data-Cut, BSC Arm)

Figure 31: DFS – KM cumulative hazard and Log Normal fit (IMpower010, DFS, Stage II-IIIA, PD-L1 ≥50%, 21 Jan 2021 Data-Cut, BSC Arm)

Figure 32: DFS – KM cumulative hazard and Generalised Gamma fit (IMpower010, DFS, Stage II-IIIA, PD-L1 ≥50%, 21 Jan 2021 Data-Cut, BSC Arm)

Figure 33: DFS – KM cumulative hazard and Log-Logistic fit (IMpower010, DFS, Stage II-IIIA, PD-L1 ≥50%, 21 Jan 2021 Data-Cut, BSC Arm)

Figure 34: DFS – KM cumulative hazard and Gompertz fit (IMpower010, DFS, Stage II-IIIA, PD-L1 ≥50%, 21 Jan 2021 Data-Cut, BSC Arm)

Figure 35: DFS – KM cumulative hazard and Gamma fit (IMpower010, DFS, Stage II-IIIA, PD-L1 ≥50%, 21 Jan 2021 Data-Cut, BSC Arm)

Appendix C – Q-Q plots

The Q-Q plots for each parametric function are provided (see Figure 36–Figure 47), showing the observed quantiles (observed times at which DFS events occurred) and the predicted ones for each parametric function corresponding to the probability estimated via the KM method after an adjustment. These plots can be useful to assess the fitting of the parametric function to the observed survival data, although after month 36 there is high uncertainty, given the small number of patients at risk and the small number of events occurring after then.

Figure 36: Q-Q plot (exponential) - IMpower010, DFS, Stage II-IIIA, PD-L1 ≥50%, 21 Jan 2021 Data-Cut, atezolizumab arm

Figure 37: Q-Q plot (Weibull) - IMpower010, DFS, Stage II-IIIA, PD-L1 ≥50%, 21 Jan 2021 Data-Cut, atezolizumab arm

Figure 38: Q-Q plot (Log-Logistic) - IMpower010, DFS, Stage II-IIIA, PD-L1 ≥50%, 21 Jan 2021 Data-Cut, atezolizumab arm

Figure 39: Q-Q plot (Log normal) - IMpower010, DFS, Stage II-IIIA, PD-L1 ≥50%, 21 Jan 2021 Data-Cut, atezolizumab arm

Figure 40: Q-Q plot (Gamma) - IMpower010, DFS, Stage II-IIIA, PD-L1 ≥50%, 21 Jan 2021 Data-Cut, atezolizumab arm

Figure 41: Q-Q plot (Gen Gamma) - IMpower010, DFS, Stage II-IIIA, PD-L1 ≥50%, 21 Jan 2021 Data-Cut, atezolizumab arm

Figure 42: Q-Q plot (Gompertz) - IMpower010, DFS, Stage II-IIIA, PD-L1 ≥50%, 21 Jan 2021 Data-Cut, atezolizumab arm

Figure 43: Q-Q plot (Exponential) - IMpower010, DFS, Stage II-IIIA, PD-L1 ≥50%, 21 Jan 2021 Data-Cut, BSC arm

Figure 44: Q-Q plot (Weibull) - IMpower010, DFS, Stage II-IIIA, PD-L1 ≥50%, 21 Jan 2021 Data-Cut, BSC arm

Figure 45: Q-Q plot (Log-logistic) - IMpower010, DFS, Stage II-IIIA, PD-L1 ≥50%, 21 Jan 2021 Data-Cut, BSC arm

Figure 46: Q-Q plot (Log normal) - IMpower010, DFS, Stage II-IIIA, PD-L1 ≥50%, 21 Jan 2021 Data-Cut, BSC arm

Figure 47: Q-Q plot (Gamma) - IMpower010, DFS, Stage II-IIIA, PD-L1 ≥50%, 21 Jan 2021 Data-Cut, BSC arm

Figure 48: Q-Q plot (Gen Gamma) - IMpower010, DFS, Stage II-IIIA, PD-L1 ≥50%, 21 Jan 2021 Data-Cut, BSC arm

Figure 49: Q-Q plot (Gompertz) - IMpower010, DFS, Stage II-IIIA, PD-L1 ≥50%, 21 Jan 2021 Data-Cut, BSC arm

Appendix D – Parametric survival analysis of the IMpower010 OS KM data

Figure 50 to Figure 53 shows the KM overlaid with the expected survival for each of the parametric functions using the IMpower010 OS and DFS Stage II-IIIA PD-L1+ KM data, for each arm. The KM survival plots with the survival expected with log-logistic distribution (company base case) is shown separately in Figure 54 to Figure 57.

Figure 50: OS - KM and parametric fits for atezolizumab arm until 60 months (IMpower010, OS, Stage II-IIIA, PD-L1 ≥50%, 21 Jan 2021 Data-Cut)

Figure 51: OS - KM and parametric fits for BSC arm until 60 months (IMpower010, OS, Stage II-IIIA, PD-L1 ≥50%, 21 Jan 2021 Data-Cut)

Figure 52: DFS - KM and parametric fits for atezolizumab arm until 60 months (IMpower010, DFS, Stage II-IIIA, PD-L1 ≥50%, 21 Jan 2021 Data-Cut)

Figure 53: DFS - KM and parametric fits for BSC until 60 months (IMpower010, DFS, Stage II-IIIA, PD-L1 ≥50%, 21 Jan 2021 Data-Cut)

Figure 54: OS - KM and log-logistic fit for atezolizumab (base case, IMpower010, OS, Stage II-IIIA, PD-L1 ≥50%, 21 Jan 2021 Data-Cut)

Figure 55 OS - KM and log-logistic fit for BSC (base case, IMpower010, OS, Stage II-IIIA, PD-L1 ≥50%, 21 Jan 2021 Data-Cut)

Figure 56: DFS - KM and log-logistic fit for atezolizumab (base case, IMpower010, DFS, Stage II-IIIA, PD-L1 ≥50%, 21 Jan 2021 Data-Cut)

Figure 57: DFS - KM and log-logistic fit for BSC (base case, IMpower010, DFS, Stage II-IIIA, PD-L1 ≥50%, 21 Jan 2021 Data-Cut)

Appendix E – Summary of OS and DFS parametric models and IMpower010 KM data

Please see Figure 58 for the summary graph showing all the IMpower010 DFS Stage II–IIIA PD-L1+ OS and DFS KM data, with the respective unadjusted log-logistic model fit to each KM curve, and the company base case projection for each endpoint.

Figure 58: Summary of DFS and OS KM data with unadjusted log-logistic model fit plus the company base case projections (both arms, IMpower010, Stage II-IIIA, PD-L1 ≥50%, 21 Jan 2021 Data-Cut)

Appendix F – Comparison of DFS events between the atezolizumab and BSC arm

Given that the different types of DFS events are competing events (i.e. observing one of them precludes observing the other events, as the definition of DFS considers the first occurrence of any DFS event and no more tumour assessments are performed afterwards), the time to metastatic recurrence has been analysed as first DFS event, censoring the other recurrences at the time of the tumour assessment and censoring the deaths at the time of the last tumour assessment. The proportion of patients with metastatic recurrence (as first DFS event) have also been compared between treatment arms until year 3.

The results presented in Table 34 and Table 35 indicate that the hazard of metastatic recurrences as the first DFS event is reduced by approximately 70% in the atezolizumab compared to the BSC arm. Even if some of the assumptions beyond these analyses may be questionable (e.g. non-informative censoring), to our knowledge this is the best attempt to answer the question of treatment effect on the type of first recurrences in the context of competing events (43).

Table 34: Sites of disease recurrence for patients with protocol defined disease recurrence in the Stage II-IIIA, SP263 TC ≥ 50% population

Disease recurrence	ATZ (n=[redacted])	BSC (n=[redacted])
Locoregional recurrence	[redacted]	[redacted]
Metastatic recurrence	[redacted]	[redacted]
Second Primary Lung Cancer	[redacted]	[redacted]

Table 35: Time to event summary of the first metastatic recurrence as DFS component – Stage II-IIIA patients, SP263 TC ≥ 50% (stratified analysis by sex, histology, tumour stage)

	Atezolizumab (N=115)	Best Supportive Care(BSC) (N=114)
Patients with event (%)	[redacted]	[redacted]
Earliest contributing event		
Metastatic Recurrence	[redacted]	[redacted]

Patients without event (%)	[redacted]	[redacted]
Time to event (months)		
Median	[redacted]	[redacted]
95% CI	[redacted]	[redacted]
25% and 75%-ile	[redacted]	[redacted]
Range	[redacted]	[redacted]
Stratified Analysis		
p-value (log-rank)	[redacted]	
Hazard Ratio	[redacted]	
95% CI	[redacted]	
Unstratified Analysis		
p-value (log-rank)	[redacted]	
Hazard Ratio	[redacted]	
95% CI	[redacted]	
Time Point Analysis		
3 Years		
Patients remaining at risk	[redacted]	[redacted]
Event Rate (%)	[redacted]	[redacted]
95% CI	[redacted]	[redacted]
Difference in Event Rate	[redacted]	
95% CI	[redacted]	
p-value (Z-test)	[redacted]	

* Censored, NE = Not estimable.

Appendix G – Comparison of cause of death between the atezolizumab and BSC arm

A competing risk is an event whose occurrence prevents the occurrence of the primary event of interest. For example, a patient who dies of a cardiovascular cause is no longer at risk of death attributable to progressive NSCLC. In the IMpower010 study, given that the different causes of death are competing events (i.e. observing one of them precludes observing the other), time to death due to progressive disease was analysed, censoring the other causes of death. The proportion of patients who died due to progressive disease until year 3 have also been compared.

Table 36 presents the death and causes of death for the PD-L1 ≥ 50% TC Stage II–IIIA population. Table 37 presents the analysis of time to death due to progressive disease and the proportion of patients who died due to progressive disease until year 3. This table indicates that the hazard of dying due to progressive disease is [redacted] in the atezolizumab arm compared to the BSC arm. It should be noted that the assumptions from these analyses may not be realistic (i.e. it assumes that deaths from other causes do not occur). To our knowledge this is the best attempt to answer the question of treatment effect on cause-specific deaths in the context of competing risks (43).

Table 36: Death and Causes of Death for the PD-L1 ≥ 50% TC Stage II–IIIA subgroup

	Atezolizumab (N=115)		Best Supportive Care (BSC) (N=114)	
	n	%	n	%
All Deaths	[redacted]	[redacted]	[redacted]	[redacted]
Progressive disease	[redacted]	[redacted]	[redacted]	[redacted]
Other	[redacted]	[redacted]	[redacted]	[redacted]

Table 37: Time to event summary of the time-to-death due to progressive disease and proportion of patients who died due to progressive disease until year 3 – Stage II-IIIA patients, SP263 TC ≥50% (stratified analysis by sex, histology, tumour stage)

	Atezolizumab (N=115)	Best Supportive Care (BSC) (N=114)
Patients with event (%)	[redacted]	[redacted]

Earliest contributing event		
Death due to progressive disease		
Patients without event (%)		
Time to event (months)		
Median		
95% CI		
25% and 75%-ile		
Range		
Stratified Analysis		
p-value (log-rank)		
Hazard Ratio		
95% CI		
Unstratified Analysis		
p-value (log-rank)		
Hazard Ratio		
95% CI		
Time Point Analysis		
3 Years		
Patients remaining at risk		
Event Rate (%)		
95% CI		
Difference in Event Rate		
95% CI		
p-value (Z-test)		

* Censored, NE = Not estimable

Single Technology Appraisal

Atezolizumab for adjuvant treatment of resected non-small-cell lung cancer [ID3852]

Company response to "Analyses to consider following ACM1" - 20th June 2022

Introduction

Following the 1st appraisal meeting for atezolizumab in adjuvant treatment of resected non-small cell lung cancer [ID3852], the committee requested further analyses to be made available before the next appraisal meeting. The requests and how they have been addressed are summarised in Table 1.

*Table 1: Summary of additional analyses requested, the company response and location in the document**

Additional analysis request	Company response	Location in document
Include immunotherapy retreatment following metastatic disease recurrence, varying the number of months after stopping treatment that a patient would receive retreatment	Scenario analyses included where retreatment is allowed 3, 6, and 12 months following treatment discontinuation.	Section 1
Adjust the modelling of the post disease-free survival health states to reflect the outcomes of previous NICE Technology Appraisals (TAs). Also, consider changes that result in the modelled overall survival (OS) matching closer to the IMpower010 stage II-IIIA PD-L1 expression on ≥ 50% of tumour cells (TC) observed OS data	Implemented an adjustment factor to the post- disease-free survival (DFS) transition probabilities so that the total QALYs from the metastatic health states of the model align with the total QALYs from previously NICE appraised models in metastatic NSCLC. Implemented an adjustment factor to the post-DFS transition probabilities so that the modelled OS matched the IMpower010 KM OS at 36 months - this was performed separately for the ATZ and the BSC arm. The model was adapted to allow patients to proceed to 1L metastatic health state after cycle 1 to explore how this affected the metastatic health state QALYs in isolation and	Section 2

	aid interpretation of full results.	
Explore other sources of literature reporting proportion cured following curative resection and conduct sensitivity analysis of the cure assumptions	The full real-world evidence (RWE) structured review has been provided in Appendix M of Submission Document B and functionality to consider an additional study (Maeda et al. 2010a) has been added to the model. A clinical expert validation of the study is provided.	Section 3
Present sensitivity analyses of disease-free survival data and commentary on the use of alternative extrapolations and the impact of cost-effectiveness	A sensitivity analysis using alternative extrapolations of disease-free survival data is provided. Justification for the company base case extrapolation is also provided (see Section 7 for new company base case settings).	Section 4
Provide justification of the external sources used for transitions in the model; supplement with additional literature searches	The RWE structured review has been provided in Appendix M of Submission Document B, which provides the Nakamichi et al. 2017 and Wong et al. 2016 references. A PubMed search (documented and provided in the Appendix B) to locate references for the locoregional recurrences to death transition (in patients treated with palliative intent or not treated) is provided. Functionality to consider an additional source (Foo et al. 2005) has been added to the model.	Section 5
Provide updated Kaplan-Meier (KM) data if available and include in the economic model	The updated OS data are provided in the updated economic model (see Sheet “Updated OS Kaplan-Meier”) and in this report.	Section 6

*All scenarios presented use the PAS price for atezolizumab

1. Inclusion of immunotherapy retreatment

During the 1st appraisal committee meeting there was a discussion around retreatment and how retreatment with an immunotherapy would be permitted from 6 months after stopping treatment, if the patient experiences a recurrence (although this is not currently stated in NICE guidance (1)). Clinical experts at the meeting stated that they would be comfortable

retreating 12 months after treatment discontinuation if there are no recurrences in that period. The scenario analyses presented in Table 2 show the impact of allowing retreatment at 6 and 12 months after treatment discontinuation.

The committee suggested a scenario was provided whereby patients could receive retreatment after 3 months (e.g. set cell O41 to '14' in the ERG sheet of the cost-effectiveness model). The scenario presented in Table 2 assumes 50% of patients who had metastatic recurrence between months 3-6 after treatment discontinuation were retreated (e.g. refer to the value of cell O44 when cell O41 is set to the proportion that can retreat with immunotherapy). It was assumed that not all patients would receive immunotherapy retreatment, possibly due to previous discontinuation as a result of an immune-related adverse event (IrAE) (2). It was also assumed that 100% of patients who had metastatic recurrence 6 months after treatment discontinuation were retreated.

Atezolizumab remains cost-effective at a threshold of £20,000 in all scenarios that were completed in relation to immunotherapy retreatment.

As the committee indicated that retreatment will be permitted, the company base case has been updated to allow retreatment with immunotherapy after 12 month (in alignment with the preferences indicated by the clinical experts).

Table 2: Scenario analysis of when immunotherapy retreatment is allowed following disease recurrence

Months after treatment initiation (model setting)*	Months after treatment stopping	ERG optimistic ICER (£)	Difference in ICER from ERG optimistic base case (£)	ERG pessimistic ICER (£)	Difference in ICER from ERG pessimistic base case (£)
999 (no retreatment)	-	[redacted]	[redacted]	[redacted]	[redacted]
14	3	[redacted]	[redacted]	[redacted]	[redacted]
17	6	[redacted]	[redacted]	[redacted]	[redacted]
23	12 (Company base case)	[redacted]	[redacted]	[redacted]	[redacted]

*Patients are treated for 16 three-weekly cycles and therefore, patients no longer receive treatment from month 11. In this case, retreatment 12 months after treatment discontinuation would equate to 23 months (11+12=23; this setting can be found in the economic model "Efficacy Inputs" sheet, Cell F153)

2. Post-DFS modelling

The committee requested additional analyses for the post DFS modelling to ensure the outcomes of the cost-effectiveness model align with previous NICE technology appraisals in metastatic non-small cell lung cancer (NSCLC; e.g., TA531, TA705, TA584 and TA683). The post-DFS transition probabilities were also adjusted to better fit the modelled OS data to the

IMpower010 II-IIIA PD-L1 expression on ≥ 50% of tumour cells (TC) observed OS data (see Section 2.1). A second analysis was carried out to test the external validity of the model outcomes within the metastatic health states (as described further in Section 2.2). A third analysis involved adapting the model to allow patients to proceed to 1L metastatic health state after cycle 1 and compared the outcomes with previous metastatic NSCLC NICE-submitted models (see Section 2.3).

A comparison of the observed OS data at 36 months within IMpower010 II-IIIA PD-L1 and the modelled OS data at 36 months using the ERG base case model is presented in Table 3. It should be noted that whilst the modelled OS at 12 and 36 months for the ATZ and BSC arms in the ERG base case model is lower than the point estimate of OS in the IMpower010 KM, the modelled estimates do lie within the 95% CI ranges presented in Table 3.

Table 3: IMpower010 KM OS data compared to modelled OS data by arm

Arm	IMpower010 II-IIIA PD-L1 expression on ≥ 50% TC observed OS data at 36 months	IMpower010 II-IIIA PD-L1 OS KM data	Modelled OS data at 36 months (ERG optimistic base case)	Modelled OS data at 36 months (ERG pessimistic base case)
Best supportive care (BSC)	95% CI: 68.3%–84.9%	76.7%	72%	72.8%
Atezolizumab (ATZ)	95% CI: 85.2%–96.6%	90.9%	85.7%	85.8%

2.1 Adjusting the transition probabilities

The revised model contains an adjustment factor input that reduces the transition probabilities applied to the post-DFS health states. This ensures that the overall survival estimates produced by the model match the Kaplan-Meier overall survival data from the IMpower010 trial.

The adjustment factor is located in cell *O47* of the *ERG* sheet and can take on five values as shown in Table 4. The adjustment factor for each scenario was estimated using the '*Goal Seek'* function and the model multiplies the transition probabilities in cells *F112, F121, F179:182, F195, F239:242* and *F252* of the *Efficacy Inputs* sheet by each adjustment factor.

The results of using these adjustment factors are presented in Table 5, Table 6, Table 7, and Table 8. The application of the adjustment factor to the post-DFS health state transition probabilities leads to an increase in OS and QALYs in the post-DFS health states for both the atezolizumab and BSC arms. The costs also increase as the patients are on immunotherapy treatment for a longer period. In all scenarios presented the ERG-preferred ICERs decrease and atezolizumab remains cost-effective at a threshold of £20,000 in all scenarios.

Table 4: The adjustment factors applied to transition probabilities in the post-DFS health states

Option number	Adjustment factor	Description
1	1	The transition probabilities do not change in value i.e. equal to values used in the **ERG base case**
2	0.702	The transition probabilities equal a value that causes the modelled OS to equal the KM OS at 36 months for the **BSC arm** using the ERG **optimistic** base case
3	0.403	The transition probabilities equal a value that causes the modelled OS to equal the KM OS at 36 months for the **ATZ arm** using the ERG **optimistic** base case
4	0.742	The transition probabilities equal a value that causes the modelled OS to equal the KM OS at 36 months for the **BSC arm** using the ERG **pessimistic** base case
5	0.407	The transition probabilities equal a value that causes the modelled OS to equal the KM OS at 36 months for the **ATZ arm** using the ERG **pessimistic** base case

*Table 5: Results on modelled OS and QALYs (in metastatic health states) using **Option 2** for the adjustment factor - ERG **optimistic** base case*

Source	OS - (month 12/36)	QALYs - (metastatic health states)	ICER
ERG optimistic base case			
ATZ – KM IMpower010	100% / 90.9%	n/a	[redacted]
ATZ - CEM	98.3% / 85.7%	0.26	
BSC - KM IMpower010	95.5% / 76.7%	n/a	
BSC - CEM	94.6% / 72%	**0.48**	
Transition probabilities adjusted with Option 2*			
ATZ – KM IMpower010	100% / 90.9%	n/a	[redacted]
ATZ - CEM	98.5% / 87.9%	0.35	
BSC - KM IMpower010	95.5% / **76.7%**	n/a	
BSC - CEM	95.7% / **76.7%**	**0.66**	

*This option ensures that the transition probabilities equal a value that lead to the modelled OS to equal the KM OS at 36 months for the **BSC arm** using the ERG **optimistic** base case

*Table 6: Results on modelled OS and QALYs (in metastatic health states) using **Option 3** for the adjustment factor - ERG **optimistic** base case*

Source	OS - (month 12/36)	QALYs - (metastatic health states)	ICER
ERG optimistic base case			
ATZ – KM IMpower010	100% / 90.9%	n/a	[redacted]
ATZ - CEM	98.3% / 85.7%	0.26	
BSC - KM IMpower010	95.5% / 76.7%	n/a	
BSC - CEM	94.6% / 72%	**0.48**	
Transition probabilities adjusted with Option 3*			
ATZ – KM IMpower010	100% / **90.9%**	n/a	[redacted]
ATZ - CEM	98.7% / **90.9%**	0.57	

BSC - KM IMpower010	95.5% / 76.7%	n/a	
BSC - CEM	97% / 83.1%	**1.04**	

*This option ensures that the transition probabilities equal a value that lead to the modelled OS to equal the KM OS at 36 months for the **ATZ arm** using the ERG **optimistic** base case

*Table 7: Results on modelled OS and QALYs (in metastatic health states) using **Option 4** for the adjustment factor - ERG **pessimistic** base case*

Source	OS - (month 12/36)	QALYs - (metastatic health states)	ICER
ERG optimistic base case			
ATZ – KM IMpower010	100% / 90.9%	n/a	[redacted]
ATZ - CEM	98.2% / 85.8%	0.39	
BSC - KM IMpower010	95.5% / 76.7%	n/a	
BSC - CEM	94.7% / 72.8%	**0.58**	
Transition probabilities adjusted with Option 4*			
ATZ – KM IMpower010	100% / 90.9%	n/a	[redacted]
ATZ - CEM	98.4% / 87.7%	0.51	
BSC - KM IMpower010	95.5% / **76.7%**	n/a	
BSC - CEM	95.6% / **76.7%**	**0.76**	

*This option ensures that the transition probabilities equal a value that lead to the modelled OS to equal the KM OS at 36 months for the **BSC arm** using the ERG **pessimistic** base case

*Table 8: Results on modelled OS and QALYs (in metastatic health states) using **Option 5** for the adjustment factor - ERG **pessimistic** base case*

Source	OS - (month 12/36)	QALYs - (metastatic health states)	ICER
ERG optimistic base case			
ATZ – KM IMpower010	100% / 90.9%	n/a	[redacted]
ATZ - CEM	98.2% / 85.8%	0.39	
BSC - KM IMpower010	95.5% / 76.7%	n/a	
BSC - CEM	94.7% / 72.8%	**0.58**	
Transition probabilities adjusted with Option 5*			
ATZ – KM IMpower010	100% / **90.9%**	n/a	[redacted]
ATZ - CEM	98.7% / **90.9%**	0.85	
BSC - KM IMpower010	95.5% / 76.7%	n/a	
BSC - CEM	97% / 83.5%	**1.26**	

*This option ensures that the transition probabilities equal a value that lead to the modelled OS to equal the KM OS at 36 months for the **ATZ arm** using the ERG **pessimistic** base case

The overall survival curves estimated by the model when the transition probabilities were adjusted to match the best supportive care arm and atezolizumab arm of the Impower010 study are presented in Figure 1, Figure 2, Figure 3, Figure 4, Figure 5, and Figure 6 (for both ERG optimistic and pessimistic base case models).

Figure 1: Survival plots (ERG optimistic base case)

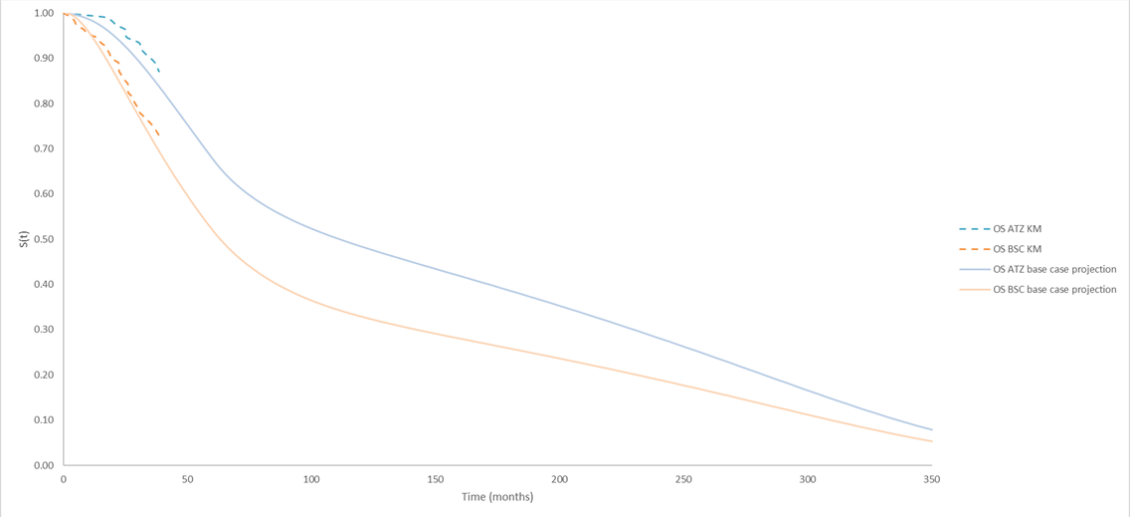


Figure 2: Adjusted survival plots (set to match best supportive care arm of Impower010, Option 2 – ERG optimistic base case)

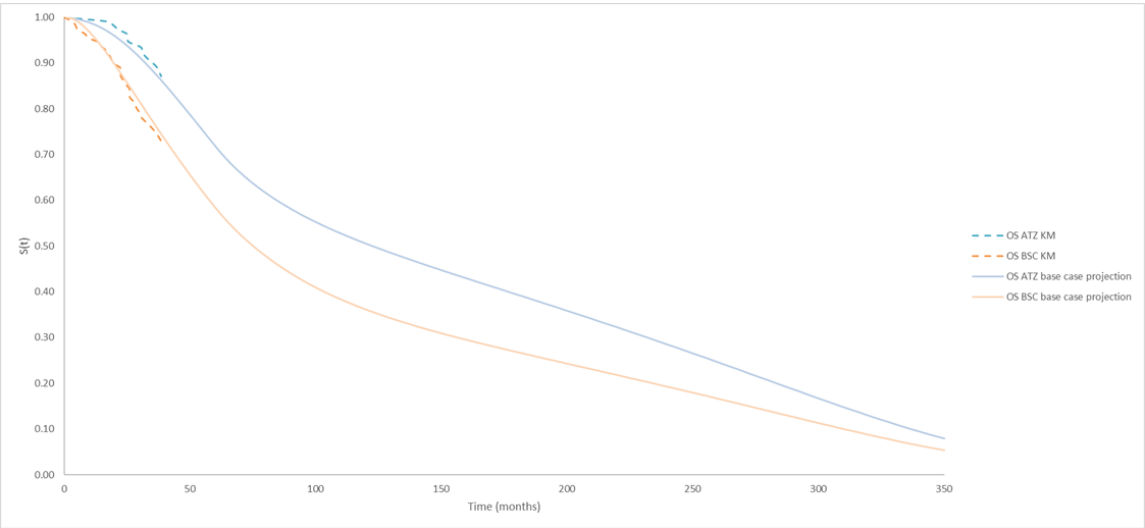


Figure 3: Adjusted survival plots (set to match atezolizumab arm of Impower010, Option 3 – ERG optimistic base case)

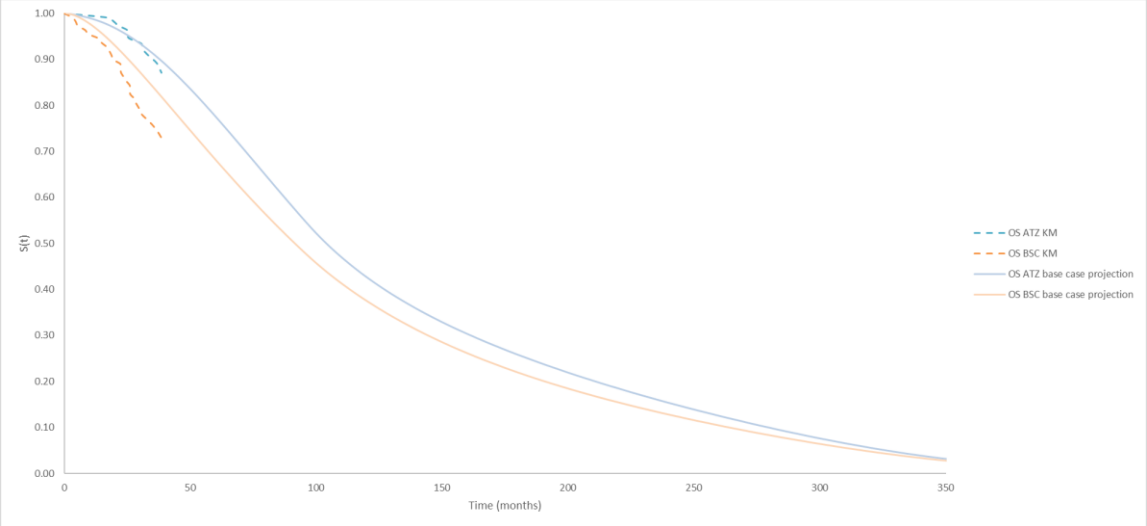


Figure 4: Survival plots (ERG pessimistic base case)

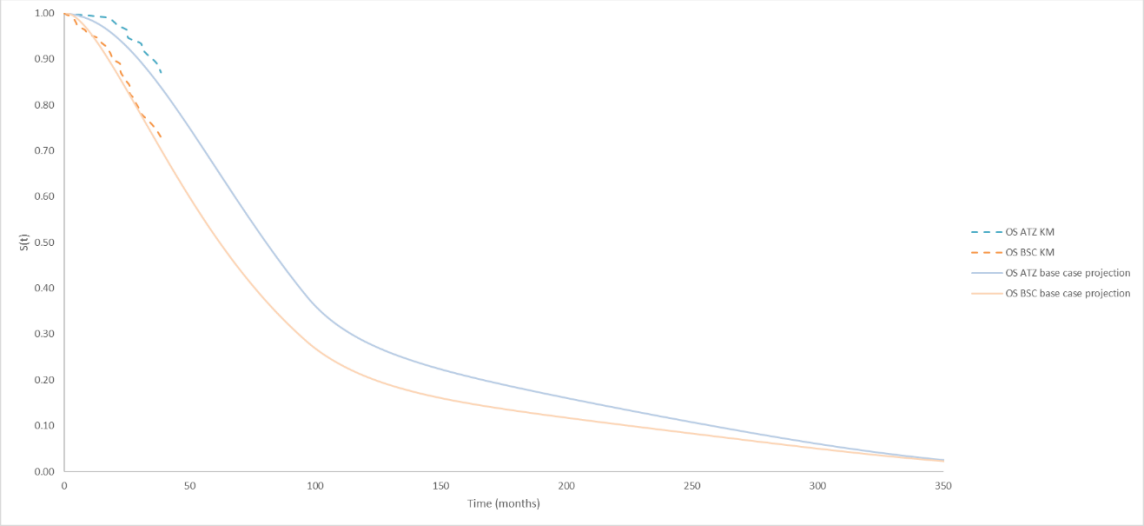


Figure 5: Adjusted survival plots (set to match best supportive care arm of Impower010, Option 4 – ERG pessimistic base case)

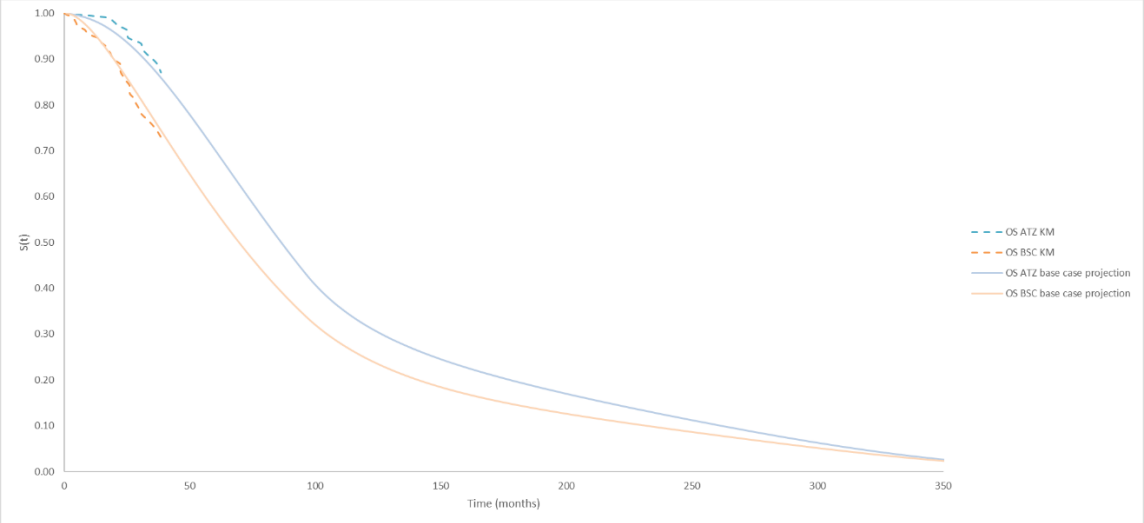
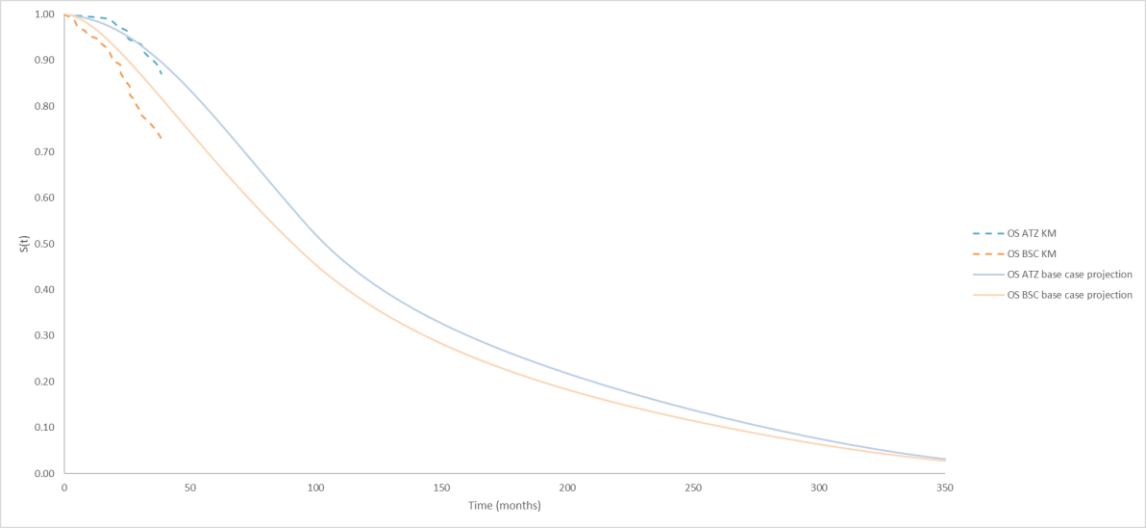


Figure 6: Adjusted survival plots (set to match atezolizumab arm of Impower010, Option 5 – ERG pessimistic base case)



2.2 Comparing metastatic health state QALY gains with previous NICE appraisals

Table 9 presents the QALY results from NICE appraisals for the treatment of metastatic and/or advanced NSCLC (e.g., TA531, TA705, TA584 and TA683). The QALY gains within the BSC arm of the ERG model were compared to the QALY gains of the immunotherapy arms of the NICE appraisals. All patients in the atezolizumab arm of the ERG model proceed to using metastatic chemotherapy treatment, therefore, the QALY gains from the atezolizumab arm were not compared with the immunotherapy arms of the NICE appraisals as this was judged to not be an appropriate comparison.

The results presented in Table 9 show that patients receiving immunotherapy (atezolizumab or pembrolizumab) in previous NICE submissions were estimated to incur QALY gains ranging from [redacted]. The QALY gains for patients in the metastatic health states from the BSC arm of the ERG model increase when the transition probabilities are adjusted (i.e. in Table 8 they increase from [redacted]). However, they do not fall within the published range of [redacted]. Total metastatic health state QALYs range from [redacted] when adjusting the transition probabilities as shown in Table 5 to Table 8. The lower QALY gains in the current model are a result of not all patients in the model transitioning to the metastatic health states (e.g. [redacted] of patients transition to metastatic treatment in the ERG optimistic base case). This is in comparison to the models from the previous NICE appraisals where all patients in the model begin in the progression-free survival health state with metastatic disease. This is illustrated in more detail in Section 2.3.

Table 9: QALYs from past Metastatic NSCLC Treatment NICE Appraisals

NICE appraisal # and indication	Source of health states for QALY	Company base case QALYs	ERG base case QALYs	Committee's preference
TA531 - Pembrolizumab for untreated PD-L1 positive metastatic non-small-cell lung cancer (3)	Reported directly by patients in the KEYNOTE-024 trial.	2.06 QALYs with pembrolizumab	2.03 QALYs with pembrolizumab	ERG base case preferred - "The ERG's approach of capping the utility value to the UK population norm is preferred"
TA705 - Atezolizumab monotherapy for untreated advanced non-small-cell lung cancer (4)	EQ-5D-3L measured directly from patients in IMpower110	[redacted] QALYs with atezolizumab [redacted] QALYs with pembrolizumab	[redacted] QALYs with atezolizumab [redacted] QALYs with pembrolizumab	No change from the company base case - The perspective and approach to discounting were in line with the NICE reference case.
TA584 - Atezolizumab in combination for treating advanced non-squamous non-small cell lung cancer (5)	IMpower110 EQ-5D individual patient data	[redacted] QALYs with Atezo + bevacizumab + CP	[redacted] QALYs with Atezo + bevacizumab + CP	No change from the company base case - "The committee concluded that there were no relevant additional benefits that had not been captured in the QALY calculations"
TA683 - Pembrolizumab with pemetrexed and platinum chemotherapy for untreated, metastatic, non-squamous non-small-cell lung cancer (6)	KEYNOTE-189 EQ-5D individual patient data	QALYs redacted	QALYs redacted. From the figure of the CE plane using ERG base case (Figure 14 of TA683 committee papers), it is approximately 1.6	ERG base case preferred - "The committee's preference from TA557 is maintained with progression based utilities with a decrement applied in the last year of life."

Since [redacted] and [redacted] of patients transition to metastatic treatment in the ERG optimistic and pessimistic base case model, respectively, the QALYs are underestimated for the metastatic

health states. A "back-of-the-envelope" calculation was carried out to test the scenario that 100% of patients transition to metastatic treatment using the ERG optimistic and pessimistic base case models (i.e., total QALYs for the metastatic health states when assuming all patients from the DFS and LRR [treated] move directly to 1L metastatic recurrence [Table 10]). Further alterations were made which increased the QALYs: removing discounting and including the transition probability adjustment factor using Option 2 (see Table 4). These alterations lead to increased QALYs as patients are spending more time in the DFS health state and gaining QALYs (total QALYs in the metastatic health state range [redacted] in the ERG optimistic and pessimistic base case model). Although it is still below the range of [redacted], this is expected as there is a proportion of DFS patients who do not receive treatment once progressed (locoregional recurrence health state) demonstrating that the cost-effectiveness model does not underestimate QALYs in the metastatic setting. The results are presented in Table 10.

Table 10: Scenario analyses looking at the total QALYs in the metastatic health states

ERG optimistic base case	
Total QALYs in metastatic health state	[redacted]
Total QALYs in metastatic health state + assuming 100% patients receive metastatic treatment*	[redacted]
Total QALYs in metastatic health state + assuming 100% patients receive metastatic treatment + remove discounting	[redacted]
Total QALYs in metastatic health state + assuming 100% patients receive metastatic treatment + remove discounting + using Option 2 for transition probability adjustment factor (see Table 4)	[redacted]
ERG pessimistic base case	
Total QALYs in metastatic health state	[redacted]
Total QALYs in metastatic health state + assuming 100% patients receive metastatic treatment*	[redacted]
Total QALY in metastatic health state + assuming 100% patients receive metastatic treatment + remove discounting	[redacted]
Total QALYs in metastatic health state + assuming 100% patients receive metastatic treatment + remove discounting + using Option 2 for transition probability adjustment factor (see Table 4)	[redacted]

*In the 'BSC' sheet, sum up columns AC, BC, and BG (i.e., the proportion moving to metastatic health states), then in 'Results Table' sheet, sum up rows H48, H50, H52, and H54 (i.e., the total metastatic QALYs in BSC arm) Divide total metastatic QALYs by the proportion moving to metastatic health states.

2.3 Converting the model to a metastatic model

A further scenario analysis was carried out to allow all patients to proceed to the 1L metastatic health state after cycle 1 in the cost-effectiveness model (i.e., crudely transform it to a metastatic model), the following changes were made:

- Cell *Z12* in the ATZ sheet set to 1
- Cell *X12* in the BSC sheet set to 1

- Cells *G35* and *G42* in the Efficacy Inputs sheet set to 100%,
- Cells *F132* and *F206* in the Efficacy Inputs sheet set to 100%

The resulting QALYs using the various adjustment options described in Table 4 are presented in Table 11. The QALYs from Option 1, Option 2, and Option 4 ([redacted] QALYs; see Table 4), which use alternative adjustment factors that ensures the transition probabilities equal a value that result in the modelled OS to equal the KM OS at 36 months for the BSC arm, fall within the range from the previous NICE appraisals ([redacted]). Options 3 and 5 in Table 11 appears to overestimate QALYs from the metastatic health states, however, as shown in Table 6 and Table 8, adjuvant atezolizumab remains cost-effective using these adjustment factors. This analysis suggests that the cost-effectiveness model is unlikely to underestimate QALYs in the metastatic health state.

Table 11: Total metastatic health state QALYs from the ERG base case model transformed to a metastatic model

Transition Probabilities Adjustment Factor	Total QALYs from Metastatic Health States - BSC Arm
Option 1	1.57
Option 2	2.20
Option 3	3.49
Option 4	2.06
Option 5	3.46

3. Cure assumptions

The use of Sonoda et al. 2019 to inform the cure assumptions was discussed at the first NICE committee meeting and the following concerns were raised:

- Whether the source was appropriate due to the location of the study (Japan) and generalisability to the UK
- 66.6% of the patient sample had Stage I disease (whereas the target population for the cost-effectiveness model is Stage II-IIIA).

The company has revisited the literature identified in the real-world evidence (RWE) structured review (provided in Appendix M of Submission Document B) and identified 5 potential sources (Table 12). Only Shin et al. 2021 (7) and Maeda et al. 2010a (8) report recurrence-free probability 5 years after complete resection by stage II and III.

Table 12: Literature identified from the RWE SLR on recurrence-free survival by stage

Source	Reasons for inclusion/exclusion
Shin et al. 2021 (7)	Include - reports recurrence-free probability beyond 5 years after complete resection by stage (graph provided without raw data)

Nomori et al. 2019 (9)	Exclude - reports for cT1 N0 M0 NSCLC (Stage IA) patients only
Koike et al. 2013 (10)	Exclude - reports for Stage IA patients only
Maeda et al. 2010a (8)	Include - reports recurrence-free probability beyond 5 years after complete resection by stage
Maeda et al. 2010b (11)	Exclude - reports for Stage IA patients only

Roche contacted a UK clinical expert[1] to discuss the appropriateness of the Maeda et al 2010a paper (8) and they commented on a few issues with using this paper:

- Asian population
- Population did not receive adjuvant chemotherapy (only resection)
- Staging system will be different but also it was before PET staging was used
- A high proportion (78%) of patients had Stage I disease
- Recurrences seem high for Stage I patients after 5 years (8.8%)

Similar critique could be applied to the Shin et al. 2021 paper (7), which has the following limitations:

- Asian population
- Population did not receive adjuvant chemotherapy (only resection)
- A high proportion (63.8%) of patients had Stage I disease
- Recurrences seem high for Stage I patients after 5 years

Although there are limitations with the Maeda et al. 2010a and Shin et al. 2021 papers, these report recurrence-free probability 5 years after complete resection by Stage II and III. Maeda et al. 2010a for Stage II patients is used in the post ACM1 company base case as the data are fully reported as opposed to Shin et al. 2021, where the data are estimated from the graphs. Maeda et al. 2010 replaces Sonoda et al. 2019 (12) as the base case because it reports the results by stage. Using Maeda et al. 2010a is conservative as patients received complete resection only but did not receive adjuvant chemotherapy, hence the data for Stage II patients rather than Stage III are used. Scenario analyses including the Shin et al. 2021 (7) and Maeda et al. 2010a (8) references are provided in Table 13.

[1] Telephone call with UK Clinical Oncologist 30th May 2022

Table 13: Scenario analyses of alternative cure assumptions

Cure assumption	ERG optimistic ICER (£)	Difference in ICER from ERG optimistic base case (£)	ERG pessimistic ICER (£)	Difference in ICER from ERG pessimistic base case (£)
ERG base case (BSC arm survival at 5 years – 52.2% and 51.6% in the ERG optimistic and pessimistic base cases respectively)	[redacted]	[redacted]	[redacted]	[redacted]
Shin et al. 2021 reports ~86% at 5 years (optimistic base case) and 8 years (pessimistic base case) for stage II disease patients	[redacted]	[redacted]	[redacted]	[redacted]
Shin et al. 2021 reports ~85% at 5 years (optimistic base case) and 8 years (pessimistic base case) for stage III disease patients	[redacted]	[redacted]	[redacted]	[redacted]
Maeda et al. 2010a reports 85.6% at 5 years (optimistic base case) and 8 years (pessimistic base case) for Stage II disease patients (8)	[redacted]	[redacted]	[redacted]	[redacted]
Maeda et al. 2010a reports 77.1% at 5 years (optimistic base case) and 8 years (pessimistic base case) for Stage III disease patients - *new company base case (as described in Section 7)* (8)	[redacted]	[redacted]	[redacted]	[redacted]

The committee requested to see further explorations around the cure assumption timing and noted the scenario provided for the TA761 osimertinib appraisal, which includes differential cure timepoints (8 years in intervention arm and 5 years in best supportive care arm). The committee acknowledged that the analysis for TA761 may not be transferable for this appraisal, given that osimertinib and atezolizumab are biologically different molecules.

In TA761, the final appraisal document (FAD) stated that "*for the active monitoring arm of the model, a 5-year cure timepoint may be appropriate, but a potential cure timepoint for the intervention arm is uncertain*". Therefore, a 5-year cure timepoint for the best supportive care (BSC) arm was used in the scenario analysis. Clinical expert advice[2] was sought regarding the 8-year cure timepoint for osimertinib, and their opinion was that it was not appropriate to use an 8-year timepoint for atezolizumab. It is important to note as well that unlike osimertinib, adjuvant atezolizumab treatment led to treatment effect observed beyond 16 cycles of treatment in the available IMpower010 trial data (see Section 6).

[2] Telephone call with UK Clinical Oncologist 30th May 2022

The logic in the TA761 appraisal of using an 8-year cure timepoint was combining a 5-year cure timepoint in the active monitoring group plus a 3-year osimertinib treatment period. By the same logic, a 6-year cure timepoint (5-year cure timepoint in the active monitoring group plus a 1-year atezolizumab treatment period) can be used for atezolizumab. However, for transparency, scenarios for 6-, 7-, and 8-year cure assumptions in the atezolizumab arm are presented in Table 14.

Table 14: Scenario analyses of alternative cure timepoints

Cure assumption	ERG optimistic ICER (£)	Difference in ICER from ERG optimistic base case (£)	ERG pessimistic ICER (£)	Difference in ICER from ERG pessimistic base case (£)
Differential cure timepoints - 6 years in intervention arm and 5 years in best supportive care arm*	[redacted]	[redacted]	[redacted]	[redacted]
Differential cure timepoints – 7 years in intervention arm and 5 years in best supportive care arm*	[redacted]	[redacted]	[redacted]	[redacted]
Differential cure timepoints - 8 years in intervention arm and 5 years in best supportive care arm*	[redacted]	[redacted]	[redacted]	[redacted]

*For this scenario, cell O16 in the ERG sheet should be set to "No" so that the cure timepoint is 5 years for the BSC arm, then cell O56 can be adjusted with alternative time periods (i.e., 6, 7, 8 years)

4. Alternative extrapolations

The committee requested sensitivity analyses and commentary on the use of alternative extrapolations of disease-free survival data and the impact on cost-effectiveness as there was no clearly best fitting model. Within the following section, the company provide justification for the DFS extrapolation using the company post ACM1 base case model (i.e. the ERG-corrected company base case model with additional alterations as described in Section 7), with consideration of the log-cumulative hazard plot, statistical fit, visual fit, and relevant literature. This is followed by sensitivity analyses showing the impact of alternative extrapolations using the ERG optimistic and pessimistic base case.

4.1 DFS extrapolation

4.1.1 Proportional hazards assumption

The proportional hazards assumption requires that the hazards of a DFS event are proportional over time across the atezolizumab and BSC arms (13). The log cumulative

hazard plot indicated that the curves separated and then converged (the curves did cross over early on, but this was not concerning due to the x-axis scale), and therefore, the proportional hazards assumption did not hold (as shown in Figure 7). Therefore, parametric distributions were fitted separately for the intervention and control arm, with seven distributions fitted to extrapolate DFS beyond the observed period (Exponential, Weibull, Log-Logistic, Log-Normal, Gompertz, Generalised Gamma and Gamma).

Figure 7: Log-cumulative hazard plot (IMpower010, DFS, Stage II–IIIA, PD-L1 ≥50%, by arm, 21 Jan 2021 data-cut)

NB: log(-log(survival)= log-cumulative hazard

4.1.2 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 AIC and BIC. A limitation of 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 15 shows that the performance of the different distributions depends on whether the AIC or BIC is prioritised and that ranking differed between the treatment arms. Table 15 also shows that there was no clearly best-fitting distribution statistically.

Table 15: AIC and BIC across parametric models (IMpower010, DFS, Stage II–IIIA, PD-L1 ≥50%, by arm, 21 Jan 2021 data-cut)

Distribution	**Atezolizumab arm**				**BSC arm**			
	AIC (Rank)		**BIC (Rank)**		**AIC (Rank)**		**BIC (Rank)**	
Exponential	325.30	7	328.10	1	514.70	5	517.50	3
Weibull	322.80	1	328.30	2	516.40	6	521.90	6
Log-logistic	323.30	4	328.80	5	513.90	3	519.40	4
Log-normal	324.40	5	329.90	6	510.30	2	515.80	1
Gompertz	322.80	1	328.30	2	514.60	4	520.10	5
Generalised Gamma	324.60	6	332.80	7	508.80	1	517.00	2
Gamma	323.10	3	328.50	4	516.60	7	522.10	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.

4.1.3 Visual fit

Figure 8 and Figure 9 also appear to show that the accuracy of the different parametric distributions in representing the observed data was comparable. This 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 8: Fit of estimated DFS to Kaplan-Meier plot across parametric models (IMpower010, DFS, Stage II–IIIA, PD-L1 ≥50%, atezolizumab arm, 21 Jan 2021 data-cut)

Figure 9: Fit of estimated DFS to Kaplan-Meier plot across parametric models (IMpower010, DFS, Stage II–IIIA, PD-L1 ≥50%, BSC arm, 21 Jan 2021 data-cut)

Figure 10 and Figure 11 present a comparison of the extrapolation of DFS across the different parametric models beyond the follow-up of the trial (trial median follow-up: 34.2 months).

Figure 10: Extrapolation of DFS across Parametric Models (IMpower010, DFS, Stage II–IIIA, PD-L1 ≥50%, atezolizumab arm, 21 Jan 2021 data-cut)

Figure 11: Extrapolation of DFS across parametric models (IMpower010, DFS, Stage II–IIIA, PD-L1 ≥50%, BSC arm, 21 Jan 2021 data-cut)

DFS events at different time points were compared; Table 16 presents the proportion of patients who did not experience a DFS event at 5, 10, 20, and 30 years according to the parametric extrapolations of the Kaplan-Meier data. However, as these parametric curves only used the available trial data, they are not representative of the benefits of adjuvant chemotherapy and underestimate DFS, as observed in the literature (described in section 4.1.4).

Table 16: Expected proportion (%) patients who are event-free at 10, 20, and 30 years after treatment initiation – BSC arm

Distribution	Proportion (%) patients event-free after treatment initiation			
	5 years	10 Years	20 Years	30 Years
Exponential	[redacted]	[redacted]	[redacted]	[redacted]
Weibull	[redacted]	[redacted]	[redacted]	[redacted]
Log-logistic	[redacted]	[redacted]	[redacted]	[redacted]
Log-normal	[redacted]	[redacted]	[redacted]	[redacted]
Gompertz	[redacted]	[redacted]	[redacted]	[redacted]
Generalised-Gamma	[redacted]	[redacted]	[redacted]	[redacted]
Gamma	[redacted]	[redacted]	[redacted]	[redacted]

NB: Proportions from the 'BSC' Sheet, for example, I71 for estimated proportion at 5 years using the Exponential

4.1.4 Literature and expert clinical opinion

As discussed in Section B.3.3.3.5 of Document B. through focused literature searching, a handful of studies reporting data on DFS and OS in the early NSCLC population were identified: Wood et al. 2021 (14), Chi et al. 2019 (15), Pignon et al. 2008 (16), and Non-Small Cell Lung Cancer Collaborative Group 1995 (17). The literature were presented to clinical oncologists during 1:1 interviews (three clinical oncologists consulted in August 2021) and overall, they agreed with estimates from Pignon et al. 2008 for the BSC arm: a five-year DFS of approximately 40% and a five-year OS of approximately 55%. Pignon et al. 2008 is a pooled analysis of large trials of cisplatin-based adjuvant chemotherapy in patients with NSCLC (16).

4.1.5 Adjusting the DFS curves

During the appraisal committee meeting, uncertainty was raised regarding the methodology used to adjust the DFS curves, however, the resulting estimations from adjusting the DFS curves are included here to justify the company base case extrapolation. The methodology is fully described in Section B.3.3.4 of Document B, however, a brief summary of the adjustments applied are as follows:

- Cure: The proportion of patients who are not at risk of a DFS event linearly increases from year three and reaches a maximum of 85.6% at year six (replacing the 91.5% cure assumption from Sonoda et al. 2019 (12) with Maeda et al. 2010a (8)).
- Mortality: The model does not allow the probability of an uncured patient dying to be smaller than that of an individual from the general population. The model adjusted

the probability of death of these patients with a standardised mortality ratio of 1.25 to account for excess mortality faced by these lung cancer survivors.

- Treatment effect: The model assumes that the treatment effect of atezolizumab ceases at year five or the same year at which the proportion of cured patients reaches its maximum.

The estimated proportions following the above adjustments are presented in Table 17.

Table 17: Expected proportion of patients event-free at 5-30 years after treatment initiation across parametric models (by arm)

Distribution	5 years		10 Years		20 Years		30 Years	
	Atezolizumab	BSC	Atezolizumab	BSC	Atezolizumab	BSC	Atezolizumab	BSC
Exponential	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Weibull	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Log-normal	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Generalised Gamma	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Log-logistic	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Gompertz	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Gamma	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

NB: Proportions from the 'BSC' and 'ATZ' Sheets, for example, AB71 in the 'ATZ' sheet for estimated proportion at 5 years using the Log-Normal is 62.5%

Using Pignon et al. 2008 (16) and previous UK clinical opinion (see Section B.3.3.4.1 of Document B), the Exponential, Weibull, and Gamma distributions appear to underestimate the proportion of BSC patients at 5 years onwards who are in the DFS health state. The Generalised Gamma and Gompertz appear to overestimate the proportion at 5 years. The Log-logistic and Log-Normal distributions produce DFS estimates for BSC that are closest to the 5-year value of 40% reported by Pignon et al. 2008 (16).

4.1.6 Overall survival

Table 18 presents the proportion of patients that the model estimated to be alive at 5, 10, 20 and 30 years for both the atezolizumab and BSC arms when each of the distributions were used to extrapolate DFS. A UK clinical oncologist commented that the BSC curves which aligned with the lower estimates from the literature were more reflective of clinical reality, i.e. approximately 50% for 5-years OS and approximately 30% for 10-year OS. From Table 18, the Generalised Gamma and Gompertz appear to overestimate OS, with a 5-year OS of [redacted] and [redacted] and a 10-year OS of [redacted] and [redacted], respectively. The magnitude of effect is further observed at 20 years with a greater relative difference to the estimates produced with the other distributions.

Table 18: Expected proportion of patients alive at 5–30 years after treatment initiation across parametric models (by arm)

Distribution	5 years		10 Years		20 Years		30 Years	
	Atezolizumab	BSC	Atezolizumab	BSC	Atezolizumab	BSC	Atezolizumab	BSC
Exponential	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Weibull	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Log-normal	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Generalised Gamma	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Log-logistic	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Gompertz	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Gamma	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

4.1.7 Company base case extrapolation

Based on the assessment above within the BSC arm, the Generalised Gamma and Gompertz overestimate the proportion event-free (DFS) and alive (OS) at 5 years. As the Log-logistic and Log-normal distributions produce DFS estimates for BSC that are closest to the 5-year value of 40% reported by Pignon et al. 2008, these are the most plausible extrapolations for BSC DFS extrapolation. The distribution used for the base case in both the atezolizumab and BSC arms was Log-normal, based upon a lower DFS AIC and BIC rank than the Log-Logistic distribution within the BSC arm (a minimal difference in AIC and BIC estimates within the atezolizumab treatment group). This is a change to the previous

company base case from using the Log-Logistic extrapolation and results from the changes made to the company base case model as detailed in Section 7.

This gives a 5-year OS estimate for the BSC arm in the model of [redacted]%, which is close to the clinical opinion of 50%. These results using the Log-normal distribution and curve adjustments were within the clinically plausible DFS ranges ([redacted]% 5-year DFS in the BSC arm) and therefore the model appears to align with the available published data and UK clinical expert validation.

4.2 Sensitivity analyses using alternative extrapolations in the ERG base case model

The ERG's optimistic base case used the Log-logistic and the pessimistic base case used the Weibull models as an alternative to the company's previous base case of Log-Logistic.

Using ERG's optimistic and pessimistic base case, sensitivity analyses using alternative extrapolations are provided in Table 19 and Table 20, respectively.

*Table 19: Sensitivity analyses of different extrapolations using the ERG **optimistic** base case*

Parameter	Atezolizumab			Best Supportive Care			ATZ vs. BSC	
	Life Years	QALYS	Costs	Life Years	QALYS	Costs	Inc. costs per LY gained	Inc. costs per QALY gained
Base case (Log-Logistic)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Exponential	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Weibull	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Log-normal	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Generalised Gamma	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Gompertz	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Gamma	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

*Table 20: Sensitivity analyses of different extrapolations using the ERG **pessimistic** base case*

Parameter	Atezolizumab			Best Supportive Care			ATZ vs. BSC	
	Life Years	QALYS	Costs	Life Years	QALYS	Costs	Inc. costs per LY gained	Inc. costs per QALY gained
Base case (Weibull)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Exponential	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Log-normal	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Generalised Gamma	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Log-logistic	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Gompertz	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Gamma	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

5. Justification of external resources for transitions in the model

The committee requested further justification or additional searches to support the external sources used for the transitions in the model. Nakamichi et al. 2017 and Wong et al. 2016 were identified via the RWE structured literature review (provided in Appendix M of Submission Document B).

An additional PubMed search was carried out on 25th May 2022 to inform the transition probabilities for patients transitioning from locoregional recurrence health state to death (patients who are treated with palliative intent or are not treated). The search strategy and results are provided in Appendix B. Two relevant papers were identified from the literature review (Foo et al. 2005 (18) and Kruser et al. 2014 (19)) and the model was adapted to allow the incorporation of both in the cost-effectiveness model. Kruser et al. 2014 remains the company base case because it is a more recent publication.

Table 21: Literature source for transition probabilities and justification of the source

Transition Probability	Source	Sample size	Justification
Locoregional recurrence health state to 1L metastatic recurrence health state and death (patients who are treated with curative intent)	Nakamichi et al. 2017	74	Identified from the RWE structured review (see Appendix M of Submission Document B). Only the Nakamichi et al. 2017 reported median months for chemotherapy and radiotherapy separately (Table 13 of RWE structured review 1st June 2021) and patient characteristics are comparable to patients in IMpower010 (see Appendix A).
Locoregional recurrence health state to death (patients who are treated with palliative intent or are not treated)	Kruser et al. 2014	37	Kruser et al. 2014 was identified by a focussed literature search in PubMed (see Appendix B). The other studies were excluded due to small sample sizes or uncertainty about the patient population (i.e. treated with radical intent or palliative intent). Foo et al. 2005 is included in the model as an alternative source and results in an ERG optimistic ICER of [redacted] and an ERG pessimistic ICER of [redacted]. Although patients can experience metastatic recurrence before death, the transition probability to death from Kruser et al. 2014 is assumed to capture this as no data have been identified to inform transition to disease progression.
1L/2L metastatic recurrence health state to death (patients who are not treated)	Wong et al. 2016	379	Identified from the RWE structured review (see Appendix M of Submission Document B), no other literature were identified in the search

6. Updated overall survival trial data

An interim OS analysis was conducted, with a clinical cut-off date (CCOD) of [redacted], providing OS data with an additional 15 months of follow up (the data are provided in the cost-effectiveness model within the 'Updated OS Kaplan-Meier' Sheet). The Kaplan-Meier curve (Figure 12) shows [redacted] in the PD-L1≥50% Stage II-IIIA population.

Figure 12: Kaplan-Meier curve of interim OS in the PD-L1≥50% Stage II-IIIA population, clinical data cut-off: [redacted] (Data on File)

[redacted]

NE; not evaluable

The previously demonstrated OS trend in favour of atezolizumab over BSC at CCOD 21st Jan 2021 (HR 0.37, 95% CI 0.18, 0.74),

[redacted]
22[redacted] Additionally
[redacted] in the PD-L1≥50% Stage II-IIIA population (Table 22).

[redacted] in the PD-L1≥50% Stage II-IIIA NSCLC population.

Table 22: Interim OS analysis for Stage II-IIIA PD-L1≥50% population, clinical data cut-off: [redacted] (Data on File)

	Atezolizumab n=115	BSC n=114
Patients with OS event	[redacted]	[redacted]
Median OS, months	[redacted]	[redacted]
HR (95% CI)	[redacted]	
p-value	[redacted]	

BSC; Best supportive care, HR; Hazard ratio, NE; not evaluable.

The company have incorporated the latest OS data into the post-ACM1 company base case model (see Section 7) and have provided a summary graph showing the updated IMpower010 DFS Stage II–IIIA PD-L1+ OS data (data cut-off date: [redacted]) and the DFS KM data (data cut-off date: 21st Jan 2021), with the respective unadjusted log-normal model fit to each KM curve, and the post-ACM1 company base case projection for each endpoint (Figure 13).

The underestimation of the OS KM data is observed here and this is discussed in Section 2. This cost-effectiveness model is modelling for the adjuvant setting rather than the metastatic setting and not all patients progress to the metastatic health states. When an adjustment factor is implemented to reduce the transition probabilities applied to the post-DFS health states, this leads to an increase in OS and QALYs in the post-DFS health states for both the atezolizumab and BSC arms (Figure 15 and Figure 16). When including these adjustment factors to the ERG-preferred optimistic and pessimistic base case, the ICERs decrease and atezolizumab remains cost-effective at a threshold of £20,000 in all scenarios.

Figure 13: Summary of DFS and OS KM data with unadjusted log-normal model fit plus the post-ACM1 company base case projections (both arms)

[redacted]

Figure 14: Survival plots (Post ACM1 company base case)

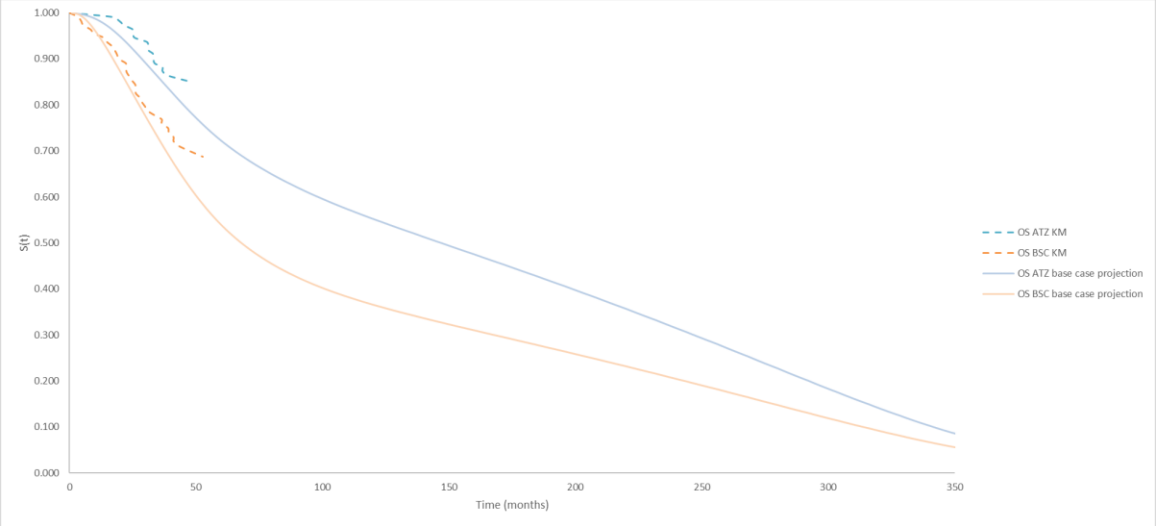


Figure 15: Adjusted survival plots (set to match best supportive care arm of IMpower010 – Post ACM1 company base case)

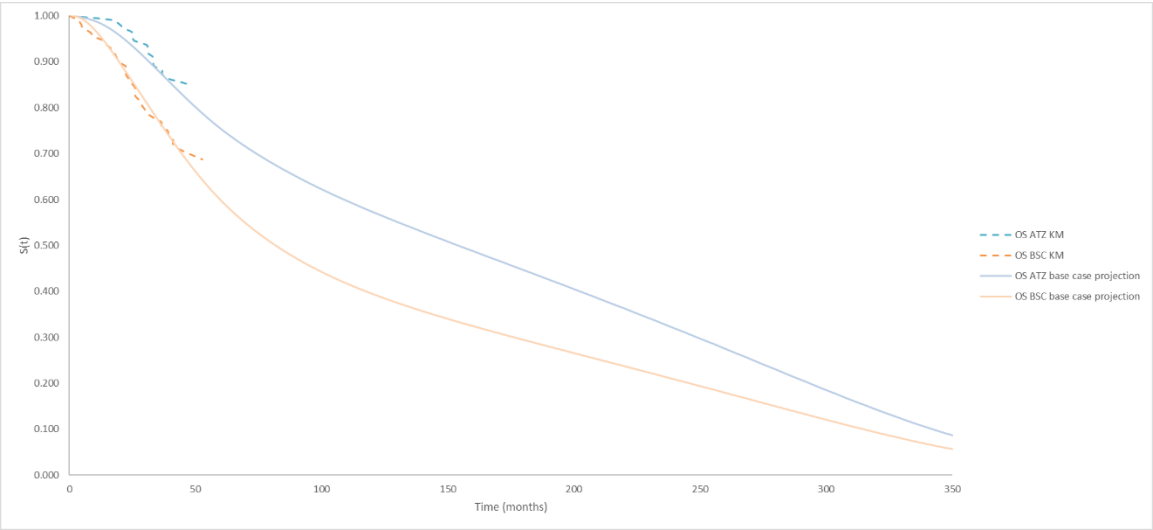
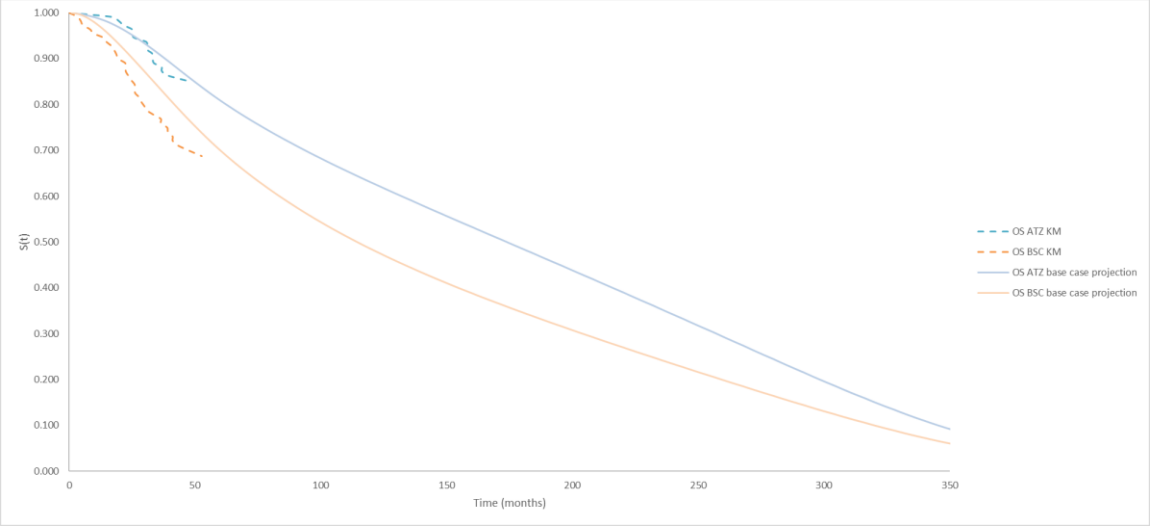


Figure 16: Adjusted survival plots (set to match atezolizumab arm of IMpower010 – Post ACM1 company base case)



7. Revised company base case results

As detailed above, a few changes have been made to the ERG-corrected company base case(and renames post-ACM1 company base case), these are:

- Including retreatment 12 months after treatment discontinuation (Section 1)
- Using Maeda et al 2010a for recurrence-free probability beyond 5 years after complete resection in Stage II patients (Section 3)
- Using the Log-Normal extrapolation with cure adjustments for DFS modelling (Section 4)
- The trial data to inform recurrence type is pooled across arms (discussed during first committee meeting)
- All patients assumed to incur terminal care costs arms (discussed during first committee meeting)
- Removal of double administration costing for combination treatments (discussed during first committee meeting)

The deterministic and probabilistic post ACM1 company base case results are presented in Table 23, Table 24, Table 25, and Table 26. PSA results were run using 3,000 iterations to ensure the results had converged. The incremental cost-effectiveness planes are presented in Figure 17 and Figure 18.

Table 23: Company post ACM1 base case cost effectiveness results – Stage II–IIIA population – list price

Technologies	Total costs	Total LYG	Total QALYs	Incremental costs	Incremental LYG	Incremental QALYs	ICER incremental (£/QALY)
Atezolizumab	[redacted]	10.17	[redacted]	[redacted]	2.49	[redacted]	£20,392
BSC	[redacted]	7.68	[redacted]				

Table 24: Company post ACM1 base case cost effectiveness results – Stage II–IIIA population – PAS price

Technologies	Total costs	Total LYG	Total QALYs	Incremental costs	Incremental LYG	Incremental QALYs	ICER incremental (£/QALY)
Atezolizumab	[redacted]	10.17	[redacted]	[redacted]	2.49	[redacted]	[redacted]
BSC	[redacted]	7.68	[redacted]				

Table 25: PSA results compared to Company post ACM1 base-case (list price)

	Costs		QALYs		ICERs	
	Deterministic base case	**PSA**	**Deterministic base case**	**PSA**	**Deterministic base case**	**PSA**
Stage II-IIIA population						
Atezolizumab	[redacted]	[redacted]	[redacted]	[redacted]	£20,392	£20,862
BSC	[redacted]	[redacted]	[redacted]	[redacted]	-	-

Table 26: PSA results compared to Company post ACM1 base-case (with PAS)

	Costs		QALYs		ICERs	
	Deterministic base case	**PSA**	**Deterministic base case**	**PSA**	**Deterministic base case**	**PSA**
Stage II-IIIA population						
Atezolizumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
BSC	[redacted]	[redacted]	[redacted]	[redacted]	-	-

Figure 17: Incremental cost effectiveness plane – atezolizumab vs BSC in Stage II–IIIA NSCLC, list price

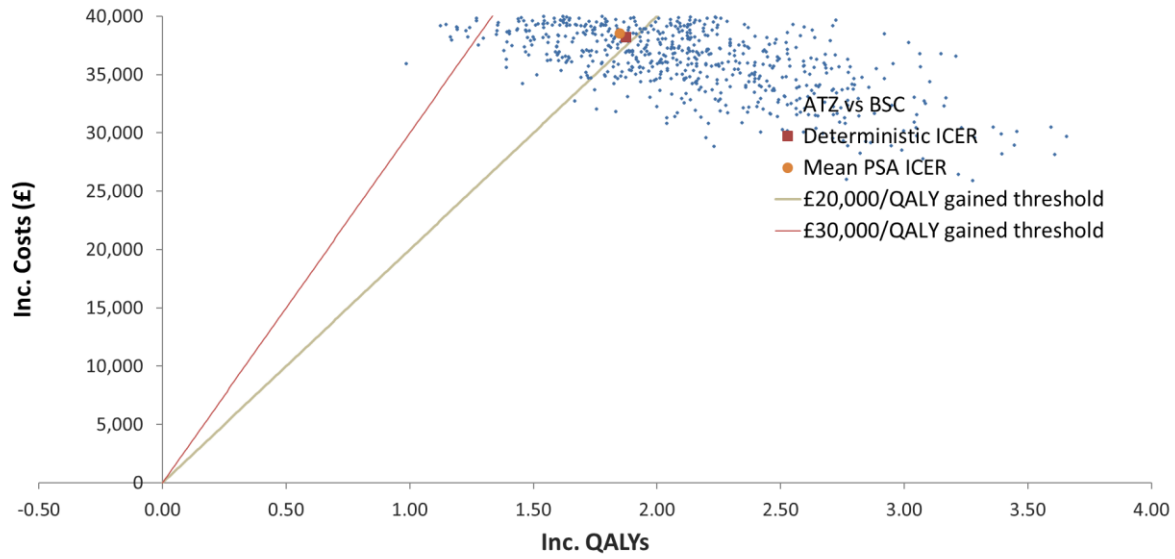


Figure 18: Incremental cost effectiveness plane – atezolizumab vs BSC in Stage II–IIIA NSCLC, PAS price

[redacted]

8. Summary

The company have addressed the requests from the committee in this response. In all but one of the presented scenarios, the ICER remains below the cost-effectiveness threshold of £20,000. The only scenario that exceeded the cost-effectiveness threshold was when using the 5-year cure assumption in the BSC arm and 8-year cure assumption in the ATZ arm, however, this is not a clinically valid scenario as confirmed by a UK clinical expert (see Section 3).

In these additional analyses, the company have explored adjusting transition probabilities and the QALYs to address the key concern that the post-DFS outcomes were being underestimated. Sensitivity analyses show that the underestimation stems from only a proportion of patients in the DFS health state (i.e., 54% in the ERG optimistic model) will receive metastatic treatment, whereas in the previous metastatic NSCLC appraisals, 100% patients will receive metastatic treatment.

Further, the updated OS results demonstrate a [redacted] in the PD-L1≥50% Stage II-IIIA NSCLC population.

The analyses presented further support the view that atezolizumab is highly likely to be a cost-effective use of NHS resources.

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Appendix A - Patient characteristics from Nakamichi et al. 2017

Table 27: Patient characteristics (20)

	Total (n=74) **n (%)**
Age, y	
Median (range)	66 (41-85)
Performance status	
0	12 (16)
1	62 (84)
Gender	
Male	57 (77)
Female	17 (23)
Histology	
Adenocarcinoma	49 (66)
Squamous	25 (34)
Pathologic stage	
I	21 (28)
II	18 (24)
III	35 (47)
Adjuvant therapy	8 (11)
Time to recurrence, mo	
Median (range)	20.7 (2.9-157.4)
Recurrence site	
T factor	
0	53 (72)
1-2	21 (28)
N factor	
0-2	51 (69)
3	23 (31)

Appendix B - Focussed Literature Search

A PubMed search was carried out 25th May 2022, to identify studies that report the outcomes of palliative treatment for patients with locoregional recurrence. The search strategy used for the focussed literature search is presented in Table 28. The studies eligible for full-text review are presented in Table 29.

With the exception of Zimmermann et al. (2003) (21), which was a research article, five studies were identified reporting outpatients for patients treated with radiotherapy (22-26). Jeremic et al. 1999 and Tada et al. 2005 were excluded due to the small sample sizes (19 and 14 patients respectively) (23, 26). Kagami et al. 1998 was also excluded due to the uncertainty associated with the patient population (24). Kruser et al. 2014 was considered the most appropriate source to inform the transition probability for patients with locoregional recurrence receiving palliative treatment because it was published more recently than Foo et al 2005 (25).

Table 28: Search strategy using PubMed

Number	Concept	Search Strategy	No. of hits (30th March 2021)
1	Disease search terms	("carcinoma, non small cell lung"[MeSH Terms] OR "carcinoma, non small cell lung"[MeSH Terms] OR "non small cell lung cancer"[Title/Abstract] OR "NSCLC"[Title/Abstract] OR "cancer*"[Title/Abstract] OR "carcinoma*"[Title/Abstract] OR "adenocarcinoma*"[Title/Abstract] OR ("umour*"[Title/Abstract] OR "tumor*"[Title/Abstract] OR "neoplasm*"[Title/Abstract] OR "malignan*"[Title/Abstract] OR "metasta*"[Title/Abstract])) AND "lung*"[Title/Abstract] AND ("non-small"[Title/Abstract] OR "non-small"[Title/Abstract])	77,526
2	Filters	#1 AND ((humans[Filter]) AND (english[Filter]))	57,143
3	Health state search term	("locoregional*"[All Fields]) AND ((humans[Filter]) AND (english[Filter]))	17,322
4	Search results	#2 AND #3	676
Screening and final included studies		Export to Endnote and remove duplicates	675
		Screen title/abstract for locoregional recurrence outcomes in NSCLC	21
		Screen full text	6

Table 29: Studies for full-text review (n=6)

Authors	Year	Title	Results	Sample size	Exclusion reason
K. Foo; V. Gebski; R. Yeghiaian-Alvandi; F. Foroudi; B. Cakir	2005	Outcome following radiotherapy for loco-regionally recurrent non-small cell lung cancer	Median survival 10.5 months	39 patients	-
B. Jeremic; Y. Shibamoto; B. Milicic; S. Milisavljevic; N. Nikolic; A. Dagovic; J. Aleksandrovic; G. Radosavljevic-Asic	1999	External beam radiation therapy alone for loco-regional recurrence of non-small-cell lung cancer after complete resection	Median survival 7 months	19 patients	Small sample size
Y. Kagami; M. Nishio; N. Narimatsu; M. Mjoujin; T. Sakurai; M. Hareyama; A. Saito	1998	Radiotherapy for locoregional recurrent tumors after resection of non-small cell lung cancer	Median survival 14 months	32 patients	Not clear what patients they focus on (i.e. those who treat with radical intent or with palliative intent)
T. J. Kruser; B. P. McCabe; M. P. Mehta; D. Khuntia; T. C. Campbell; H. M. Geye; G. M. Cannon	2014	Reirradiation for locoregionally recurrent lung cancer: outcomes in small cell and non-small cell lung carcinoma	Median survival 5.1 months	37 patients	-
T. Tada; H. Fukuda; K. Matsui; T. Hirashima; M. Hosono; Y. Takada; Y. Inoue	2005	Non-small-cell lung cancer: reirradiation for loco-regional relapse previously treated with radiation therapy	Not palliative treatment	14 patients	Small sample size
F. B. Zimmermann; M. Molls; B. Jeremic	2003	Treatment of recurrent disease in lung cancer	-	-	A review article

Atezolizumab for adjuvant treatment of resected non-small-cell lung cancer [ID3852]:

A Single Technology Appraisal

Addendum #1

ERG critique of company's additional analyses post-ACM1

June 2022

Produced by	Peninsula Technology Assessment Group (PenTAG) University of Exeter Medical School South Cloisters St Luke's Campus Heavitree Road Exeter EX1 2LU
Linked to ERG report reference	Barnish MS, Sullivan W, Matthews J, Day C, Robinson S, Long L, Philips Z, Dorey N, Crathorne L. Atezolizumab for adjuvant treatment of resected non-small-cell lung cancer [ID3852]: A Single Technology Appraisal. Peninsula Technology Assessment Group (PenTAG), 2022.
Correspondence to	**Dr Maxwell Barnish** 3.09 South Cloisters, St Luke's Campus, Heavitree Road, Exeter, EX1 2LU; m.s.barnish@exeter.ac.uk
Date completed	28 June 2022
Source of funding	This report was commissioned by the NIHR Systematic Reviews Programme as project number 13/52/64.
Declared competing interests of the authors	None declared.
Rider on responsibility for document	The views expressed in this report are those of the authors and not necessarily those of the NIHR HTA Programme. Any errors are the responsibility of the authors.

1. INTRODUCTION

Following the first Appraisal Committee meeting (ACM) for this topic on 5 May 2022, the committee requested further analyses and data from the company to aid its deliberations. These requests were communicated in writing to the company, under the subheadings “Primary analysis”, “Sensitivity analyses” and “Additional considerations for the cost-effectiveness analyses”. In this document, the ERG describes and critiques the extent to which the company’s post-ACM evidence submission has addressed the committee’s requests, and attempts to summarise the evidence and analyses requested by the committee, where possible.

In focusing on additional analyses that address the committee’s post-ACM written request, this short report does not comment on every aspect of the company’s recent evidence submission. For example, the company presents a revised company base case that deviates from the ERG preferred analyses in many respects. From the wording of the committee’s post-ACM request, the ERG does not expect this to be of interest to the committee, and it is not discussed further here.

The company submitted an updated version of the cost-effectiveness model alongside a written account of their post-ACM analyses. This included helpful commentary on where and how model changes had been made, but as code had been overwritten, it was not possible to easily recreate latest ERG results. Primarily for this reason, the ERG chose to incorporate the company’s latest model changes as options within the latest ERG model.

The remainder of this report is structured as follows. Section 2 addresses the company’s response to the committee’s “Primary analysis” requests; Section 3 addresses the company’s response to the committee’s “Sensitivity analyses” requests; Section 0 addresses the extent to which the company has addresses the committee’s additional considerations. Section 0 contains references.

2. PRIMARY ANALYSIS

The committee's "Primary analysis" request asked for an updated analysis to include assumptions in the ERG's optimistic and alternative preferred analyses and to assume immunotherapy retreatment in line with comments from the Cancer Drugs Fund (CDF) clinical lead in ACM1. The committee noted that an additional key aspect of the primary analysis request was improvement to the approach to model post-disease-free-survival (post-DFS) health states, to better fit NICE appraisal precedent (i.e., that post-DFS outcomes of the model offer a better fit to the outcomes reported from previous NICE appraisals for metastatic NSCLC; specifically, Technology Appraisals (TAs) 531, 705, 584 and 683), and better fit the observed IMpower010 PD-L1 ≥50% Stage II–IIIA overall survival (OS) Kaplan-Meier (KM) data.

Table 1 contains the ERG's view of key results addressing the committee's primary analysis requests, drawing on additional evidence provided by the company where possible. Analyses 1a (in **bold)** in Table 1 are the ERG's preferred analyses at ACM1, with (immunotherapy) retreatment included as described in Section 6.2.15 of the ERG report. This approach assumes first-line metastatic recurrence treatment assumptions are equivalent across arms, and does not explicitly attempt to capture time since discontinuation to inform retreatment probability.

Table 1: Key results addressing primary analysis requests, atezolizumab PAS only

Analyses	ICER, using ERG's optimistic assumptions	ICER, using ERG's alternative assumptions
1a ERG-preferred analyses, ACM1, with retreatment	[redacted]	[redacted]
1b Scenario using company's retreatment approach	[redacted]	[redacted]
1ci Scenario using company's adjustments to post-DFS transitions to hit IMpower010 atezolizumab OS KM at 36 months	[redacted]	[redacted]
1cii Scenario using company's adjustments to post-DFS transitions to hit IMpower010 BSC OS KM at 36 months	[redacted]	[redacted]
Company model adjustments to improve modelling of post disease-free survival, "to ensure they [predicted outcomes] better reflect the expected outcomes of previous NICE Technology Appraisals in the metastatic treatment setting"	None provided	None provided

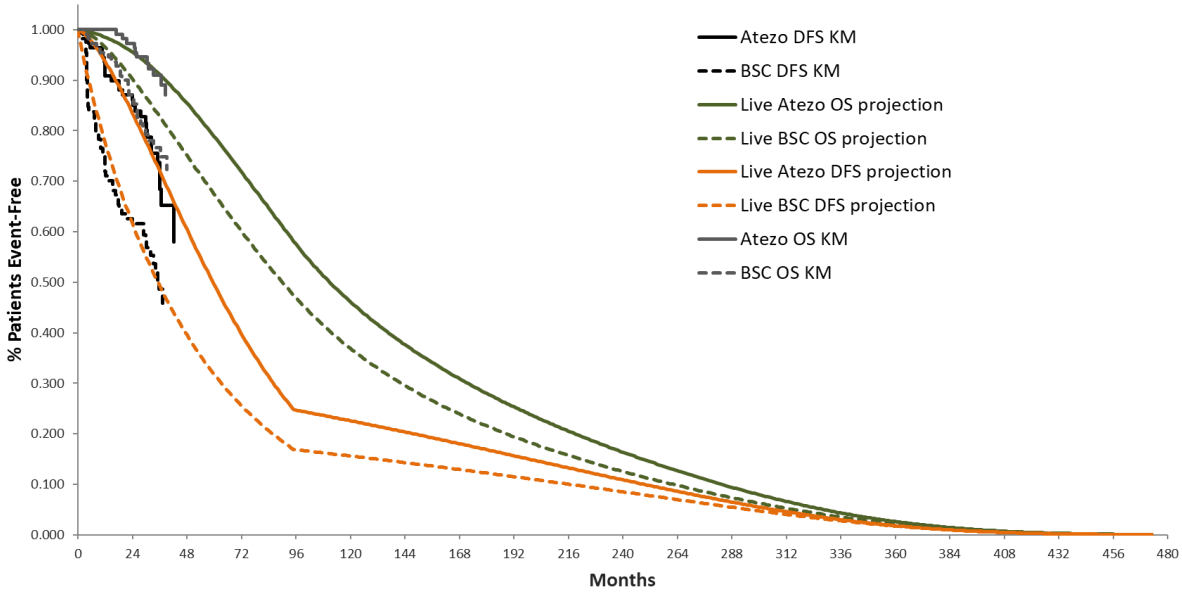
Abbreviations: ACM, appraisal committee meeting; BSC, best supportive care; DFS, disease-free survival; ERG, External Review Group; ICER, incremental cost-effectiveness ratio; KM, Kaplan-Meier; NICE, National Institute for Health and Care Excellence; OS, overall survival; PAS, patient access scheme

Analyses 1b in Table 1 use the company's alternative approach to capture immunotherapy retreatment. The key strength of this approach is its attempt to capture timing of retreatment to

inform its likelihood, in line with comments from the CDF clinical lead. However, in the ERG's view there are limitations in the company's approach that make it less useful than the ERG's more simplistic approach. To capture time from discontinuation, the company approach assumes all discontinuations occur at 11 months. In reality, and as described in Section 4.2.3 of the ERG report, in the PD-L1 ≥50% TC Stage II–IIIA group, there were discontinuations at most treatment cycles, and by Cycle 16 (week 48, approximately 11 months), 75.2% of those randomised to atezolizumab remained on-treatment. The added nuance of the company's approach is to apply a 50% chance of eligibility for retreatment for those entering the first metastatic recurrence state between Cycles 14 and 17, before assuming all are eligible from Cycle 18 onwards. The company's scenario reduces the predicted ICERs versus the ERG's approach, as Table 1 shows, owing primarily to lower predicted 1st line metastatic recurrence treatment acquisition costs.

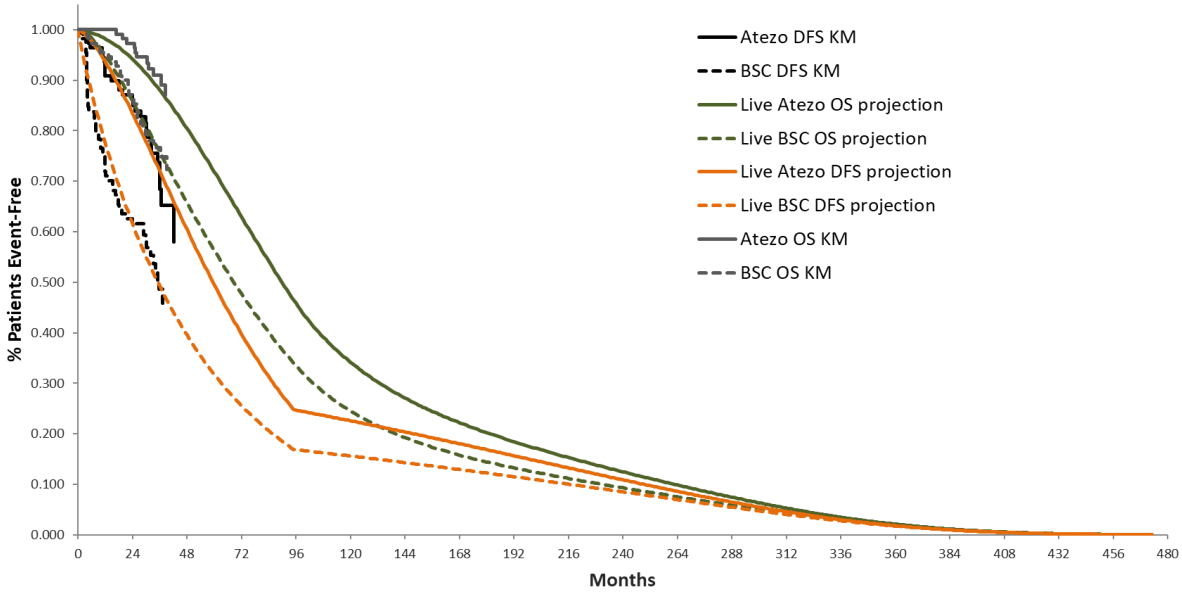
Analyses 1ci and 1cii in Table 1 incorporate the company's post-ACM1 post-DFS adjustments to force projections to fit different IMpower010 OS KM projections, across different scenarios. These analyses, like analyses 1b, use the ERG-preferred analyses 1a as a baseline from which to deviate. This is consistent with the company's reported analysis, as the adjustments were made using Excel's Goal Seek functionality to adjust post-DFS transition probability estimates so that predicted OS met the (January 2021) IMpower010 PD-L1 ≥50% Stage II–IIIA OS KM data at 36 months, *given ERG-preferred DFS projections*. The results in Table 1 highlight the sensitivity of headline ICER results to different post-hoc adjustments to post-DFS transition probabilities. In each case, forcing the post-DFS transitions to meet one arm's KM OS curve did not produce a good visual fit to the other arm's KM OS curve. Figure 1 and Figure 2, illustrate this, depicting lifetime DFS and OS projections in scenarios 1ci and 1cii. Figure 1 also highlights that given the shape of the atezolizumab OS KM data, forcing atezolizumab OS projections to meet the corresponding KM data at 36 months did not even provide a good overall visual fit to the rest of the atezolizumab OS KM curve. Overall, the ERG does not find any of these scenarios to be a preferable alternative to the company's existing approach.

Figure 1: Lifetime DFS and OS projections from Table 1's scenario 1ci, using ERG's alternative assumptions



Abbreviations: Atezo, atezolizumab; BSC, best supportive care; DFS, disease-free survival; ERG, External Review Group; ICERs, incremental cost-effectiveness ratios, KM, Kaplan-Meier, OS, overall survival

Figure 2: Lifetime DFS and OS projections from Table 1's scenario 1cii, using ERG's alternative assumptions



Abbreviations: Atezo, atezolizumab; BSC, best supportive care; DFS, disease-free survival; ERG, External Review Group; ICERs, incremental cost-effectiveness ratios, KM, Kaplan-Meier, OS, overall survival

As noted in Table 1, the company did not provide any additional cost-effectiveness analyses that better fit expected outcomes in previous appraisals. Instead, the company argues that while the current analysis is at the lower end of the range of the health benefit predictions of immunotherapeutic 1st metastatic recurrent treatments in previous appraisals highlighted by the committee (TAs 531, 705, 584 and 683), it is within, not below the range. The first argument the company uses refers to the higher post-metastatic QALY projections in BSC arms of post-DFS transition probability adjusted analyses 1ci and 1cii, discussed above; the company found these scenarios to produce a higher post-metastatic QALY projection than unadjusted analyses. The ERG does not find this argument convincing, given the limitations of these scenarios. The company's second argument is that the lower QALY benefits of immunotherapy for metastatic recurrence in this model versus metastatic recurrence appraisal history is largely affected by only a proportion of the mean patient in the current model experiencing metastatic recurrence. The ERG feels this argument is valid, but notes that even in the company's QALY scenario assuming all patients receive metastatic treatment, the projected QALYs are below the range in previous TAs the company present. The company also present a QALY scenario in which all patients enter the 1st metastatic recurrence state after Cycle 1. In this situation, the model predicts QALYs just within the lower bound of the range of estimates from previous appraisals, but the ERG notes that the patients in the relevant (Stage II-IIIA) IMpower010 sample are expected to be younger than those in the 1st metastasis setting. Further, it is not clear whether time-preference discounting was applied in this QALY scenario. Overall, the ERG feels that the company's efforts to explore consistency of the model at hand with those that have informed decision-making in previous NICE appraisals of treatments for metastatic lung cancer are useful, but ultimately indicate that the committee's concern remains valid; the approach taken by the company in this appraisal likely underestimates the benefit of immunotherapy for metastatic lung cancer.

3. SENSITIVITY ANALYSES

In the communication to the company following the first ACM, the committee expressed its concern that the company's source for estimating a proportion of patients who will be "cured", Sonoda et al. (2019)[1], may have limited generalisability. Further, the committee wondered whether additional relevant evidence may be available.

To address the committee's concerns around the use of the Sonoda et al. (2019)[1] study to inform cure assumptions, the company revisited a review reported in Appendix M of its original

submission which was conducted to comprehensively collect and collate evidence on clinical burden and treatment patterns on early non-small cell lung cancer (NSCLC). Broadly, prospective and retrospective studies conducted in adults with early resectable NSCLC (Stage I to III) who were either in DFS or locoregional recurrence health states were eligible for inclusion (PICOS criteria were specified in Table 38 of Appendix M). It was not possible for the ERG to verify the study selection process as no PRISMA flow diagram was presented by the company.

In Appendix M of the original CS, seven studies were selected for inclusion by the company that reported the proportion of patients who remained recurrence-free over time (Marushima 2020; Park 2016; Park 2013; Shin 2021;[2] Nomori 2019;[3] Maeda 2010a;[4] Maeda 2010b[5]). The company only appeared to rescrutinise four of these studies in its updated analysis (Shin 2021;[2] Nomori 2019;[3] Maeda 2010a;[4] Maeda 2010b[5]) and included an additional study (Koike 2013[6]) for which the means of identification was unclear . It selected two of these studies for inclusion (Shin 2021;[2] Maeda 2010a[4]), summary characteristics for these studies are provided in Table 2 alongside those for Sonoda (2019)[1] and the IMpower010 PD-L1 ≥50% Stage II–IIIA sample.

The company and its clinical expert acknowledged similar limitations as previously highlighted for Sonoda (2019)[1] in terms of applicability to UK clinical practice: studies conducted in Asian population; study population did not receive adjuvant chemotherapy; potential differences in staging in Maeda (2010a)[4] (pre PET staging); the inclusion of a high proportion of participants with Stage 1 disease and high recurrence in Stage 1 patients at five years. However, while the additional evidence does not address committee concerns regarding generalisability of evidence to the UK setting or the high proportion of study participants with Stage 1 disease, both the Maeda et al. (2010a)[4] and Shin et al. (2021)[2] analyses reported recurrence-free probability five years after complete resection by disease stage, allowing isolation of Stage 2 and 3 probability estimates.

Table 2. Cure assumptions: data sources

Study	**IMpower10[7,8] PD-L1 TC ≥50% Stage II-IIIA[a]**		**Sonoda et al. 2019[1]**	**Shin et al. 2021[2]**	**Maeda et al. 2010a[4]**
Intervention	Atezolizumab	BSC	NA	NA	NA
Study design	Randomised controlled trial		Prospective cohort (consecutive cases)	Retrospective cohort from a single institution	Retrospective cohort
Country	Multi (Australia, Belgium, Canada, China, France, Germany, Hong Kong, Hungary, Israel, Italy, Japan, Korea, The Netherlands, Poland, Portugal, Romania, Russian Federation, Spain, Taiwan, Ukraine, UK, USA)		Japan	Korea	Japan
Study population	Completely resected (4-12 weeks prior to enrolment) Stage 1B (≥4 cm)-3A NSCLC (AJCC/UICC v7) and ECOG PS 0-1. PD-L1 TC ≥50% Stage 2-3A[a] (n=229)		Patients with primary NSCLC who underwent lobectomy or more extensive resection complete with systematic lymph node dissection and achieved complete resection (n=1,458)	Patients with NSCLC who received pulmonary resection for curative purpose excluding age <20 yrs, synchronous double cancer, chemo- or radio-therapy before surgery, Stage 4 disease, and R0 resection (n=8,798)	Patients with NSCLC who underwent complete resection (cancer free surgical margins both macroscopically and histologically) with systematic lymph node dissection (n=1,358)
Baseline characteristics					
Age years mean (SD)	[redacted]	[redacted]	NR for overall cohort (703 [51.8%] <65 years and 755 [48.2%] ≥65 years)	61.7 (±9.8)	NR (556 [67.9%] <70 years and 263 [32.1%] ≥70 years)
Sex male n (%)	89 (77)	78 (68)	880 (60.4)	5,732 (65.2)	479 (58.5)
Stage 1 n (%)	NA[a]	NA[b]	768 (52.7)	5,617 (63.8)	637 (77.8)
Stage 2 (%)	62 (54)	57 (50)	336 (23.0)	1,943 (22.1)	96 (11.7)
Stage 3 n (%)	53 (46)	57 (50)	354 (24.3)	1,238 (14.1)	86 (10.5)

Study	**IMpower10[7,8] PD-L1 TC ≥50% Stage II-IIIA[a]**	**Sonoda et al. 2019[1]**	**Shin et al. 2021[2]**	**Maeda et al. 2010a[4]**
Median follow-up duration (IQR)	34.2 months	10.1 years from initial resection	2.0 years (1.0, 4.7) RFS and 4.1 years (2.1, 7.3 OS)	40 mths after the 5 year recurrence free point (range 1, 92 months)
5-year recurrence-free probability	NA	Recurrence developed within the first 5 years in 436 (91.6%) cases, late recurrence developed at 5–10 years in 28 (5.9%) cases, and ultra-late recurrence developed after 10 years in 12 (2.5%) cases	Graph; raw data by stage not reported. Company interpret the data as ~86% for Stage 2 and ~85% for Stage 3	88.3% (n=89 [Stage 1]); **85.6% (n=23 [Stage 2]**); **77.1% (n=27 [Stage 3]**)

Abbreviations: IQR, interquartile range; mths, months; OS, overall survival; RFS, relapse free survival; SD, standard deviation

Notes:

[a]23 patients in the stage II-IIIA population had unknown PD-L1 status as assessed by SP263.

[b]Population was PD-L1 TC ≥50% Stage 2-3A.

Importantly, the estimates from Shin et al. and Maeda et al. are five-year recurrence-free probability estimates, from the point of (and conditional upon) survival up to five years. Unless the post-10-year recurrence-free probability is zero, the lifetime recurrence-free probability estimates conditional upon survival to five years (as interpreted for the model), will be higher, and the true “cure” proportion will be lower.

As well as uncertainty around the proportion of patients who can be assumed to be effectively cured, the committee have also expressed concern about cure timing assumptions, and requested that these be explored. Table 3 and Table 4, created by the ERG using cure proportion data from Table 2, demonstrate the effect of cure timing and proportion assumptions upon ICER results. The probability estimates from Maeda et al are used, with the Stage II probability (85.6%) serving as a proxy for the approximate probability estimates from Shin et al Stage II (86%) and Stage III (85%) patients.

Table 3 and Table 4 differ in the underlying DFS parametric model structure assumed; Table 3 results assume a log-logistic distribution, while Table 4 results assume a Weibull distribution. Otherwise, the underlying assumptions are those of ERG-preferred analyses, with immunotherapy retreatment assumed. As such, the ERG-preferred analyses 1a in Table 1 are captured across Table 3 and Table 4, as indicated in notes below each table.

The results in Table 3 and Table 4 illustrate interesting trends. All else equal and as expected, delaying the timing of cure equally across arms worsens the predicted cost-effectiveness of atezolizumab, as does delaying the timing of cure for the atezolizumab arm only. When the timing of cure is assumed equal across arms, assuming a lower cure proportion worsens the predicted cost-effectiveness of atezolizumab, as expected. However, as the timing of atezolizumab cure is assumed to move further into the future while the timing of BSC cure is held constant, a lower cure proportion improves the predicted cost-effectiveness of atezolizumab. The ERG considers this to be mostly explained by the effective cure proportion being determined by both the proportion who are predicted to remain disease-free to the cure point and the proportion assumed to be cured from that point. As the assumed cure point for the atezolizumab arm moves away from the equivalent point for the BSC arm, the proportion predicted to remain disease free at the cure point in the atezolizumab arm falls, and eventually falls below the proportion predicted to remain disease free at the cure point in the BSC arm. In this situation, a lower cure proportion implies a lower effective cure proportion advantage for the BSC arm.

Table 3: Effect of cure timing and proportion assumptions upon ICER results, using an underlying pre-cure log-logistic fit to DFS data and otherwise using ERG-preferred analysis assumptions, with immunotherapy retreatment

ICERs, ERG-preferred analyses, underlying log-logistic, with retreatment	Cure timing (Atezo|BSC), in years				
Cure proportion assumption source, proportion	**5|5**	**6|5**	**7|5**	**8|5**	**8|8**
Sonoda et al (all ACM1 analyses): **91.5%**	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Maeda et al, Stage II patients: **85.6%**	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Maeda et al, Stage III patients: **77.1%**	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: ACM, appraisal committee meeting; BSC, best supportive care; DFS, disease-free survival; ERG, External Review Group; ICERs, incremental cost-effectiveness ratios

[a]ERG's optimistic base case, with retreatment

Table 4: Effect of cure timing and proportion assumptions upon ICER results, using an underlying pre-cure Weibull fit to DFS data and otherwise using ERG-preferred analysis assumptions, with immunotherapy retreatment

ICERs, ERG-preferred analyses, underlying Weibull, with retreatment	Cure timing (Atezo|BSC), in years				
Cure proportion assumption source, proportion	**5|5**	**6|5**	**7|5**	**8|5**	**8|8**
Sonoda et al (all ACM1 analyses): **91.5%**	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Maeda et al, Stage II patients: **85.6%**	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Maeda et al, Stage III patients: **77.1%**	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: ACM, appraisal committee meeting; BSC, best supportive care; DFS, disease-free survival; ERG, External Review Group; ICERs, incremental cost-effectiveness ratios

[a]ERG's alternative base case, with retreatment

In addition to sensitivity analyses around cure timing and proportion assumptions, the committee requested further sensitivity analyses around different parametric model fits to DFS. While the results in Table 3 and Table 4 illustrate how assuming a Weibull distribution instead of a log-logistic distribution leads to a worse cost-effectiveness prediction for atezolizumab (all else equal), Table 5 shows how the headline ICER changes when each tested parametric model is assumed in turn, across “no cure”, “five-year cure and “eight-year cure” scenarios. The most pessimistic projections for atezolizumab are those assuming Gompertz or generalized gamma models; in these scenarios, atezolizumab is predicted to offer a lifetime QALY loss relative to BSC, at a higher cost. When exponential, gamma or log-normal models are assumed, the results are more favourable for atezolizumab than when log-logistic, Weibull, Gompertz or generalized gamma models are assumed.

The sensitivity of results to different underling parametric model assumptions is explained by the variability in lifetime projections of DFS across different parametric model fits. This was illustrated in Figure 7 of the ERG report, reproduced as Figure 3 here. As the company fitted parametric models to data from each trial arm separately, and owing to the different shapes of the KM curves across arms, projections have a tendency to converge across arms, most rapidly when Gompertz or generalized gamma models are assumed. As expressed in the ERG report, the ERG considers that the five-year DFS estimates the company identified in the literature; reiterated in the company’s latest correspondence; were broadly consistent with the five-year estimates from all BSC parametric survival models tested, bar the generalized gamma model. Overall, the ERG advises that the uncertainty around cost-effectiveness results highlighted when structural parametric model assumptions are varied is reflective of the uncertainty in the long-term DFS benefit offered by adjuvant atezolizumab.

Table 5: Effect of underlying parametric model and cure assumptions

Underlying parametric model for DFS	No cure ICERs	5-year cure ICERs	8-year cure ICERs
Log-logistic	[redacted]	[redacted]	[redacted]
Weibull	[redacted]	[redacted]	[redacted]
Exponential	[redacted]	[redacted]	[redacted]
Gompertz	[redacted]	[redacted]	[redacted]
Gamma	[redacted]	[redacted]	[redacted]
Log-normal	[redacted]	[redacted]	[redacted]
Generalized Gamma	[redacted]	[redacted]	[redacted]

Abbreviations: DFS, disease-free survival; ICERs, incremental cost-effectiveness ratios

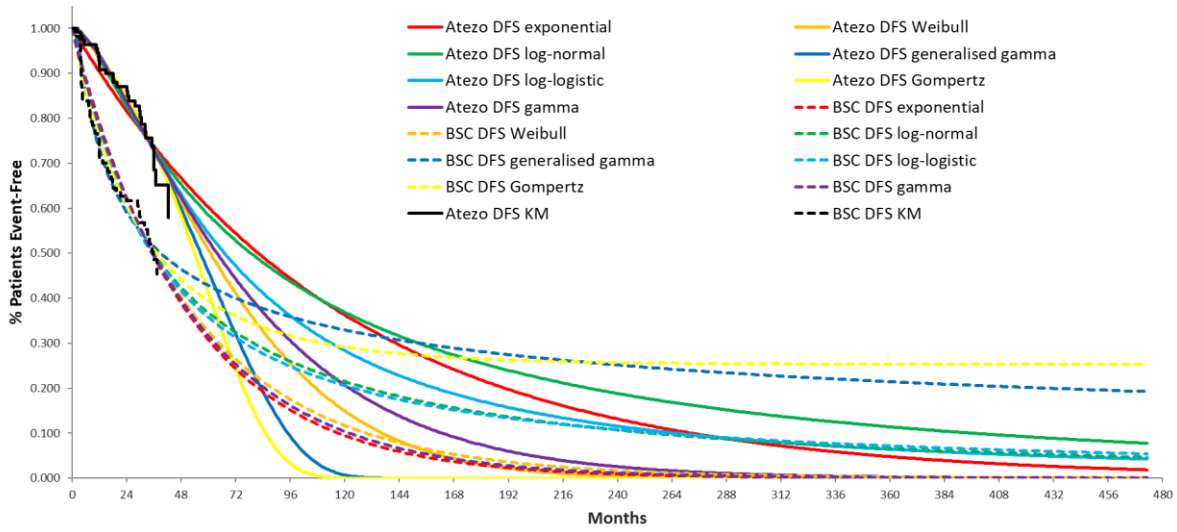
Notes: cure timing assumed equivalent across arms

[a] ERG's optimistic base case, with retreatment

[b] ERG's alternative base case, with retreatment

[c] Atezolizumab predicted to be dominated by BSC

Figure 3: [CS Figure 7]. Parametric model fits to IMpower010 DFS KM data (PD-L1 ≥50% TC Stage II–IIIA subgroup)



Abbreviations: Atezo, atezolizumab; BSC, best supportive care; DFS, disease-free survival; KM, Kaplan-Meier; PD-L1, programmed cell death ligand 1; TC, tumour cells

4. ADDITIONAL CONSIDERATIONS FOR THE COST-EFFECTIVENESS ANALYSES

Noting the reliance on various external sources for many transitions in the model without strong justification, the committee requested additional literature searches and justification for choices.

In response, the company reported conducting an additional search for evidence on one such aspect of the model only. Specifically, the company conducted an additional focused search on 25 May 2022 to inform the transition probabilities for patients transitioning from locoregional recurrence health state to death (patients who are treated with palliative intent or are not treated). To be correctly constructed this would have combined [all terms for lung (combined with OR)] AND [all terms for cancer (combined with OR)]; the two different concepts have been intermingled within one search line which means the search strategy may well not be very effective. It is not possible to confidently determine how PubMed would have combined these different search concepts when all searched together as one search string. This part of the search has been combined with a free text search for 'locoregional' which is not very comprehensive and does not include any synonyms, alternative terms, or subject headings. It is therefore highly likely that the search has missed relevant papers.

The company identified one additional study (Foo 2005),{Foo, 2005 #263} but provided no comment on its suitability to inform the decision problem at hand beyond noting that the newly identified study is older than the study currently used (Kruser 2014).{Kruser, 2014 #268} The newly identified study reports median survival of 10.5 months following radiotherapy for those treated with palliative intent; a subgroup of 55 patients from one hospital in Sydney, Australia. Despite this estimate being more than twice the corresponding median survival estimate in the company's base case (5.1 months), using the newly identified estimate has only a minor affect upon headline results, increasing ERG optimistic and alternative analysis ICERs by [redacted] and [redacted], respectively, in scenario analyses conducted by the company.

It is not clear why the company did not extend the additional search to cover evidence for all post-DFS transition risks. The additional work conducted serves to confirm that data identification and selection for these aspects of the analysis was not and is not comprehensive. While the company's scenario analysis highlighted uncertainty around one post-DFS transition probability estimate as unimportant for results within the chosen modelling approach, the

difference in median survival estimates across the originally identified study and newly identified study highlights the uncertainty in post-DFS aspects of the analysis.

Lastly, the committee stressed that any additional trial data would be beneficial to help address committee uncertainty, if available. In response, the company provided a recent interim analysis of IMpower010 PD-L1 ≥50% Stage II–IIIA OS KM data, with 15 months additional follow-up in comparison to the data cut included up to this point. The company did not provide a corresponding interim analysis of DFS data, nor explain the rationale for the recent database lock.

The company provided an interim OS analysis representing an additional 15 months of follow up. [redacted] Figure 4 and Table 6, [redacted]. These data [redacted] in the PD-L1≥50% Stage II-IIIA NSCLC population.

The committee asked the company to provide any additional KM data as datapoints within the economic model, with KM steps included. The company did provide the updated OS KM data as datapoints within the economic model, but did not include KM steps. The ERG are unclear why the company have not been able to adhere to this request at this and previous stages of this appraisal. The latest OS KM data as provided by the company are shown in Figure 5, alongside the January 2021 cut of the OS KM data and the ERG's alternative base case projections of OS. While the latest OS data [redacted].

Figure 4: Kaplan-Meier curve of interim OS in the PD-L1≥50% Stage II-IIIA population, clinical data cut-off: [redacted] (Data on File)

Abbreviations: NE; not evaluable

Table 6: Interim OS analysis for Stage II-IIIA PD-L1≥50% population, clinical data cut-off: [redacted] (Data on File)

	21 January 2021		[redacted]	
	Atezolizumab	BSC	Atezolizumab	BSC
	n=115	n=114	n=115	n=114
Patients with OS event	[redacted]	[redacted]	[redacted]	[redacted]
Median OS, months	[redacted]	[redacted]	[redacted]	[redacted]
HR (95% CI) (unstratified)	[redacted]		[redacted]	
p-value			[redacted]	

Abbreviations: BSC; Best supportive care, HR; hazard ratio, NE; not evaluable.

Figure 5: Latest OS KM data alongside January 2021 OS KM data and ERG alternative base case lifetime OS projections

Abbreviations: Atezo, atezolizumab; BSC, best supportive care; ERG, Evidence Review Group; KM, Kaplan-Meier; OS, overall survival.

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National Institute for Health and Care Excellence

Centre for Health Technology Evaluation

ERG critique of company's additional analyses post-ACM1, June 2022 – factual accuracy check

Atezolizumab for adjuvant treatment of resected non-small-cell lung cancer [ID3852]

Description from ERG critique	Company response
Page 2 Introduction "...but as code had been overwritten, it was not possible to easily recreate latest ERG results."	The code had to be overwritten in order to allow cure assumptions to be conditional by arm. As agreed with the committee and ERG in the post-ACM call, clear instructions were provided on what was changed in the model. It is possible to revert back to ERG base case with the updated company model.
Page 3 Table 1 Row 6 (last row) of the table "None provided"	"None provided" implies the company did not provide additional analyses on this point, however, it is provided in the company response and the ERG discuss it in page 6.
Page 4 Primary Analysis "However, in the ERG's view there are limitations in the company's approach that make it less useful than the ERG's more simplistic approach."	The ERG approach assumes that patients re-challenge with immunotherapy directly after recurrence. According to clinical opinion during the 1st ACM, this is not the case for patients who recur within 6 months as clinicians would not re-treat these patients. If patients recur earlier, it means they did not respond to treatment, so are unlikely to be re-treated.
Page 4 Primary Analysis "Figure 2 also highlights that given the shape of the atezolizumab OS KM data, forcing atezolizumab OS projections to meet the corresponding KM data at 36 months did not even provide a good overall	The company believe an error was made here as Figure 2 is the analysis that adjusted transition probabilities so as to ensure modelled OS for the BSC arm (not atezolizumab arm) at month 36 equals that of the KM. However, as can been seen in Figure 1, the modelled OS for the

visual fit to the rest of the atezolizumab OS KM curve”	atezolizumab arm provides a good overall visual fit to the rest of the atezolizumab OS KM curve.
Page 4 Primary Analysis “Overall, the ERG does not find any of these scenarios to be a preferable alternative to the company’s existing approach.”	The company are unsure why the ERG do not agree with the scenarios presented in the Primary Analysis section. A post-ACM1 call was held between the company, the ERG and NICE, plus a response outline was provided for the ERG on 19th May 2022 to comment on. The company response to the committee request for additional analysis reflects the feedback provided during the call and the review comments from the ERG. The company response present the following: ● Re-treatment scenario is relevant as stated by the CDF clinical lead and clinicians at ACM1 ● Adjusting the transition probabilities (an approach discussed in a post ACM1 call was deemed an appropriate analysis) show that when improving the fit to OS data, the ICER remains within threshold ● Adjustments to the model so that QALYs match previous appraisals show that our model is unlikely to underestimate QALYs
Page 6 Primary Analysis “As noted in Table 1, the company did not provide any additional cost-effectiveness analyses that better fit expected outcomes in previous appraisals.”	The company did provide additional analysis; more thorough analyses was not conducted as the approach was discussed during a call and reviewed by the ERG and it was agreed that time constraints limited the ability for the company to provide the more detailed analysis and for the ERG to review this thoroughly.
Page 6 Primary Analysis “...the approach taken by the company in this appraisal likely underestimates the benefit of immunotherapy for metastatic lung cancer.” “...it is not clear whether time-preference discounting was applied in this QALY scenario.”	The QALYs produced from the scenario where all patients enter the 1st metastatic recurrence state after Cycle 1 are between 1.57–3.49. QALYs from past appraisals range from 1.44–2.32. It is evident from the updated company model that time-preference discounting was applied to this QALY scenario.
Page 7	Koike et al 2013 was identified in the RWE

Primary Analysis "...included an additional study (Koike 2013) for which the means of identification was unclear."	review. The company apologise that only the abbreviated report was provided in Appendix M and have provided the full report with this response.
Page 7 Primary Analysis "However, while the additional evidence does not address committee concerns regarding generalisability of evidence to the UK setting or the high proportion of study participants with Stage 1 disease…"	From the literature reviews and clinical opinion, the evidence required does not exist, therefore it is not possible to address this concern.
Page 10 Sensitivity Analysis "...the lifetime recurrence-free probability estimates conditional upon survival to five years (as interpreted for the model), will be higher, and the true "cure" proportion will be lower."	In clinical expert interviews carried out April 2021 (provided to the ERG), clinicians stated that, in current clinical practice, after 5 years, they are confident the disease is cured. Any new tumours are suspected to be new primaries rather than recurrence of the old disease.
Page 11 Table 3 and Table 4	As discussed above, it is not clinically plausible that patients are treated immediately following recurrence. Also, as stated in the previous company response, clinical expert advice is that an 8-year cure time point for atezolizumab is not appropriate.
Page 12 Sensitivity Analysis "Overall, the ERG advises that the uncertainty around cost-effectiveness results highlighted when structural parametric model assumptions are varied is reflective of the uncertainty in the long-term DFS benefit offered by adjuvant atezolizumab."	Some of the distributions presented are not clinically valid so it is not reasonable to use the table to comment on the uncertainty. Table 10 of the previous company response to "Analyses to consider following ACM1" show that the Gompertz and Generalised Gamma estimated proportion of patients event-free after treatment initiation at 10 years is [redacted] and [redacted], which is clinically implausible.
Page 14 Additional Considerations for the Cost-effectiveness Analysis "It is not clear why the company did not extend the additional search to cover evidence for all post-DFS transition risks."	IPD was used from internal Roche trials as this provides more accurate results. It has been previously published in an indirect treatment comparison that immunotherapies, including pembrolizumab and atezolizumab, show similar survival and safety (1). Hence using atezolizumab or pembrolizumab data should not impact the ICER.
Page 15 Additional Considerations for the Cost-effectiveness Analysis	DFS is event driven - The interim analysis DFS was conducted in 2021, when we met the threshold for events in the primary

“The company did not provide a corresponding interim analysis of DFS data, nor explain the rationale for the recent database lock.”	analysis population. The DFS final analysis will occur when we meet the pre-specified target number of DFS events. Given event projections, this is not anticipated to occur until [redacted]. In order to control the overall Type I error rate, there is no updated DFS analysis conducted at the 1st OS interim analysis. OS is also event driven and analyses are based on a pre-specified number of events occurring.
Page 15 Additional Considerations for the Cost-effectiveness Analysis “The company did provide the updated OS KM data as datapoints within the economic model, but did not include KM steps”	The company have provided the KM plot (Figure 4 of the ERG critique) and the KM raw data in the model (used to produce Figure 5 of the ERG critique). Please can the ERG clarify what they believe to be missing.

References

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