NICE National Institute for Health and Care Excellence

Single Technology Appraisal

Atezolizumab monotherapy for untreated PD-L1 positive metastatic non-small-cell lung cancer [ID1678]

Committee Papers

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NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

SINGLE TECHNOLOGY APPRAISAL

Atezolizumab monotherapy for untreated PD-L1 positive metastatic non-small-cell lung cancer [ID1678]

Contents:

The following documents are made available to consultees and commentators:

The **final scope and final stakeholder list** are available on the NICE website.

1. **Company submission** from Roche Products
2. **Company response to NICE's request for clarification**
3. **Evidence Review Group report** prepared by Aberdeen HTA Group
4. **Evidence Review Group – factual accuracy check**
5. **Technical engagement response from** Roche Products
6. **Technical engagement responses from experts:**
   a. Yvonne Summers – clinical expert, nominated by Roche Products
7. **Evidence Review Group critique of company response to technical engagement** prepared by Aberdeen HTA Group
8. **Evidence Review Group addendum** prepared by Aberdeen HTA Group
   a. Post technical engagement addendum
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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 monotherapy for untreated advanced non-small-cell lung cancer [ID1678]

Document B

Company evidence submission

September 2020

File name	Version	Contains confidential information	Date
ID1678 Atezolizumab Document B_1L NSCLC [no ACIC] v2.0	v2.0	Yes	7th October 2020

Contents

Tables and figures

Abbreviations

ADCC	antibody dependent cell-mediated cytotoxicity
AE	adverse event
AESI	adverse event of special interest
AIC	Akaike information criteria
ALK	anaplastic lymphoma kinase
AST	aspartate aminotransferase
ATZ	atezolizumab
AUC	area under the curve
BEP	biomarker-evaluable population
BIC	Bayesian information criteria
BNF	British National Formulary
BSA	body surface area
BSC	best supportive care
CCOD	clinical cutoff date
CDF	Cancer Drugs Fund
CE	Conformité Européene
CI	Confidence interval
CR	complete response
CTCAE	Common Terminology Criteria for Adverse Events
CUA	cost utility analysis
DIC	deviance information criterion
DOR	duration of response
DSU	Decision Support Unit
ECG	electrocardiogram
ECOG	Eastern Cooperative Oncology Group
EGFR	epidermal growth factor receptor
EMA	European Medicines Agency
EORTC	European Organisation for the Research and Treatment of Cancer
EQ-5D	EuroQol 5 Dimensions
ERG	Evidence Review Group
ES-SCLC	extensive-stage small cell lung cancer
FDA	Food and Drug Administration
FE	fixed effects
FP	fractional polynomial
GHS	global health status
GLM	generalised linear model
GP	general practitioner
HCHS	hospital and community health services
HR	hazard ratio
HRG	Healthcare Resource Groups
HRQoL	Health related quality of life
HS	health state
HSUV	health state utility value
HTA	Health Technology Assessment
IC	immune cells
ICER	incremental cost effectiveness ratio
IHC	immunohistochemistry
INV	investigator-assessed
IPD	individual patient data
IRC	independent review committee
ITT	intent-to-treat
IV	intravenous
KM	Kaplan Meier
LYG	life years gained

MCMC	Markov chain Monte Carlo
NCI-CTCAE	National Cancer Institute Common Terminology Criteria for Adverse Events
NE	not estimable
NHS	National Health Service
NICE	National Institute for Health and Care Excellence
NMA	network meta analysis
NMB	Net Monetary Benefit
NPT	non-protocol therapies
NSCLC	non-small cell lung cancer
ORR	objective response rate
OS	overall survival
OWSA	one-way sensitivity analysis
PAS	patient access scheme
PD	progressive disease
PFS	progression-free survival
PH	proportional hazard
PR	partial response
PRO	patient-reported outcomes
PSA	partitioned survival analysis
PSS	Personal Social Services
PSSRU	Personal Social Services Research Unit
QALY	quality-adjusted life year
QLQ	quality of life questionnaire
QLU	quality of life utility
QoL	quality of life
RCT	randomised-controlled trial
ROS1	ROS proto-oncogene 1 ,
RECIST	Response Evaluation Criteria in Solid Tumours.
RPSFT	Rank Preserving Structural Failure Time
SAE	serious adverse advent
SCLC	small cell lung cancer
SD	stable disease/standard deviation
SE	standard error
SILC	Symptoms in Lung Cancer
SLR	systematic literature review
SOC	standard of care
TA	technology appraisal
TC	tumour cells
TNBC	triple negative breast cancer
TNM	tumour, node, metastasis
TPS	tumour proportion score
TRAE	treatment-related adverse event
TRSAE	treatment-related serious adverse event
TSD	technical support document
TTD	time to treatment discontinuation
TTE	time to event
TTO	time trade off
UC	urothelial carcinoma
UK	United Kingdom
US	United States
VAS	visual analogue score
VAT	value added tax
WT	wild type
WTP	willingness to pay

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

B.1.1 Decision problem

The submission [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 non-squamous or squamous untreated metastatic non-small cell lung cancer (NSCLC) with PD-L1 positive tumour expression and without epidermal growth factor receptor (EGFR)- or anaplastic lymphoma kinase (ALK)-positive mutations.	Adult patients with [redacted].	Population in accordance with anticipated licence and trial population, i.e. metastatic NSCLC patients with high PD-L1 expression.
Intervention	Atezolizumab	Per final scope.	N/A

Comparator(s)	For people whose tumours express PD-L1 with at least a 50% tumour proportion score: • Pembrolizumab For people with non-squamous NSCLC whose tumours express PD-L1 with a tumour proportion score below 50%: • Atezolizumab plus bevacizumab, carboplatin and paclitaxel • Chemotherapy (docetaxel, gemcitabine, paclitaxel or vinorelbine) in combination with a platinum drug (carboplatin or cisplatin) o with or without pemetrexed maintenance treatment For people with adenocarcinoma or large-cell carcinoma whose tumours express PD-L1 with a tumour proportion score below 50%: • Pemetrexed in combination with a platinum drug (carboplatin or cisplatin) o with (following cisplatin-containing regimens only) or without pemetrexed maintenance treatment For people with squamous NSCLC whose tumours express PD-L1 with a tumour proportion score below 50%: • Chemotherapy (gemcitabine or vinorelbine) in combination with a platinum drug (carboplatin or cisplatin)	Pembrolizumab	Per final scope, pembrolizumab is the appropriate comparator with respect to the patient population, i.e. metastatic NSCLC patients with high PD-L1 expression.

Outcomes	The outcome measures to be considered include: • overall survival • progression-free survival • response rate • adverse effects of treatment • health-related quality of life	Per final scope.	
Subgroups to be considered	If evidence allows, subgroup analysis by: • Level of PD-L1 expression • Squamous and non-squamous status	No subgroups considered.	The population under consideration for this appraisal is already limited to the highest level of PD-L1 expression and cannot be subgrouped further. The IMpower110 study included patients with both squamous and non-squamous histology. However, the trial was not statistically powered to assess efficacy in either subgroup. Consequently, subgroup analysis by histology is not appropriate.
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	An application for a license extension of atezolizumab for the following indication was submitted to the European Medicines Agency (EMA) on 27th November 2019: “[redacted]” Marketing authorisation for this indication is expected in [redacted].
Indications and any restriction(s) as described in the summary of product characteristics (SmPC)	Atezolizumab is currently approved by the EMA for the following indications: **Atezolizumab 1,200 mg concentrate for solution for infusion (8):**

	• 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% • 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 • 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 nab-paclitaxel and carboplatin, is indicated for the first-line treatment of adult patients with metastatic non-squamous NSCLC who do not have EGFR mutant or ALK-positive NSCLC • In combination with carboplatin and etoposide, for the first-line treatment of adult patients with extensive-stage small cell lung cancer (ES-SCLC) **Atezolizumab 840 mg concentrate for solution for infusion (9)** • As monotherapy, for the treatment of adult patients with locally advanced or metastatic UC after prior platinum-containing chemotherapy, or in those who are considered cisplatin ineligible, and whose tumours have a PD-L1 expression ≥ 5% • 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 also have received targeted therapies before receiving atezolizumab • 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. The initial dose of atezolizumab must be administered over 60 minutes. If the first infusion is well tolerated, all subsequent infusions may be administered over 30 minutes. Treatment with ateozlizumab is recommended until loss of clinical benefit or unmanageable toxicity (8).
Additional tests or investigations	[redacted](8).
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 (840mg) Price for full treatment course: [redacted]
Patient access scheme (if applicable)	Atezolizumab: [redacted] (existing patient access scheme [PAS])

ADCC: antibody dependent cell-mediated cytotoxicity; CE: Conformité Européene; EMA: European Medicines Agency; ES-SCLC: extensive-stage small cell lung cancer; IC: immune cells; NSCLC: non-small cell lung cancer; PD-L1: programmed death-ligand 1; TC: tumour cells; TNBC: triple-negative breast cancer; UC: urothelial carcinoma

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

B.1.3.1 Disease overview

Incidence and prevalence

Lung cancer remains the leading cause of cancer deaths in men and the second leading cause in women worldwide (10). In the UK, lung cancer is the third most common cancer and there are approximately 47,200 new lung cancer cases every year (11). In 2016, there were 38,381 new cases of lung cancer in England (11).

Histology

Non-small cell lung cancer (NSCLC) is the predominant subtype of lung cancer (12); in the 2018 National Lung Cancer Audit, 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 (the remaining types are: large cell carcinoma, neuroendocrine tumours, and sarcomatoid carcinoma) (14). Non-squamous histology accounts for more than half of all NSCLC, whereas squamous histology accounts for approximately 25-30% of cases (15, 16).

Diagnosis and staging

Molecular testing for EGFR (epidermal growth factor receptor) mutations, ROS1 (ROS proto-oncogene 1) mutations, ALK (anaplastic lymphoma kinase) rearrangements, or PD-L1 (programmed death-ligand 1) expression is recommended in all patients with NSCLC (17). Determination of PD-L1 expression is used to judge suitability for checkpoint inhibitor therapy (18). According to the ID1349 Pembrolizumab for untreated PD-L1–positive metastatic non-small-cell lung cancer (Cancer Drugs Fund [CDF] Review of TA447) committee papers (19): “NHS (National Health Service) England is confident that 100% of lung cancer units/centres are offering PD-L1 testing to their lung cancer patients.” In the UK, several PD-L1 immunohistochemistry (IHC) assays are routinely used, including 22C3 (Dako), SP142 (Ventana) and SP263 (Ventana)[1]. To determine the prevalence of PD-L1 expression in patients with locally advanced or metastatic NSCLC, a global, observational study was carried out using the 22C3 test and found that of 2368 patients with PD-L1 data,

[1] The 22C3 test measures tumour proportion score (TPS), the SP142 test measures tumour cells (TC) and immune cells (IC), and the SP263 test measures TC. Clinical expert engagements were used to gain insights into the choice of assays, the usage of the tests were as follows: 22C3 (n=21), SP263 (n=5), and SP142 (n=1) (Data on File).

22% had high PD-L1 expression (tumour proportion score [TPS] ≥50%), 52% had TPS ≥1%, and 48% had TPS <1% (20).

The extent of the disease is evaluated by staging, which determines the most appropriate form of treatment and provides an indication of prognosis. The tumour, node, metastasis (TNM) system is the basis of staging in NSCLC according to the American Joint Committee on Cancer/Union for International Cancer Control system (21, 22) and allows categorisation into Stages 0 to IV. In 2016, 70% of patients diagnosed with lung cancer in the UK had stage III or IV disease (23). The focus of this submission is patients with chemotherapy-naïve stage IV (metastatic) non-squamous or squamous NSCLC with high PD-L1 tumour expression and without EGFR- or ALK-positive mutations.

Mortality

According to Cancer Research UK (with data up to 2018, derived from the Office for National Statistics), the 5-year survival of all treated and untreated lung cancer patients diagnosed with stage IV lung cancer was only 3% (24). There are no publicly available survival data for metastatic NSCLC patients in the UK, however, according to estimates from the American Cancer Society, 5-year survival rates for patients with distant metastatic NSCLC is low at 6% (25).

Factors for poor survival prognosis in patients with NSCLC include advanced stage of disease at the time of initial diagnosis, poor performance status, and a history of unintentional weight loss (26). More than half of patients with NSCLC are diagnosed with distant disease, which directly contributes to poor survival prospects (27).

Quality of life

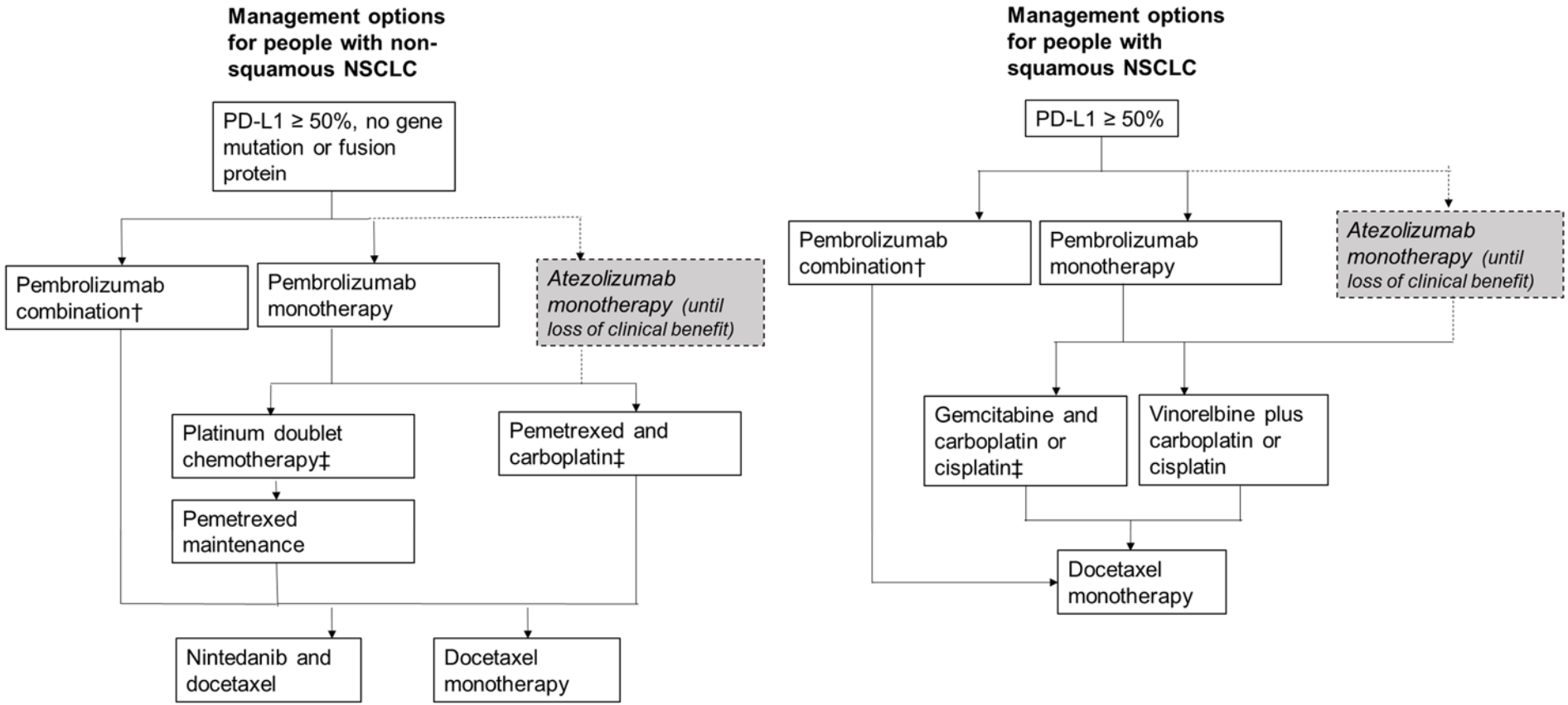
Advanced stage NSCLC has a negative impact on overall HRQoL. Pain, fatigue, dyspnoea, and cough are the most frequent and clinically relevant disease related symptoms experienced by patients with NSCLC (28, 29). With chemotherapy treatment, most disease-related symptoms for lung cancer increase in frequency and intensity during disease progression, in particular chest pain, back pain and dyspnoea (30-32).

B.1.3.2 Disease management pathway

The information presented below describes the current management of metastatic NSCLC and is based on the current NICE (National Institute for Health and Care Excellence) guidelines for the diagnosis and management of lung cancer [NG122] (33).

Figure 1 depicts the current clinical pathway for the treatment of adult patients with metastatic squamous and non-squamous NSCLC whose tumours have a PD-L1 expression ≥50% and who do not have EGFR mutant or ALK-positive NSCLC.

Figure 1: First-line treatment algorithm for adult patients with metastatic non-squamous and squamous NSCLC whose tumours have a PD-L1 expression ≥50% and who do not have EGFR mutant or ALK-positive NSCLC (including atezolizumab positioning) (33)



† Available via the Cancer Drugs Fund

‡ This combination/some of these combinations of drugs do not have a UK marketing authorisation for this indication

The grey box indicates the proposed positioning of atezolizumab

Non-squamous non-small-cell lung cancer (stages IIIB and IV)

In patients whose tumours express PD-L1 at 50% or above and who have no gene mutation or fusion protein, initial treatment is with pembrolizumab monotherapy or pembrolizumab with pemetrexed and platinum chemotherapy (the pembrolizumab combination is available on the Cancer Drugs Fund).

On progression after pembrolizumab monotherapy, pemetrexed with carboplatin or other platinum doublet chemotherapy is recommended[2]. For those who do not immediately progress after chemotherapy, pemetrexed is an option for maintenance treatment if:

- Their disease has not progressed immediately after 4 cycles of pemetrexed and cisplatin induction therapy and their Eastern Cooperative Oncology Group (ECOG) performance status is 0 or 1 at the start of maintenance treatment
- Their disease has not progressed immediately following platinum-based chemotherapy in combination with gemcitabine, paclitaxel, or docetaxel

Following progression after chemotherapy or pembrolizumab combination, NICE recommends either nintedanib in combination with docetaxel or docetaxel monotherapy.

Squamous non-small-cell lung cancer (stages IIIB and IV)

In patients whose tumours express PD-L1 at 50% or above, initial treatment is with pembrolizumab monotherapy or pembrolizumab with carboplatin and paclitaxel (the pembrolizumab combination is available on the Cancer Drugs Fund).

On progression, gemcitabine or vinorelbine and cisplatin or carboplatin is recommended. Following progression after first-line chemotherapy, docetaxel monotherapy is recommended.

Prescribing patterns in the UK

Roche carried out insights gathering on the prescribing patterns of clinicians in this setting (Data on File) and the results are shown in Table 3. These insights show that pembrolizumab monotherapy or combination (through CDF) is the current standard of care. Although chemotherapy alone is not recommended by NICE as a first-line option for

[2] At the time of publication (March 2019), some combinations of platinum doublet chemotherapy did not have a UK marketing authorisation for this indication

metastatic non-squamous and squamous NSCLC, a small number of patients are being prescribed chemotherapy alone by clinicians.

Table 3: UK clinicians prescribing patterns (n=24)*

	1L Non-squamous NSCLC	1L Squamous NSCLC
Pembrolizumab monotherapy	66%	81%
Pembrolizumab + chemotherapy combination	29%	17%
Chemotherapy	5%	2%

1L: first-line; NSCLC: non-small cell lung cancer

* Overall, insights were collected from 32 Lung Cancer Consultants from NHS hospitals in England and Scotland between October 2019-March 2020, although only 24 clinicians were approached for describing their prescribing patterns.

The treatment algorithm shown above and the results of the prescribing patterns survey in Table 3 indicate that pembrolizumab monotherapy is the primary comparator for atezolizumab in the scope of this appraisal and will consequently be used in the base case economic analysis in section B.3. The pembrolizumab combination is currently only available in the CDF, therefore it is not considered as a comparator in this submission, as per the NICE position statement on how companies should consider medicines recommended for use in the CDF as comparators, or in a treatment sequence, in the appraisal of a new cancer medicine.

B.1.4 Equality considerations

Roche does not consider the use of atezolizumab in the first-line treatment of metastatic squamous or non-squamous NSCLC will raise 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 cost-effectiveness of atezolizumab in this appraisal is from IMpower110 (Table 4). The clinical development programme of atezolizumab monotherapy in NSCLC included two single arm Phase II studies, BIRCH (study GO28754 - first-line atezolizumab monotherapy in PD-L1–selected patients with advanced NSCLC) and FIR (study GO28625 - atezolizumab monotherapy in PD-L1–selected patients with advanced NSCLC). These studies demonstrated that atezolizumab monotherapy provide clinically meaningful activity, with durable responses as first-line treatment (34-36).

The median overall survival (OS) for BIRCH was 26.9 months (minimum follow-up of 22.5 months) (37) and 15.8 months for FIR (follow-up of 33.5 months) (36) in the chemotherapy-naïve high expressor subpopulation treated with atezolizumab. These trials will not be presented in full in this submission as they are single arm studies that do not inform the economic model.

Table 4: Clinical effectiveness evidence (38)

Study	IMpower110				
Study design	Randomised, Phase III, global, multicentre, open-label study				
Population	PD-L1–selected (≥1% of TC or IC covering ≥1% of the tumour area [TC1/2/3 or IC1/2/3]*), chemotherapy-naive patients with Stage IV non-squamous or squamous NSCLC without EGFR mutations or ALK translocations				
Intervention(s)	Atezolizumab				
Comparator(s)	Cisplatin or carboplatin and pemetrexed (non-squamous) or gemcitabine (squamous)				
Indicate if trial supports application for marketing authorisation	Yes	✓	**Indicate if trial used in the economic model**	Yes	✓
	No			No	
Rationale for use/non-use in the model	The IMpower110 trial comprises the relevant population, intervention, comparators and outcomes				
Reported outcomes specified in the decision problem	• overall survival • progression-free survival • response rate				

	• adverse effects of treatment • health-related quality of life
All other reported outcomes	N/A

IC: immune cells; NSCLC: non-small cell lung cancer; TC: tumour cells

* Please refer to Table 5 for the definition of TC1/2/3 or IC1/2/3

B.2.3 Summary of methodology of IMpower110

- **IMpower110 investigates the efficacy and safety of atezolizumab as first-line monotherapy compared with cisplatin or carboplatin and pemetrexed or gemcitabine in advanced non-squamous and squamous NSCLC without ALK or EGFR mutations (wild-type; WT)**
- **In this submission, we report the:**
    - **Primary OS analysis (CCOD: 10th September 2018) for IMpower110 in patients with advanced NSCLC without EGFR mutations or ALK alterations (WT), whose tumours have high PD-L1 expression (TC3 or IC3)**
    - **Exploratory OS analysis (CCOD: 4th February 2020) for IMpower110 in patients with advanced NSCLC without EGFR mutations or ALK alterations (WT), whose tumours have high PD-L1 expression (TC3 or IC3)**
- **This corresponds to the** [redacted]

B.2.3.1 Methodology

Study design

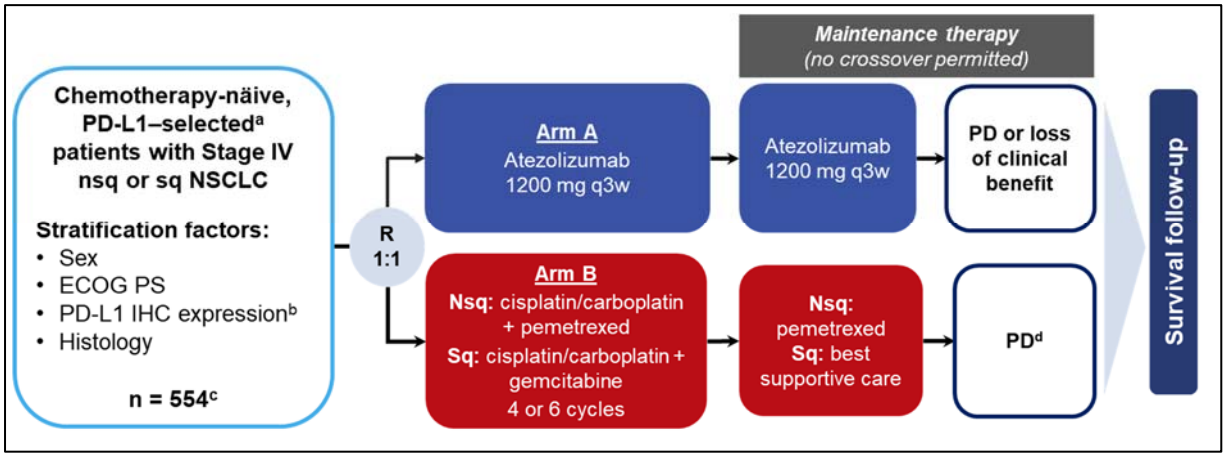
IMpower110 (NCT02409342) is a global, randomised, open-label Phase III trial designed to evaluate the efficacy and safety of atezolizumab monotherapy compared with chemotherapy consisting of a platinum agent (cisplatin or carboplatin per investigator discretion) combined with either pemetrexed (non-squamous disease) or gemcitabine (squamous disease) in PD-L1-selected, chemotherapy-naïve patients with Stage IV NSCLC without EGFR mutations or ALK alterations (wild type [WT]). The study schema is presented in Figure 2.

Initially, patients with a known sensitising EGFR mutation or ALK translocation were eligible provided they had received prior targeted therapy. The protocol was subsequently amended

to exclude these patients from analysis (n=18) because emerging data suggested that they may not benefit from immune checkpoint inhibitor monotherapy (see Appendix F).

The IMpower110 study population referred to throughout this submission is the 'wild-type' (WT) unless otherwise stated.

Figure 2: IMpower110 study schema for adult patients with metastatic non-squamous and squamous NSCLC[a] (39)



ECOG-PS: Eastern Cooperative Oncology Group performance status; IC, tumour-infiltrating immune cells; Nsq, non-squamous; PD: progressive disease; Sq, squamous; TC, tumour cells; WT, wild-type

[a] PD-L1 positive defined as TC1/2/3 or IC1/2/3 (PD-L1 expression ≥1% on TC or IC), with tumour PD-L1 expression determined by IHC assay (VENTANA SP142 IHC assay) performed by a central laboratory.

[b] TC1/2/3 and any IC vs TC0 and IC1/2/3.

[c] WT population excludes patients with EGFR+ and/or ALK+ NSCLC.

[d] Patients in the atezolizumab arm were permitted to continue treatment if RECIST v1.1 criteria for progressive disease were met (listed in section below headed "Treatment beyond progression")

Patients with non-squamous disease were randomised 1:1 to receive either atezolizumab alone or pemetrexed in combination with cisplatin or carboplatin. Patients with squamous disease were randomised 1:1 to receive either atezolizumab alone or gemcitabine in combination with cisplatin or carboplatin.

Randomisation

Randomisation was stratified by sex (male vs. female), Eastern Cooperative Oncology Group (ECOG) Performance Status (0 vs. 1), histology (non-squamous vs. squamous), and

PD-L1 tumour expression by IHC (TC1/2/3 and any IC vs. TC0 and IC1/2/3 – see Table 5 for definition of cut-offs).

Cycles of treatment

The intended number of cycles planned for the platinum-based induction chemotherapy (i.e., four or six cycles) was specified by the investigator prior to study randomisation. Chemotherapy treatment continued until disease progression, unacceptable toxicity, or death. Given the toxicities associated with platinum-based chemotherapies (e.g., neutropenia, anaemia) and the requirement for pre-medications, this was an open-label study. No crossover was allowed from the control arm (platinum-based chemotherapy) to the experimental arm (atezolizumab).

Treatment beyond progression

Atezolizumab treatment continued as long as patients were experiencing clinical benefit as assessed by the investigator (i.e., in the absence of unacceptable toxicity or symptomatic deterioration attributed to disease progression as determined by the investigator after an integrated assessment of radiographic data, biopsy results [if available], and clinical status) or until unacceptable toxicity or death. During treatment, patients who were treated with atezolizumab and who showed evidence of clinical benefit were permitted to continue atezolizumab treatment after RECIST (Response Evaluation Criteria in Solid Tumours) v1.1 criteria for progressive disease if they met all of the following criteria:

- Evidence of clinical benefit as assessed by the investigator
- Absence of symptoms and signs (including worsening of laboratory values [e.g., new or worsening hypercalcemia]) indicating unequivocal progression of disease
- No decline in ECOG Performance Status that was attributed to disease progression
- Absence of tumour progression at critical anatomical sites (e.g., leptomeningeal disease) that could not be managed by protocol-allowed medical interventions
- Patients must have provided written consent to acknowledge deferring other treatment options in favour of continuing study treatment at the time of initial radiographic progression per RECIST v1.1

Assessments

All patients underwent tumour assessment at baseline and every 6 weeks for 48 weeks following Cycle 1, Day 1 regardless of treatment delays. After 48 weeks, tumour assessment

was required every 9 weeks regardless of treatment delays, until radiographic disease progression per RECIST v1.1 (or loss of clinical benefit for atezolizumab-treated patients who had continued treatment with atezolizumab after radiographic disease progression according to RECIST v1.1), withdrawal of consent, death, or study termination by the Sponsor, whichever occurred first. Patients who discontinued treatment for reasons other than radiographic disease progression per RECIST v1.1 (e.g., toxicity, symptomatic deterioration) continued scheduled tumour assessments until one of the above occurred, regardless of whether patients started a new anti-cancer therapy.

Adverse events (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) v22.0.

An independent Data Monitoring Committee (iDMC) evaluated safety data and the primary analysis of the overall survival (OS) in the IC3 or IC3 subpopulation

B.2.3.2 Inclusion/exclusion criteria

At screening, tumour specimens from each potentially eligible patient were tested for PD-L1 expression by a central laboratory using the Ventana SP142 immunohistochemistry (IHC) assay. Only patients who were PD-L1 positive (TC1/2/3 or IC1/2/3; corresponding to ≥1% PD-L1 expressing TCs and/or ≥1% of tumour area occupied by PD-L1 expressing ICs, see Table 5 for definition of cut-offs) were enrolled. Please see Appendix E for the full inclusion/exclusion criteria.

Analyses were performed in predefined PD-L1 subpopulations based on the proportion of PD-L1 expressing TCs or tumour area occupied by PD-L1 expressing ICs**. As** [redacted] Please refer to Section B.2.3.5 for the study rationale.

B.2.3.3 PD-L1 IHC assay comparison

Two additional PD-L1 IHC assays were carried out to assess assay comparability with regard to clinical outcomes: SP263 (Ventana; secondary efficacy endpoint) and 22C3 (Dako; exploratory analysis).

The SP142 scoring algorithm (Ventana, Tuscon, AZ) measures PD-L1 expression on both TC and IC[3], whereas the 22C3 (Dako, Carpinteria, CA) and SP263 (Ventana, Tuscon, AZ) scoring algorithms specifically measure PD-L1 expression on TC. The PD-L1 expression cut-offs for each of the assays are presented in Table 5.

Table 5: Summary of PD-L1 cut-offs for the main PD-L1 IHC assays

PD-L1 IHC assay	PD-L1 expression			
	High	**Medium or high**	**Any**	**None**
Scope	**Within scope of this appraisal**	**Outside scope of this appraisal**	**Outside scope of this appraisal**	**Outside scope of this appraisal**
SP142 PD-L1 IHC (VENTANA) ***Based on key atezolizumab studies***	**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)
22C3 PD-L1 IHC (Dako) ***Based on key pembrolizumab studies***	**TPS ≥50%** PD-L1 expression on ≥50% of TCs	**TPS ≥20%** PD-L1 expression on ≥20% of TCs	**TPS ≥1%** PD-L1 expression on ≥1% of TCs	**TPS <1%** PD-L1 expression on <1% of TCs
SP263 PD-L1 IHC (VENTANA) ***Based on key durvalumab studies***	**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

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

Column highlighted pink: This is the subpopulation of interest for this submission

B.2.3.4 Endpoints and assessments

The primary efficacy analysis were performed for the TC3 or IC3 subpopulation, the TC2/3 or IC2/3 subpopulation, and the TC1/2/3 or IC1/2/3 population (all WT only and identified

[3] PD-L1 is expressed in TC and tumor-infiltrating IC and higher PD-L1 expression detected in these cells in tumour tissue, is correlated with increased objective response rates, progression-free survival, and overall survival in patients with NSCLC 40. Vennapusa B, Baker B, Kowanetz M, Boone J, Menzl I, Bruey J-M, et al. Development of a PD-L1 Complementary Diagnostic Immunohistochemistry Assay (SP142) for Atezolizumab. Appl Immunohistochem Mol Morphol. 2019;27(2):92-100.

using the Ventana SP142 IHC assay - see Section B.2.4 on the hierarchical testing). Secondary efficacy endpoints included:

- Investigator-assessed progression-free survival (PFS) per RECIST 1.1
- Objective response rate (ORR) and duration of response (DOR)
- OS and investigator-assessed PFS per RECIST 1.1 in pre-specified PD-L1 IHC (Ventana SP263) and bTMB subgroups[4]
- Patient-reported outcomes (PRO) of lung cancer-related symptoms and treatment impact on functioning and health-related quality of life (HRQoL) using the Symptoms in Lung Cancer (SILC), European Organisation for the Research and Treatment of Cancer quality of life questionnaire (EORTC QLQ-C30) and EORTC quality of life lung cancer module (QLQ-LC13)
- Safety was assessed in all treated patients (the intent-to-treat [ITT] population) regardless of PD-L1 expression or EGFR/ALK status

Exploratory endpoints included:

- OS and investigator-assessed PFS per RECIST 1.1 in pre-specified PD-L1 IHC (22C3) subgroups

For this submission, the subpopulation of interest for OS and PFS outcomes is PD-L1–high expressors (TC3 or IC3, tumour proportion score [TPS] ≥50%, or TC ≥50%).

B.2.3.5 Rationale for the IMpower110 study design and the target patient population in this submission

This IMpower110 study was based on the hypothesis that in patients with stage IV NSCLC who were chemotherapy-naïve and whose tumours are selected for PD-L1 expression, treatment with atezolizumab could prolong OS compared with platinum-based chemotherapy. The following describes the previous studies which supports the rationale for focussing on the PD-L1 population.

Improvement in OS was previously observed in atezolizumab monotherapy versus docetaxel trials, OAK and POPLAR, in previously treated patients with NSCLC across PD-L1

[4] bTMB subgroup analysis data are not presented in this submission as bTMB is not routinely tested in UK clinical practice and the data are not included in the economic model

expression subgroups (41, 42). In OAK, for the TC1/2/3 or IC1/2/3 subpopulation, OS was significantly improved with atezolizumab compared with docetaxel (median OS, 15.7 vs. 10.3 months; hazard ratio [HR]: 0.74; 95% confidence interval [CI]: 0.58, 0.93; p = 0.0102) (42). In POPLAR, for the TC1/2/3 or IC1/2/3 subpopulation, the median OS was 15.5 months in the atezolizumab arm vs.9.2 months in the docetaxel arm (HR:0.59; 95%: 0.40, 0.85; p = 0.005) (41).

Data from FIR, an open-label of atezolizumab monotherapy in PD-L1–selected patients with first- or second-line NSCLC also showed clinically meaningful activity; in patients with TC3 or IC3 tumours treated with first-line atezolizumab, median OS was 15.8 months (36). In addition, data from BIRCH, a single-arm phase II study of atezolizumab monotherapy across different lines of treatment (including first-line) demonstrated a clinically meaningful benefit of atezolizumab monotherapy as first-line treatment for PD-L1-selected patients (TC3 or IC3) with NSCLC, with a median OS of 26.9 months (37).

These data provide the rationale for the IMpower110 trial, given that first-line (1L) treatment with platinum-based chemotherapy generally results in median overall survival of 8 to 10 months (34, 43). Furthermore, this submission is focussed specifically on the TC3 or IC3 subpopulation as supported by the studies mentioned above (34, 36, 41, 42).

B.2.3.6 Baseline characteristics

Between July 21, 2015, and February 20, 2018, 572 patients (including 18 with EGFR mutations or ALK rearrangements – see Section B.2.3.1 for rationale of exclusion and Appendix D.1.2 for the patient flow) were recruited at 144 centres in 19 countries, with 285 and 287 patients randomised to receive atezolizumab and chemotherapy, respectively. Analyses were performed in predefined PD-L1 populations based on the proportion of PD-L1 expressing TCs or tumour area occupied by PD-L1 expressing ICs:

- The TC1/2/3 or IC1/2/3 population (i.e., all WT randomised patients) comprised 554 patients (277 patients in each arm)
- The TC2/3 or IC2/3 subpopulation comprised 328 patients (166 in the atezolizumab arm and 162 in the comparator arm)
- The TC3 or IC3 subpopulation comprised 205 patients (107 in the atezolizumab arm and 98 in the comparator arm)

Baseline characteristics were generally balanced between treatment arms for both the TC1/2/3 or IC1/2/3 population and the TC3 or IC3 subpopulation (Table 6). Overall, 107

(38.6%) patients in the atezolizumab arm and 98 (35.4%) in the chemotherapy arm had tumour PD-L1 TC3 or IC3 status. PD-L1 status was determined using the Ventana SP142 IHC assay.

Table 6: Patient Demographics and Baseline Characteristics

	TC1/2/3 or IC1/2/3 population		TC3 or IC3 subpopulation	
Characteristic	**Atezo n=277**	**Chemo n=277**	**Atezo n=107**	**Chemo n=98**
Scope	**Not in scope of appraisal**		**In scope of appraisal**	
Age, years				
Median	63.2	65	63	65.5
Range	30-81	30-87	33-79	33-87
Age group, n (%)				
<65 years	143 (51.6)	134 (48.4)	59 (55.1)	43 (43.9)
65-74 years	106 (38.3)	117 (42.2)	33 (30.8)	47 (48.0)
75-84 years	28 (10.1)	24 (8.7)	15 (14.0)	7 (7.1)
≥85 years	0	2 (0.7)	0	1 (1.0)
Sex, n (%)				
Male	196 (70.8)	193 (69.7)	79 (73.8)	64 (65.3)
Race, n (%)				
White	227 (81.9)	240 (86.6)	87 (81.3)	82 (83.7)
Asian	45 (16.2)	30 (10.8)	20 (18.7)	15 (15.3)
Black or African American	2 (0.7)	2 (0.7)	0	0
Multiple	1 (0.4)	0	0	0
Unknown	2 (0.7)	5 (1.8)	0	1 (1.0)
ECOG performance status, n (%)				
0	97 (35.0)	102 (36.8)	35 (32.7)	38 (38.8)
1	180 (65.0)	175 (63.2)	72 (67.3)	60 (61.2)

Tobacco use history, n (%)				
Never	37 (13.4)	35 (12.6)	9 (8.4)	15 (15.3)
Current	74 (26.7)	81 (29.2)	20 (18.7)	29 (29.6)
Previous	166 (59.9)	161 (58.1)	78 (72.9)	54 (55.1)
Histology at diagnosis, n (%)				
Non-squamous	192 (69.3)	193 (69.7)	80 (74.8)	75 (76.5)
Squamous	85 (30.7)	84 (30.3)	27 (25.2)	23 (23.5)

B.2.4 Statistical analysis

See appendix D.1.2 for a participant flow diagram, which provides details of the number of participants eligible to enter the trial.

The IMpower110 trial will explore efficacy of atezolizumab monotherapy in the following populations as defined by PD-L1 status: TC3 or IC3, TC2/3 or IC2/3 and TC1/2/3 or IC1/2/3. Only data from the TC3 or IC3 subpopulation will be presented in this submission [redacted] the decision problem for this appraisal. Below is the description of the overall statistical plan for the IMpower110 trial. Notable protocol amendments are presented in Appendix F.

B.2.4.1 Statistical testing plan

To control for the overall type I error rate at a two-sided significance level of 0.05, the primary OS endpoint was tested hierarchically:

- TC3 or IC3 (≥50% TC or ≥10% IC),
- then TC2/3 or IC2/3 (≥5% TC or IC),
- then TC1/2/3 or IC1/2/3 (≥1% TC or IC; also referred to as the ITT population)

If the primary OS endpoint is statistically positive in all three primary analysis populations, a two-sided significance level of 0.05 will be passed down to compare PFS between the atezolizumab and control arms.

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B.2.4.2 Interim analysis timing

The plan for this trial was to conduct one interim efficacy analysis for the primary endpoint of OS in the TC3 or IC3, the TC2/3 or IC2/3, and the TC1/2/3 or IC1/2/3 subpopulations, respectively.

An interim OS analysis in the TC3 or IC3 subpopulation was to be conducted when approximately 96 OS events and an event-patient ratio of 45% had occurred. If the OS interim analysis in the TC3 or IC3 subpopulation was not claimed as statistically significant, the final analysis would be conducted when approximately 135 OS events have occurred in this population. If this final analysis was claimed statistically significant, the OS in the TC2/3 or IC2/3 and TC1/2/3 or IC1/2/3 subpopulations would be tested at the planned interim and final analyses accordingly.

The efficacy analyses carried out in IMpower110 were as follows:

- Analyses of OS and PFS were performed using a stratified log-rank test
- The hazard ratio (HR) and its 95% CI (confidence interval) were estimated using a stratified Cox regression model
- Kaplan-Meier methodology was used to estimate medians
- Brookmeyer-Crowley methodology was used to generate 95% CIs for the medians
- ORR and its 95% CI were calculated using the Clopper-Pearson method
- DOR was estimated using Kaplan-Meier methodology
- Pre-specified subgroup analyses was performed to assess the consistency of the treatment effect using unstratified hazard ratios that were estimated from a Cox proportional-hazards model

B.2.4.3 Statistical testing in this submission

Since the pre-specified OS interim analysis alpha boundary was not crossed in the TC2/3 or IC2/3 population at the clinical cut off date (CCOD) of 10th September 2018, PFS could not be formally tested. However, the primary efficacy endpoint for OS was met with a statistically significant and clinically meaningful improvement for the atezolizumab arm compared to the chemotherapy arm in the TC3 or IC3 subpopulation (Section B.2.7.1), therefore this submission presents the primary OS analysis for this population.

Also presented in this submission is an [redacted] (Section B.2.7).

B.2.5 Quality assessment of the relevant clinical effectiveness evidence

The quality assessment of the IMpower110 trial is shown in Table 7 - see appendix D.1.3 for the complete quality assessment of the included trials.

Table 7: Risk of bias assessment for IMpower110

Trial	Was the allocation sequence adequately generated?	Was the concealment of treatment allocation adequate?	Was knowledge of the allocated interventions adequately prevented from participants and personnel	Was knowledge of the allocated interventions adequately prevented from outcome assessors	Were incomplete outcome data adequately addressed?	Are reports of the study free of suggestion of selective outcome reporting?	Was the study apparently free of other problems that could put it at a high risk of bias?
IMpower 110	Yes	Yes	No	Unclear	Yes	Yes	Yes

B.2.6 Clinical effectiveness results from IMpower110 in the TC3 or IC3 subpopulation – Primary analysis

- **Treatment with atezolizumab compared with chemotherapy was associated with a 41% reduction in the risk of death. The Kaplan-Meier estimated median OS was 7.1 months longer in the atezolizumab arm (20.2 months) compared to the chemotherapy arm (13.1 months) (stratified HR: 0.59; 95% CI: 0.40, 0.89; p=0.0106)**

- **Among the TC3 or IC3 subpopulation, 2 (1.9%) and 29 (29.6%) patients in the atezolizumab and chemotherapy arms, respectively, received subsequent**

immunotherapy and the majority of patients in the atezolizumab arm received subsequent chemotherapy

- **PFS could not be formally tested and the p-values provided are, therefore, descriptive only. Treatment with atezolizumab relative to chemotherapy reduced the risk of disease progression or death by 37% (stratified HR: 0.63; 95% CI: 0.45, 0.88). The median PFS was 3.1 months longer in the atezolizumab arm (5.0 months chemotherapy vs. 8.1 months atezolizumab)**
- **Treatment with atezolizumab resulted in a numerically higher confirmed objective response compared with chemotherapy (28.6% chemotherapy vs. 38.3% atezolizumab) assessed by investigator per RECIST v1.1**
- **The median DOR for responders has not yet been reached in the atezolizumab arm and was 6.7 months in the chemotherapy arm**
- **QLQ-C30 and QLQ-LC13 completion rates were high at baseline and most study visits**
- **Time to deterioration of lung cancer–related symptoms was similar in both arms, indicating that patients' low symptom burden at baseline was maintained for a similar duration in both treatment arms**
- **Patients receiving atezolizumab sustained numerical improvements in physical functioning through Week 42 relative to baseline and no worsening in lung cancer–related symptoms compared with chemotherapy**
- **OS favoured atezolizumab vs. chemotherapy across nearly all key subgroups within the TC3 or IC3 subpopulation**
- **The survival benefit with atezolizumab was observed in patients with high PD-L1 expression across all PD-L1-IHC assays**

B.2.6.1 Overview of efficacy

The efficacy results presented are: the primary analysis of overall survival (OS); the final investigator-assessed PFS (PFS-INV) without formal statistical testing (the secondary endpoint of PFS can only be tested formally when the primary endpoint is positive in all three PD-L1 subgroups - see Section 2.4.1 on the statistical analysis); ORR and DOR in the TC3

or IC3 subpopulation. At the clinical cutoff date (CCOD) of 10th September 2018, 101 death events had occurred in the TC3 or IC3 subpopulation. The median duration of survival follow-up in the TC3 or IC3 subpopulation was 15.7 months.

The primary efficacy endpoint was met with a statistically significant and clinically meaningful improvement in OS for the atezolizumab arm compared to the chemotherapy arm in the TC3 or IC3 subpopulation. Atezolizumab monotherapy improved median OS by 7.1 months vs. chemotherapy (20.2 months vs. 13.1 months, respectively; stratified HR: 0.59 [95% CI, 0.40-0.89]; p=0.0106).

In the TC3 or IC3 subpopulation, median PFS-INV showed a clinically meaningful improvement in the atezolizumab arm, which was 3.1 months longer (8.1 months) compared to the chemotherapy arm (5.0 months). Confirmed ORR was higher in the atezolizumab arm compared to chemotherapy; DOR in confirmed responders is still immature and median DOR has not yet been reached for the atezolizumab arm.

An overview of the efficacy results in the TC3 or IC3 subpopulation is shown in Table 8.

Table 8: Overview of efficacy in the TC3 or IC3 subpopulation of IMpower110 (44)

Parameter	Atezolizumab	Chemotherapy
Primary Endpoint: Overall Survival		
TC3 or IC3 subpopulation	n = 107	n = 98
Patients with event (%)	[redacted]	[redacted]
Median duration of survival (95% CI) (months)		
Median OS, months	20.2	13.1
Stratified Hazard Ratio (95% CI)	0.59 (0.40, 0.89)	
p-value (Stratified log-rank)	0.0106	
Secondary Endpoints		
Progression-Free Survival		
TC3 or IC3 subpopulation	n =107	n = 98
Patients with event (%)	[redacted]	[redacted]
Median duration of PFS-INV (95% CI) (months)	8.1 (6.8, 11.0)	5.0 (4.2, 5.7)
Stratified Hazard Ratio (95% CI)	0.63 (0.45, 0.88)	
p-value (Stratified log-rank)	0.007[a]	
Objective Response Rate		
TC3 or IC3 subpopulation	n =107	n = 98
ORR (%)	38.3%	28.6%

(95% CI)	(29.08, 48.22)	(19.90, 38.58)
Duration of Response		
TC3 or IC3 subpopulation	n = 41	n = 28
Median DOR	NE	6.7
(95% CI)	(11.8, NE)	(5.5, 17.3)

CI: confidence interval; DOR: duration of response; NE: Not estimable; PFS: progression-free survival; WT: wild-type

Summaries of Time-to-Event (median, percentiles) were Kaplan-Meier estimates. 95% CI for median was computed using the method of Brookmeyer and Crowley. Hazard ratios were estimated by Cox regression. Stratification factors for the TC3 or IC3-WT population were: sex (male vs. female) and ECOG (0 vs. 1).

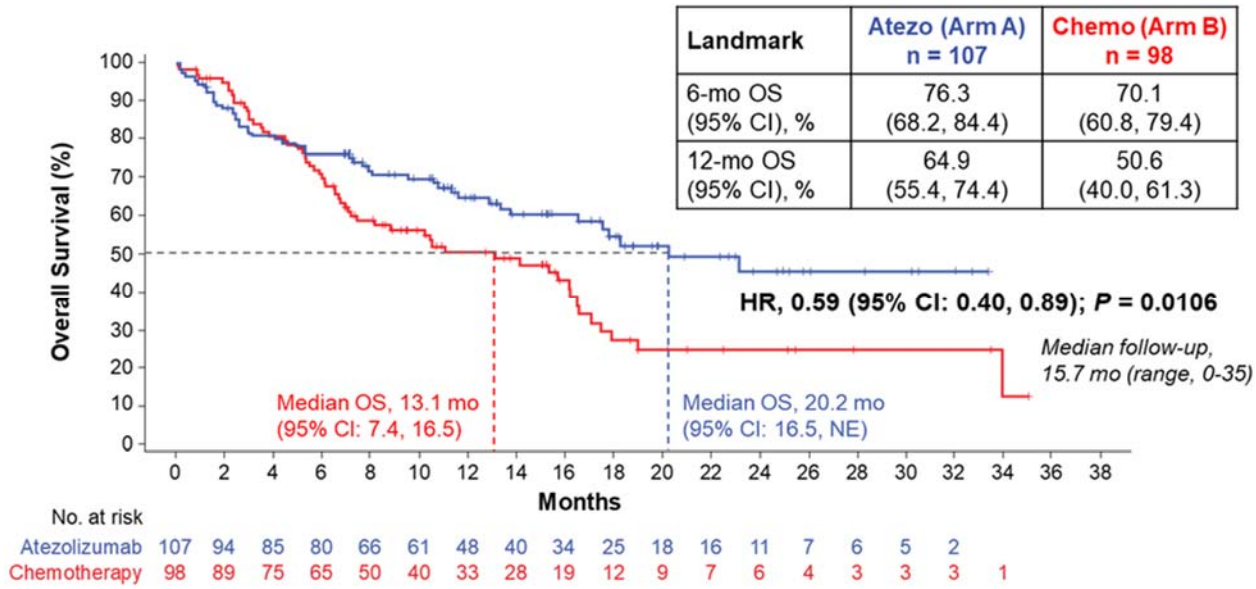
[a] p-value is descriptive only

B.2.6.2 Overall survival

At CCOD September 10th 2018, median survival follow-up times in the TC3 or IC3 subpopulation was 15.7 months (range, 0-35). Overall, 101 of 205 patients (49.3%) in the TC3 or IC3 subpopulation had died.

The primary analysis endpoint was met as the pre-specified interim analysis alpha boundary (α=0.0413) was crossed for OS in the TC3 or IC3 subpopulation with a statistically significant and clinically meaningful OS benefit in the atezolizumab treatment arm. Treatment with atezolizumab compared with chemotherapy was associated with an improvement of 7.1 months in median OS (20.2 vs 13.1 months; stratified HR, 0.59 [95% CI, 0.40-0.89]; P=0.0106), (Figure 3). The landmark OS rate was higher in the atezolizumab arm compared with the chemotherapy arm at six months (76.3% vs. 70.1%) and one year (64.9% vs. 50.6%) after randomisation.

Figure 3: Kaplan-Meier estimates of overall survival in the TC3 or IC3 subpopulation (44)



B.2.6.3 Subsequent anti-cancer therapy

Previous studies have suggested that immunotherapies have a prolonged effect and may influence the efficacy of subsequent therapies to continue the long-term effect (45). Therefore, it was of interest to observe subsequent therapies in this trial. Among the TC3 or IC3 subpopulation, 2 (1.9%) and 29 (29.6%) patients in the atezolizumab and chemotherapy arms, respectively, received subsequent immunotherapy and the majority of patients in the atezolizumab arm received subsequent chemotherapy (Table 9).

Table 9: Subsequent Anti-Cancer Therapy in the TC3 or IC3 subpopulation

	TC3 or IC3 subpopulation	
	Atezolizumab n=107	**Chemotherapy n=98**
Patients with ≥1 therapy, n (%)	26 (24.3)	46 (46.9)
Chemotherapy	23 (21.5)	18 (18.4)
Carboplatin	13 (12.1)	3 (3.1)
Docetaxel	5 (4.7)	11 (11.2)
Gemcitabine	8 (7.5)	1 (1.0)
Pemetrexed	8 (7.5)	0
Cisplatin	4 (3.7)	0
Paclitaxel	7 (6.5)	3 (3.1)

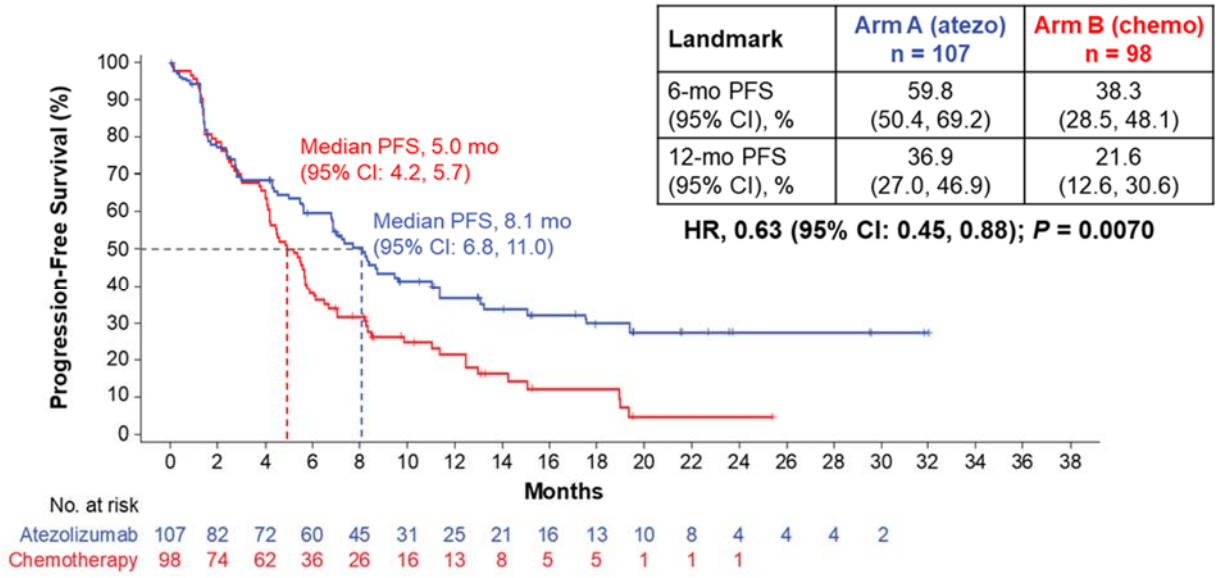
Etoposide	0	1 (1.0)
Vinorelbine	0	2 (2.0)
Paclitaxel albumin	1 (0.9)	1 (1.0)
Vinorelbine tartrate	0	0
Gimeracil; oteracil potassium; tegafur	1 (0.9)	0
Pemetrexed disodium	1 (0.9)	0
Gemcitabine hydrochloride	2 (1.9)	0
Irinotecan	0	0
Amrubicin	0	0
Carboplatin; pemetrexed	0	0
Cisplatin; gemcitabine	0	0
Cisplatin; pemetrexed	0	0
Immunotherapy	2 (1.9)	29 (29.6)
Nivolumab	2 (1.9)	11 (11.2)
Pembrolizumab	0	17 (17.3)
Atezolizumab	0	1 (1.0)
Immunotherapy	0	0
Ipilimumab	0	1 (1.0)
Targeted therapy	9 (8.4)	7 (7.1)
Bevacizumab	3 (2.8)	1 (1.0)
Nintedanib	1 (0.9)	2 (2.0)
Ramucirumab	1 (0.9)	0
Custirsen	0	2 (2.0)
Erlotinib	2 (1.9)	0
Capmatinib	0	0
Dasatinib	1 (0.9)	0

Erlotinib hydrochloride	0	1 (1.0)
Everolimus	0	0
Necitumumab	0	1 (1.0)
Selumetinib	1 (0.9)	0
Unknown	0	1 (1.0)
All other therapeutic products	0	1 (1.0)
Investigational anti-neoplastic drugs	0	0
Monoclonal antibodies	0	0

B.2.6.4 Progression-free survival

At CCOD September 10th 2018, since the OS has not yet reached statistical significance in the TC2/3 or IC2/3 subpopulation, there was no formal statistical testing of the PFS-INV and therefore, the p-values provided are descriptive only. Overall, 146 of 205 (71.2%) patients in the TC3 or IC3 subpopulation had a PFS event. PFS showed an improvement in the atezolizumab vs chemotherapy arm in TC3 or IC3 subpopulation (8.1 vs 5.0 months; stratified HR, 0.63 [95% CI, 0.45-0.88]) (Figure 4). The landmark PFS rate was higher in the atezolizumab arm compared with the chemotherapy arm at six months (59.8% vs. 38.3%) and one year (36.9% vs. 21.6%) after randomisation.

Figure 4: Progression-free survival in the TC3 or IC3 subpopulation (44)



Treatment comparisons for PFS were based on a stratified log-rank test; a stratified Cox regression model was used to estimate HRs, and 95% CIs were calculated using Brookmeyer-Crowley methodology. Medians were estimated using Kaplan-Meier methodology.

B.2.6.5 Objective response rate and duration of response

In the TC3 or IC3 subpopulation, investigator-assessed confirmed ORR was 38.3% and 28.6% for the atezolizumab and chemotherapy arms, respectively (Table 10). Median DOR in these patients was not reached for the atezolizumab arm and was 6.7 months for the chemotherapy arm (Table 10) (44).

The proportion of patients in the TC3 or IC3 subpopulation with a confirmed objective response (complete response [CR] or partial response [PR]), as assessed by investigator per RECIST v1.1, was higher in the atezolizumab arm (38.3%; 95% CI: 29.08, 48.22) compared to the chemotherapy arm (28.6%; 95% CI: 19.90, 38.58; Table 10).

[redacted]

Table 10: Investigator-assessed confirmed best overall response and duration of response in the TC3 or IC3 subpopulation (44, 46)

TC3 or IC3 subpopulation	Atezolizumab (N=107)	Chemotherapy (N=98)
Responders	41 (38.3%)	28 (28.6%)
Non-Responders	66 (61.7%)	70 (71.4%)
95% CI for Response Rate (Clopper-Pearson)	(29.1, 48.22)	(19.90, 38.58)
Median DOR (range), months	NE (1.8+ to 29.3+)	6.7 (2.6 to 23.9+)
Difference in Response Rates	[redacted]	
95% CI for Difference in Response Rates (Wald with Continuity Correction)	[redacted]	
p-Value* (Cochran-Mantel-Haenszel)	[redacted]	
Odds Ratio*	[redacted]	
95% CI for Odds Ratio*	[redacted]	
Complete Response (CR)	[redacted]	[redacted]
95% CI	[redacted]	[redacted]
Partial Response (PR)	[redacted]	[redacted]
95% CI	[redacted]	[redacted]
Stable Disease (SD)	[redacted]	[redacted]
95% CI	[redacted]	[redacted]
Progressive Disease (PD)	[redacted]	[redacted]
95% CI	[redacted]	[redacted]
Non-CR / Non-PD	[redacted]	[redacted]

95% CI	[redacted]	[redacted]
Missing or unevaluable	[redacted]	[redacted]

+: censored; NE: not estimable; WT: wild type

* Stratified by: Sex (male vs. female) and ECOG (0 vs. 1).

Wald is the normal approximation.

Patients were classified as missing or unevaluable when no post-baseline response assessments were available or all post-baseline response assessments were unevaluable.

B.2.6.6 Patient-reported outcomes

Patient-reported outcome assessment and analysis

Patient-reported outcomes (PROs)[5] of lung cancer-related symptoms and treatment impact on functioning and HRQoL (as measured by the Symptoms in Lung Cancer [SILC], European Organisation for the Research and Treatment of Cancer [EORTC] QLQ-C30, and EORTC QLQ-LC13) were descriptively evaluated as (46):

- Secondary efficacy (time-to-deterioration) and change from baseline of lung cancer-related symptoms) and,
- Exploratory endpoints (change from baseline in disease and treatment-related symptoms, functioning, and HRQoL)

Each of the scale and single-item measure scores is transformed to a score that ranges from 0 to 100. Higher scores on functional and global health status (GHS) and HRQoL scales represent healthier functioning and quality of life (QoL), respectively. Higher scores on a symptom scale or items represent worsening of symptoms. A ≥10-point change in the score on either EORTC scale is perceived by patients as clinically significant (47).

PRO assessments were completed by patients on an electronic PRO device (48):

- Prior to administration of study drug and any other study assessments according to the following schedule:
    - Every 6 weeks (± 7 days) for 48 weeks following Cycle 1, Day 1
    - Every 9 weeks (± 7 days) thereafter until PD or loss of clinical benefit

[5] Health status was also measured using the EuroQol 5-Dimension, 5-Level version (EQ-5D-5L) questionnaire and these data are included in the health economic modeling.

- After progression (at 3 and 6 months in survival follow-up)

The PRO data were scored according to the EORTC scoring manual (49). Time to deterioration in QLQ-LC13 lung cancer symptoms of dyspnoea (multi-item scale), coughing, and pain in chest, as well as a 3-symptom composite scale, were evaluated in a time-to-event analysis of deterioration (48):

- Clinically meaningful deterioration was defined as a ≥10-point increase from the baseline score in any of the 3 symptom scores, whichever occurred first, held for ≥2 consecutive cycles, or first ≥10-point increase above baseline followed by death prior to the next scheduled assessment (within 6 weeks through Week 48, and within 9 weeks from Week 48 thereafter)

- The Kaplan-Meier method was used to estimate survival function of time to deterioration

QLQ-C30 and QLQ-LC13 score changes from baseline were descriptively analysed using summary statistics (mean, standard deviation [SD], median, interquartile range, and range). Completion rates were calculated as the number of patients who completed a PRO assessment divided by the number of patients expected to complete a PRO assessment at each time point.

Assessment completion rates

High PRO completion rates were observed throughout treatment in both arms. At baseline, 90% of patients in the atezolizumab arm and 86% in the chemotherapy arm completed the QLQ-C30. The completion rate remained ≥80% at most study visits and patients completed assessments until Week 138 (inclusive) (48).

At baseline, 89% of patients in the atezolizumab arm and 85% in the chemotherapy arm completed the EORTC QLQ-LC13. The completion rate remained ≥80% at most study visits and patients completed assessments until Week 138 (inclusive) (48).

At Week 57, the completion rate was based on a total of 41 TC3 or IC3 patients from the combined arms who remained on study treatment and were expected to complete PRO assessments. Interpretation beyond Week 57 may be limited because of the low number of patients remaining on treatment and expected to complete PRO assessments.

Baseline disease burden

At baseline (i.e., before initiating study treatment), mean disease-related symptom, functioning, and HRQoL were comparable between treatment arms (Table 11). Patients reported low disease burden at baseline and, on average, moderate global health status, symptoms and physical functioning at baseline (46) (48).

Table 11: Mean baseline disease burden on select scales for the TC3 or IC3 subpopulation (48)

Baseline measure, Mean	Atezolizumab (n=107)	Chemotherapy (n=98)
GHS/HRQoL	**Higher scores indicate better HRQoL (scale, 0-100)**	
Global health status	62.8	59.9
Physical functioning	74.2	75.1
Role functioning	72.1	70.8
Disease burden	**Lower scores indicate lower symptom severity (scale, 0-100)**	
Coughing (QLQ-LC13)	36.2	29.3
Dyspnoea (QLQ-LC13)	24.0	25.0
Pain in chest (QLQ-LC13)	20.0	15.3
Pain in arm or shoulder (QLQ-LC13)	18.3	16.9
Pain in other parts (QLQ-LC13)	19.3	22.5
Pain (QLQ-30)	26.0	23.4
Fatigue (QLQ-30)	36.8	32.7
Appetite loss (QLQ-30)	25.7	22.6

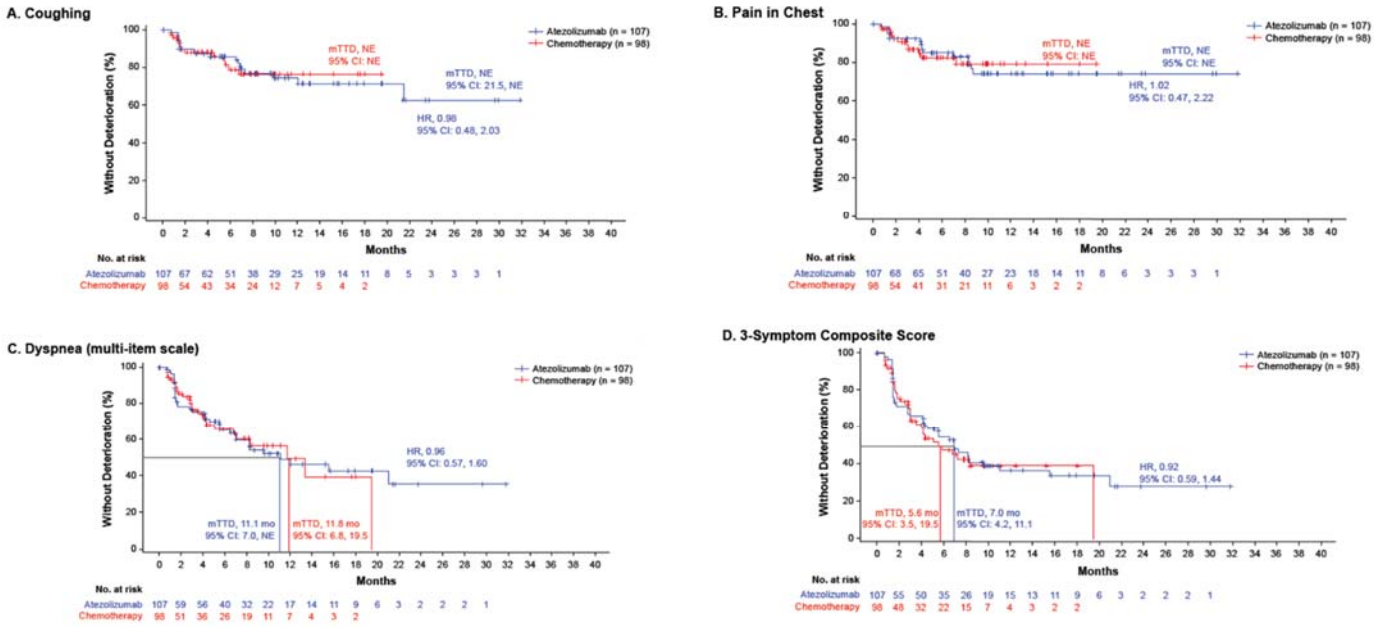
GHS: global health status; HRQoL: health-related quality of life

Time to deterioration in lung cancer symptoms

[redacted] between treatment arms for cough, chest pain, dyspnoea (multi-item), and 3-symptom composite for EORTC QLQ-LC13 in time to deterioration (defined as the time the first ≥10-point increase above baseline in any of the three symptom scores held for at least two consecutive assessments or followed by death within 6 weeks from the last assessment through Week 48 or death within 9 weeks from the last assessment from Week 48 thereafter) (46).

Median time to deterioration for dypsnoea was shorter than for coughing or pain in chest. Also median time to deterioration for the 3-symptom composite score was shorter than for any of the component symptoms (Figure 5) (48).

Figure 5: Time to confirmed deterioration of QLQ-LC13 symptoms in the TC3 or IC3 subpopulation (48)

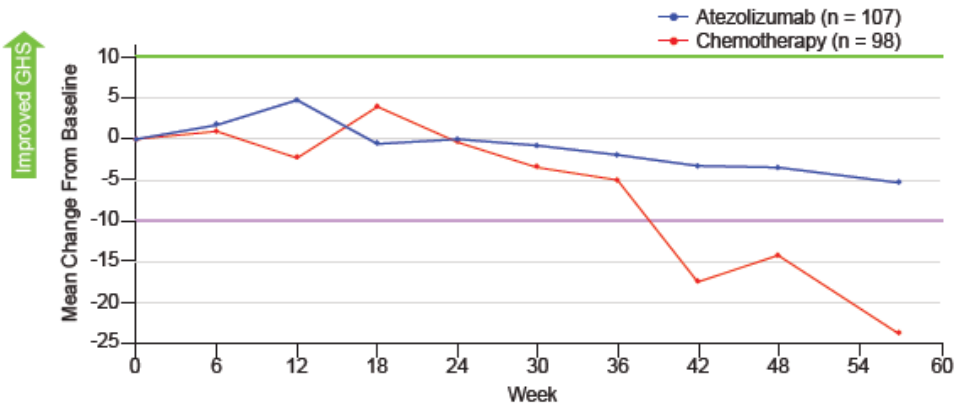


HR: hazard ratio; mTTD: median time to deterioration; mo: months; NE: not estimable; TTD: time to deteriorationarm at Week 6, 12, and 18 for both symptoms (46).

Mean change from baseline in HRQoL, functioning and symptoms

From Week 24 to Week 57, the decline in mean HRQoL was smaller for the atezolizumab arm than the chemotherapy arm, with no clinically meaningful improvement in mean HRQoL in either arm (Figure 6). Patients in the atezolizumab arm experienced a minimal improvement from baseline in mean HRQoL at Weeks 6 and 12 and then a minimal decrease throughout the study. Patients in the chemotherapy arm had minimal improvement in mean HRQoL at Weeks 6 and 18 before experiencing a minimal decrease throughout the study (48).

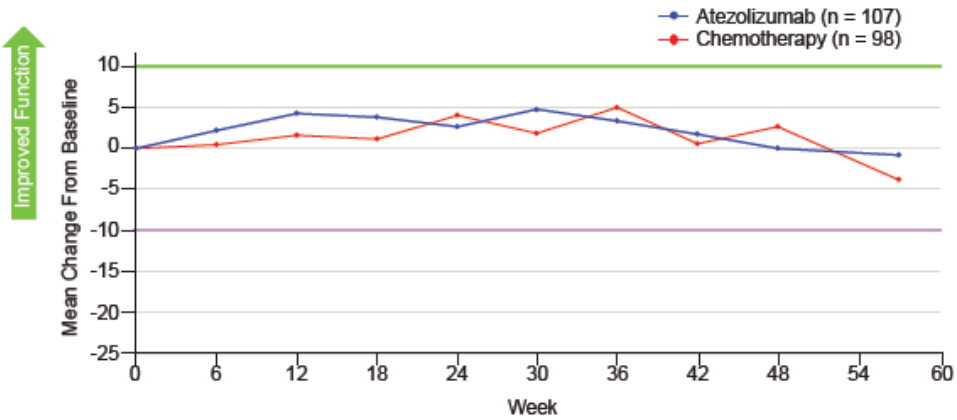
Figure 6: Mean change from baseline on the QLQ-C30 global health status in the TC3 or IC3 subpopulation (48)



The boundaries for clinically significant change are indicated for improvement (green line) and worsening (purple line).

At most study visits through Week 42, improvement was greater in the atezolizumab arm compared with the chemotherapy arm (Figure 7). Patients in the atezolizumab arm experienced modest improvement from baseline in mean physical functioning starting from Week 6 that was sustained through Week 42. Patients in the chemotherapy arm experienced modest improvement in mean physical functioning that was maintained through Week 48 (48).

Figure 7: Mean change from baseline on the QLQ-C30 physical functioning scales in the TC3 or IC3 subpopulation (48)

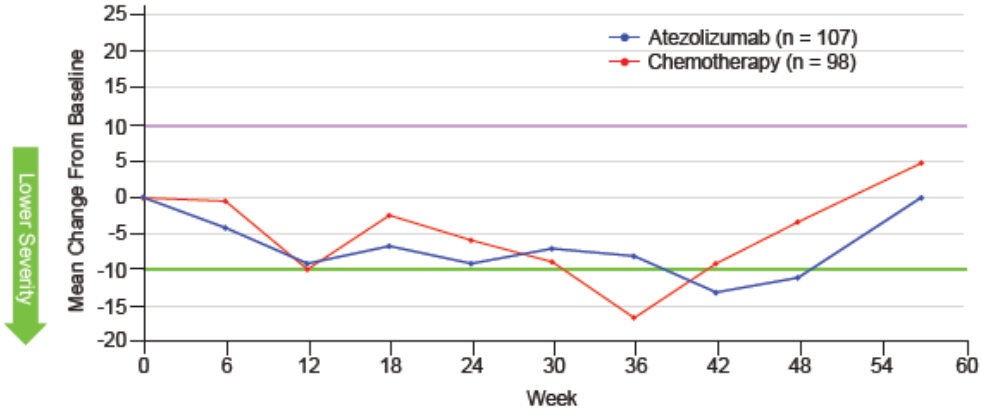


The boundaries for clinically significant change are indicated for improvement (green line) and worsening (purple line).

At most study visits, improvements in coughing symptoms in the atezolizumab arm were numerically better than or similar to the chemotherapy arm (Figure 8). Patients in the

atezolizumab arm experienced a numerical improvement from baseline in disease-related symptoms of coughing starting at Week 6 that was maintained through Week 48. Clinically meaningful improvement was achieved at Week 42 and Week 48 in the atezolizumab arm (48).

Figure 8: Mean change from baseline in EORTC QLQ-LC13 coughing symptoms in the TC3 or IC3 subpopulation (48)

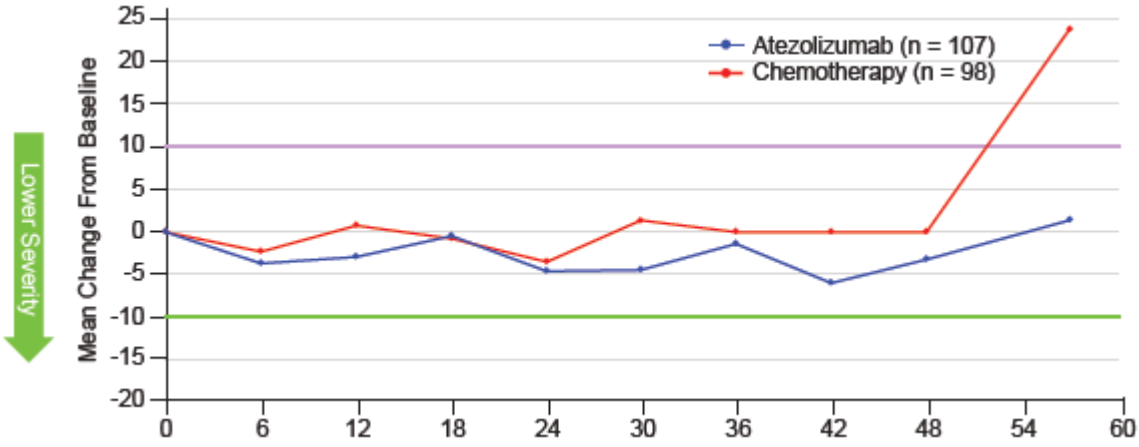


The boundaries for clinically significant change are indicated for improvement (green line) and worsening (purple line).

Patients in the atezolizumab arm experienced a numerical improvement from baseline in disease-related symptoms of pain in chest starting at Week 6 that was maintained through Week 48 (Figure 9). Improvements were not clinically meaningful in either arm.

Improvements in pain in chest in the atezolizumab arm were either numerically larger than or comparable to the chemotherapy arm (48).

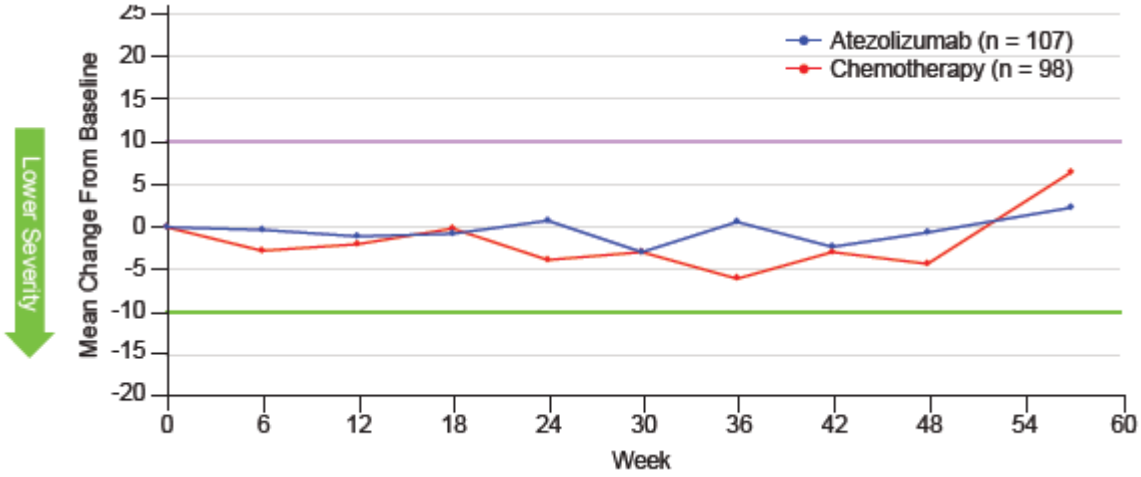
Figure 9: Mean change from baseline in EORTC QLQ-LC13 chest pain symptoms in the TC3 or IC3 subpopulation (48)



The boundaries for clinically significant change are indicated for improvement (green line) and worsening (purple line).

Improvements from baseline in disease-related symptoms of dyspnea were not clinically meaningful in either treatment arm (Figure 10) (48).

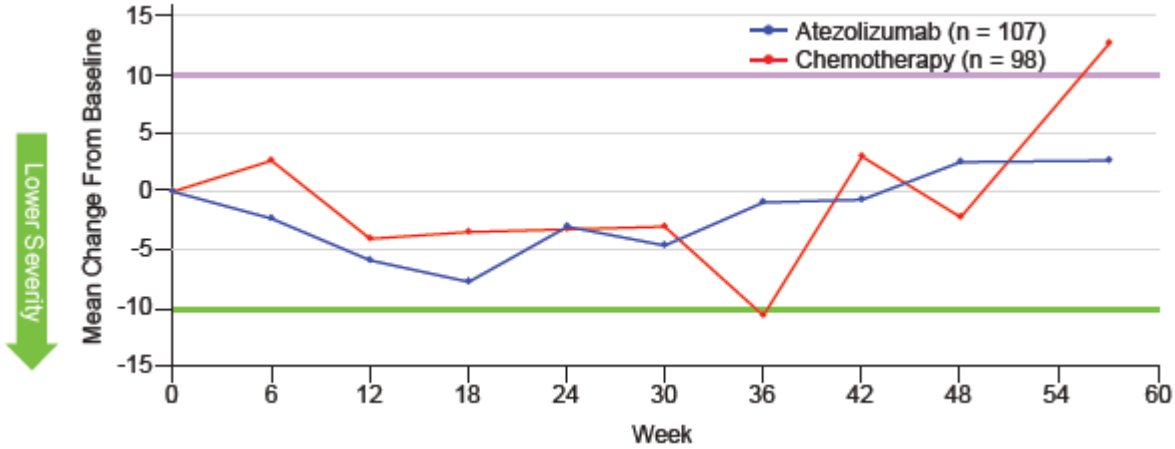
Figure 10: Mean change from baseline in EORTC QLQ-LC13 dypsnoea symptoms in the TC3 or IC3 subpopulation (48)



The boundaries for clinically significant change are indicated for improvement (green line) and worsening (purple line).

Improvements from baseline in fatigue in the atezolizumab arm were numerically higher than those in the chemotherapy arm at Weeks 6, 12 and 18 (Figure 11).

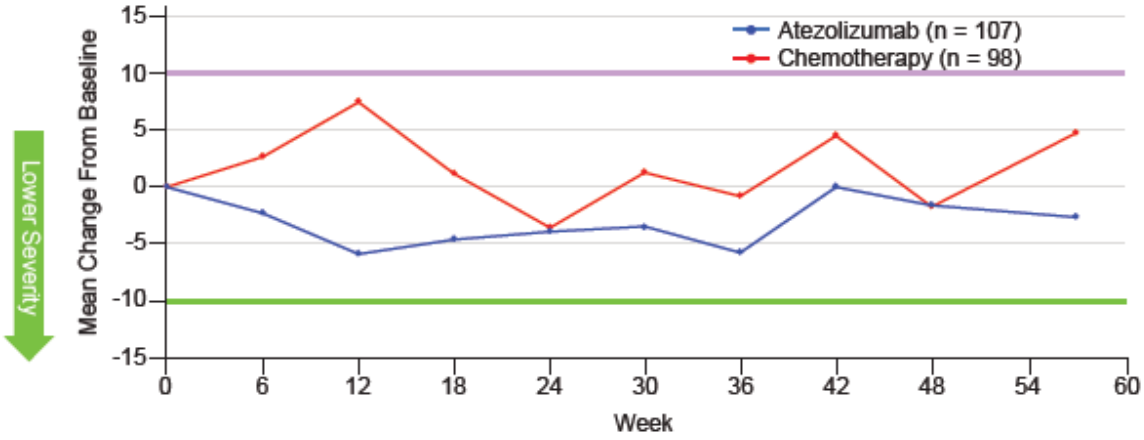
Figure 11: Mean change from baseline in the EORTC QLQ-C30 fatigue symptoms in the TC3 or IC3 subpopulation



The boundaries for clinically significant change are indicated for improvement (green line) and worsening (purple line).

Improvements from baseline in nausea and vomiting numerically improved from Week 6 and were maintained through Week 48 in the atezolizumab arm (Figure 12).

Figure 12: Mean change from baseline in the EORTC QLQ-C30 nausea and vomiting symptoms in the TC3 or IC3 subpopulation



The boundaries for clinically significant change are indicated for improvement (green line) and worsening (purple line).

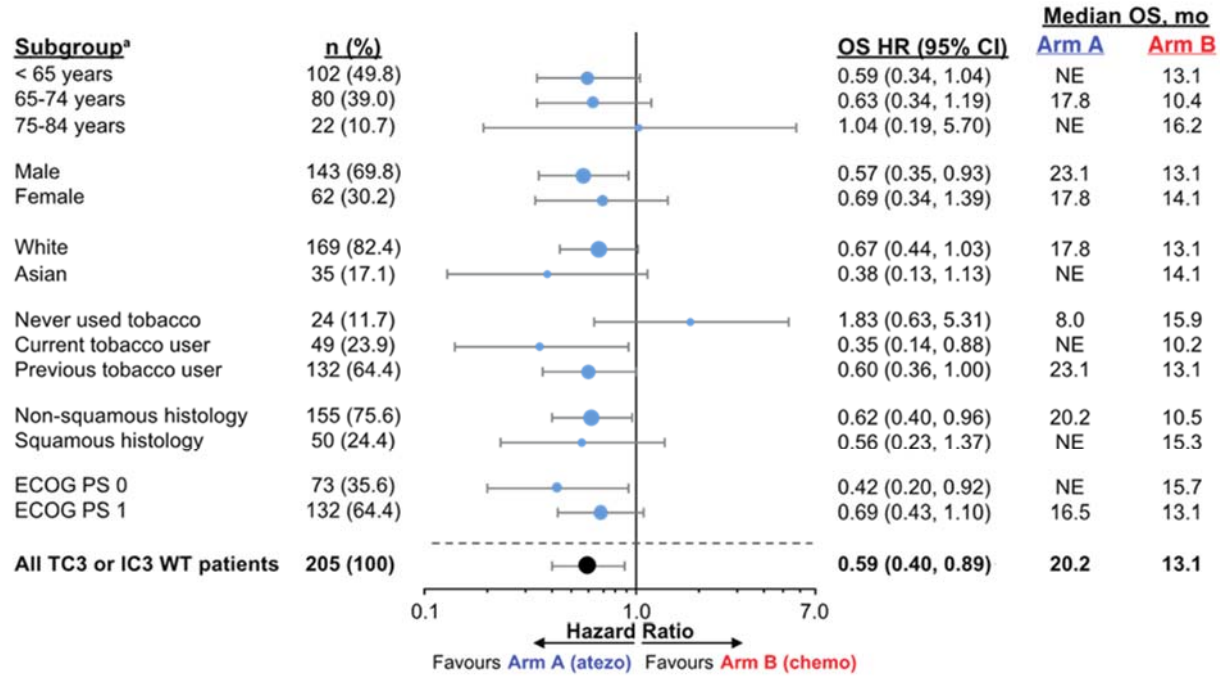
B.2.6.7 Subgroup analysis from IMpower110 in the TC3 or IC3 subpopulation

Overall survival by key subgroups within the TC3 or IC3 subpopulation

The consistency of OS was investigated by estimating the treatment effect in pre-defined subgroups based on stratifying factors (age, sex, race/ethnicity) and other baseline prognostic factors (histology, ECOG performance status, smoking history; Figure 13) (46). Full subgroup analysis of investigator-assessed PFS and ORR is presented in Appendix G.

OS favoured atezolizumab vs. chemotherapy across nearly all key subgroups within the TC3 or IC3 subpopulation, including non-squamous and squamous histology, which had similar hazard ratios (Figure 13). This is consistent with the benefit observed in the atezolizumab arm for the overall TC3 or IC3 subpopulation.

Figure 13: Key subgroups within TC3 or IC3 subpopulation (44)



Atezo: atezolizumab; BEP: biomarker-evaluable population; chemo: chemotherapy; CI: confidence interval; HR: hazard ratio; IC: immune cells; NE: not estimable; OS: overall survival; TC: tumour cell; WT: wild type.

[a] One patient in the ≥85-years subgroup is not included; 1 patient's race is unknown.

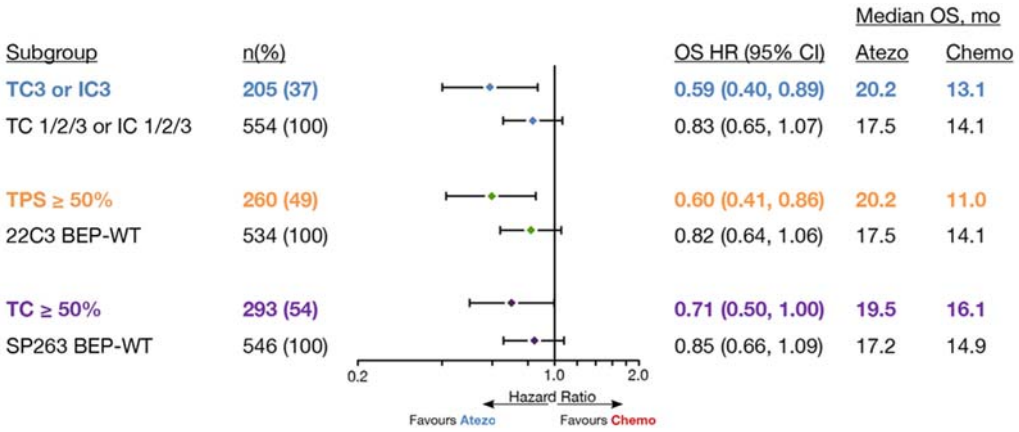
Overall survival by different IHC assays

Alternative, validated PD-L1 IHC assays (SP263 and 22C3) were used to define PD-L1 subgroups based on PD-L1 expression specifically on TCs (the SP142 assay evaluates expression on both TC and IC, Table 5). To explore the consistency between the assays, OS was evaluated by the (46):

- Ventana SP142 IHC assay (OS: primary analysis),
- SP263 IHC assay (secondary analysis),
- and 22C3 IHC assay (exploratory analysis)

In addition to the TC3 or IC3 subpopulation identitied using the SP142 IHC assay, the PD-L1 high subgroups based on the 22C3 and SP263 IHC assays also demonstrated improvement in OS in the atezolizumab arm compared with the chemotherapy arm (Figure 14). These results show the consistency of the benefit of atezolizumab across the IHC assays. In addition, the observed clinical benefit further supports atezolizumab monotherapy for the treatment of 1L NSCLC (50).

Figure 14: OS by high PD-L1 expression subgroups (defined by the SP142, SP263, and 22C3 assays) (39)



BEP: biomarker-evaluable population; CI: confidence interval; HR: hazard ratio; IC: immune cells; OS: overall survival; TC: tumour cells; TPS: tumour proportion score

Colour code: blue = SP142, orange = 22C3, purple = SP263

Note:

- TC1/2/3 or IC1/2/3 population represents the SP142-enrolled IMpower110 population without EGFR or ALK genetic alterations
- TC3 or IC3 = TC ≥ 50% or IC ≥ 10% PD-L1
- Stratified HRs for SP142 and unstratified HRs for 22C3 and SP263

The prevalence of PD-L1 expression for each IHC assay and the overlap between these assays is presented in Appendix G. The results for PFS by PD-L1 status is also presented in Appendix G.

B.2.7 Clinical effectiveness results from IMpower110 in the TC3 or IC3 subpopulation – exploratory analysis

- **In the exploratory analysis, at the median follow up of [redacted]:**
  - **The Kaplan-Meier estimated median OS was [redacted] in the atezolizumab arm and chemotherapy arm, respectively**
  - **PFS [redacted]. Treatment with atezolizumab relative to chemotherapy [redacted] The median PFS was [redacted]**
- **The objective reponse rate was [redacted] in the atezolizumab and chemotherapy arm, respectively**
- **The median duration of response was [redacted] in the atezolizumab and chemotherapy arm, respectively**
- **Among the TC3 or IC3 subpopulation, [redacted] subsequent chemotherapy**
- **In the exploratory biomarker analysis, there was [redacted]**

B.2.7.1 Overall survival (CCOD: 4th February 2020)

An exploratory analysis of the TC3 or IC3 subpopulation was completed at the same time as the final analysis of OS for the TC2/3 or IC 2/3 and IC1/2/3 or IC1/2/3 subpopulations (CCOD of 4th February 2020). This analysis shows a [redacted] benefit in the longer term follow up of [redacted]

Treatment with atezolizumab compared with chemotherapy was associated, with an [redacted] (Figure 15). The landmark OS rate was [redacted]

Figure 15: Kaplan-Meier estimates of overall survival in the TC3 or IC3 subpopulation - Exploratory analysis (CCOD: 04 February 2020) (51)

[redacted]

B.2.7.2 Subsequent anti-cancer therapies (CCOD: 4th February 2020)

Among the TC3 or IC3 subpopulation, [redacted] patients in the atezolizumab and chemotherapy arms, respectively, received subsequent immunotherapy (Table 12).

[redacted] received non-protocol therapies, especially immunotherapy.

Table 12: Subsequent Anti-Cancer Therapy in the TC3 or IC3 subpopulation (CCOD: 04 February 2020) (51)

TC3 or IC3 subpopulation	Atezolizumab n=107	Chemotherapy n=98

Total # with at least one NPT	[redacted]	[redacted]
Immunotherapy	[redacted]	[redacted]
Chemotherapy	[redacted]	[redacted]
Targeted Therapy	[redacted]	[redacted]

NPT: non-protocol therapies

B.2.7.3 Progression-free survival (CCOD: 4th February 2020)

At CCOD 4th February 2020, since the [redacted] in the TC2/3 or IC2/3 subpopulation [redacted] PFS showed an [redacted] (Figure 16). The landmark PFS rate was [redacted] after randomisation.

Figure 16: Kaplan-Meier estimates of progression-free survival in the TC3 or IC3 subpopulation – exploratory analysis (CCOD: 04 February 2020) (51)

[redacted]

B.2.7.4 Objective response rate and duration of response (CCOD: 4th February 2020)

[redacted] of patients in the TC3 or IC3 subpopulation achieved an objective response with atezolizumab versus [redacted] with

chemotherapy. The median duration of response was [redacted] with atezolizumab and [redacted] with chemotherapy.

B.2.7.5 Overall survival by different IHC assays (CCOD: 4th February 2020)

[redacted] in the atezolizumab arm compared with the chemotherapy arm using the SP142 IHC assay, but also using the 22C3 and SP263 IHC assays in patients with high PD-L1 expression (Table 13).

Table 13: OS by high PD-L1 expression subgroups as defined by the SP142, SP263, and 22C3 Assays (CCOD: 04 February 2020) (51)

Subgroups	n	HR	Atezolizumab Median OS, months	Chemotherapy Median OS, months
TC3 or IC3 (SP142)	205	[redacted]	[redacted]	[redacted]
TPS ≥50% (22C3)	260	[redacted]	[redacted]	[redacted]
TC ≥50%) (SP263)	293	[redacted]	[redacted]	[redacted]

B.2.7.6 Summary of exploratory analysis

The exploratory follow-up analysis of the TC3 or IC3 population was performed at an arbitrary time point (having already achieved statistical significance on 10th September 2018) when formal statistical analysis was conducted on the broader ITT population. The analysis showed that the [redacted] analysis and [redacted] of atezolizumab monotherapy for patients with metastatic NSCLC with high PD-L1 expression after an [redacted] of follow up.

The proportion of patients in the chemotherapy arm who received a subsequent non-protocol immunotherapy [redacted] between the two analyses, with an [redacted] of follow-up for crossover therapy to influence the performance of the chemotherapy arm. A rank preserving structural failure time (RPSFT) adjustment method was used to explore the impact of the cross over and this resulted in a [redacted], highlighting the effect that this crossover and length of follow up time had on the results (further details of analysis available in Appendix L).

B.2.8 Meta-analysis

Only one randomised controlled trial (RCT; IMpower110) has investigated the efficacy and safety of atezolizumab versus chemotherapy in treatment-naïve PD-L1–high NSCLC patients. Consequently, a meta-analysis was not conducted.

B.2.9 Indirect and mixed treatment comparisons

Appendix D includes full details of the methodology for the indirect comparison or mixed treatment comparison.

Key information for the indirect treatment comparisons

- An indirect treatment comparison (ITC) was necessary to enable atezolizumab to be compared with pembrolizumab in first-line stage IV squamous or non-squamous non-small cell lung cancer (NSCLC) and PD-L1 expression ≥ 50%
- Comparator studies were identified through a systematic literature review (SLR)
- The ITC followed NICE DSU recommendations and appropriate methodology
- A fractional polynomial NMA approach was implemented to allow for the different mechanism of action between cancer immunotherapies and chemotherapies
- Results of the NMA demonstrate that there is no evidence of a difference between atezolizumab and pembrolizumab for the outcomes assessed here
- NMA approaches are associated with a series of uncertainties and limitations relating primarily to the availability of evidence, the comparability of the included studies and the extrapolation of modelled outcomes. These are discussed at the end of Section B.2.9

B.2.9.1 Systematic literature review

A systematic literature review (SLR) was conducted to identify trials of specified interventions used as 1L therapy for stage IV squamous or non-squamous NSCLC in patients who have not received prior chemotherapy treatment for stage IV NSCLC and express PD-L1. In the absence of direct head-to-head data of atezolizumab against the

relevant comparators, an NMA was conducted based on a connected network of randomised controlled trials (RCTs).

The SLR used an Embase search strategy to identify RCTs in the population of interest. The strategy was devised using a combination of subject indexing terms and free text search terms in the title and abstract fields.

The strategy excluded animal studies from Embase using a standard algorithm. The strategy also excluded some publication types which were unlikely to yield relevant study reports, records which were indexed with the subject heading 'phase 1 clinical trial', unless other phases were also indicated, and records with the phrase ‘case report’ in the title field. The strategy was not restricted by date or language.

The Embase strategy was translated appropriately for other databases and information sources searched. The searches were first conducted in February 2018 then updated in October 2018 and September / October 2019. Overall, the most recent search identified 44,013 records and a further 7 records were identified from other sources. Following de-duplication, 28,399 records were screened based on the title and abstract, of which 27,046 were excluded. Overall, 1,353 documents were assessed at full text review and 1,229 were excluded with reasons, and 124 documents reporting on 12 trials were eligible for inclusion. Of these 12 trials, only three (IMpower110, KEYNOTE-024, and KEYNOTE-042) reported data on the treatments of interest to this submission, in the relevant population.

Appendix D summarises the methods and results of the SLR, and includes additional results from the NMA that are not covered here.

Comparators of interest

The comparator of interest for the analysis that is presented here, pembrolizumab, reflects the comparator considered in the decision problem addressed in this submission (please see Section B.1.1).

Please note that additional interventions were included in the eligibility criteria for the SLR, to account for treatment landscapes in other territories, ongoing trials of atezolizumab combinations in first-line NSCLC, and for upcoming comparator interventions in first-line NSCLC. However, these interventions are not included in the scope of this appraisal; the relevant studies were taken into account in the SLR for the purpose of informing future updates of the NMA network of evidence.

B.2.9.2 Networks and treatments used for the NMA

Of the studies identified during the SLR, it was decided that for the purpose of the current evidence submission, in order to align with the marketing authorisation and reimbursement from NICE, to exclude the CHECKMATE and atezolizumab combination trials (i.e. IMpower150, IMpower130, IMpower131 and, IMpower132), which included treatments that are not relevant to this appraisal. The patient population considered was the PD-L1 ≥ 50% or TC3/IC3 population, with mixed (non-squamous or squamous) histology.

The treatments considered for this analysis are listed in Table 14 with an overview of the included studies considering these treatments listed Table 15.

Table 14: List of included treatments and associated abbreviated names

Treatment name	Abbreviated treatment name for output labelling
Atezolizumab monotherapy	ATZ
Pembrolizumab monotherapy	PEMB
Chemotherapy	Chemo

Table 15: Summary of the trials used to carry out the indirect treatment comparison, with trial population sizes

Trial	N	ATZ	Chemo	PEMB
IMpower110	205	107	98	-
KEYNOTE-024	305	-	151	154
KEYNOTE-042	599	-	300	299

B.2.9.3 Analyses conducted

Analyses were conducted for the following outcomes:

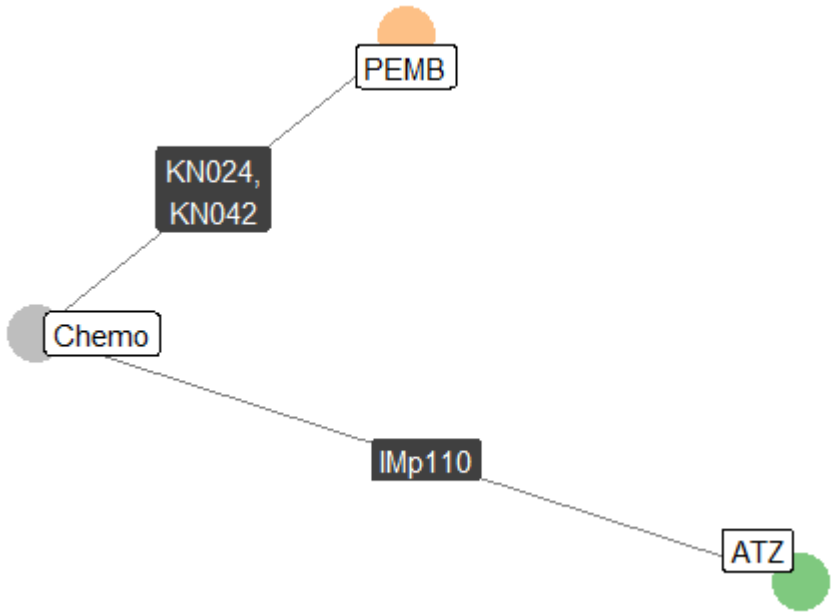
- Overall survival (OS)
- Progression free survival (PFS)
- Objective response rate (ORR)
- Safety outcomes

- Any treatment-related adverse event (TRAE)
- Any treatment-related serious adverse event (TRSAE)
- Any treatment-related adverse event grade 3 or above
- Withdrawal due to adverse event (AE)

For OS and PFS, analyses were conducted on both reported hazard ratio (HR) data and on individual patient survival times (reconstructed from Kaplan-Meier [KM] data for the KEYNOTE studies (52)).

No sensitivity or subgroup analyses were conducted. Figure 17 below shows the network informing each outcome.

Figure 17: Network of studies informing the NMA



B.2.9.4 Analysis methods

For aggregate hazard ratio (HR) data, we conducted the NMA using a Normal distribution and an identity link; the input data was log transformed prior to analysis i.e. log HRs and associated standard errors. We followed the recommendations laid out in NICE decision support unit (DSU) technical support document (TSD) 2 for generalised linear model (GLM) NMAs (53).

Since the mechanism of action for atezolizumab is novel, it was considered as a possibility that the survival profile over time is not proportional to chemotherapy. The NMA of OS and

PFS using time to event data takes this into account and allow for time-varying hazard ratios through the use of a fractional polynomial model (54).

For the ORR and safety outcomes, we conducted the NMA assuming a binomial distribution and a logit-link. We followed the recommendations laid out in NICE DSU TSD 2 for GLM NMAs (53).

For all outcomes, we evaluated both fixed and random effects models. We used informative priors for the between study variance for the random effects models, following Turner et al (55); see Table 16.

For all models analysis, R version 3.6.1 (56) was used in combination with the R package rjags (57) and JAGS v4.3.0 (58). The convergence of the Markov chain Monte Carlo (MCMC) chains were assessed via visual inspection of the trace plots and with Gelman-Rubin statistics (59). We used 3 chains, 5000 burn-in iterations followed by 30000 samples, thinned by a factor of 6.

More details on the methodology used to implement the different NMA can be found in Appendix D.

Table 16: Between-study heterogeneity prior distributions from Turner, 2015 (55)

Outcome	Outcome type as defined by Turner 2015	Prior
OS	All-cause mortality	~Log-normal (-4.18, 1.41^2)
PFS	Internal/external structure-related outcomes (e.g. radiograph outcomes)	~Log-normal (-2.94, 1.79^2)
ORR	Internal/external structure-related outcomes (e.g. radiograph outcomes)	~Log-normal (-2.94, 1.79^2)
AEs	Adverse events	~Log-normal (-2.10, 1.58^2)

B.2.9.5 Model selection

For all outcomes, when comparing the fixed and random effects models, the deviance information criterion (DIC) values were very close to each other. We therefore decided to use the random effects models for the primary results as this is a more conservative approach.

For the fractional polynomial (FP) model, both first and second-order FP models were assessed along with a proportional hazards exponential model.

The second order polynomials had a tendency to produce unrealistic extrapolations, with the predicted PFS or OS either reaching zero quickly, resulting in some cases in unrealistically low expected survival times, or mostly plateauing at a high proportion of survival when the underlying hazard dropped to near zero, leading to unrealistically high survival times. We therefore decided not to use these models.

Of the remaining models (exponential and first-order FP models: p1=0 Weibull, p1=1 Gompertz), for PFS, the Weibull model had a lower DIC, and for OS, the Gompertz was the best in terms of DIC.

Table 17: DIC values for fixed and random effects models for non-FP models

Outcome	Fixed effects	Random effects
OS	4.3	5.0
PFS	11.8	6.5
ORR	11.5	11.6
Any TRAE	13.1	12.8
Any TRAE grade 3+	10.8	11.2
Any TRSAE	7.8	7.7
Withdrawal due to AE	10.1	10.4

Table 18: DIC values for the exponential and first-order fixed and random effects FP models

Outcome	Fixed effects			Random effects		
	Exponential	Weibull (FP P1=0)	Gompertz (FP P1=1)	Exponential	Weibull (FP P1=0)	Gompertz (FP P1=1)
OS	725.3	712.8	700.0	725.9	713.4	700.8
PFS	840.6	826.4	817.5	836.0	817.2	808.5

Visual inspection indicated that within the range of observed data, the curves for the two models were very close and overlapping. They only diverged outside the range of observed

data. We therefore decided the difference in DIC did not reflect practical differences in predictive ability. In addition, the Weibull model generally led to survival estimates at the end of the time horizon either between those from the exponential and Gompertz models or very close to them. For ease of comparison, we therefore adopted the Weibull model for both the OS and PFS outcomes.

B.2.9.6 NMA results presentation

For the OS and PFS analyses based on reported HRs, a forest plot is presented for each analysis showing the hazard ratio for each comparator compared with atezolizumab (Figure 20 and Figure 21). The black dots indicate the best estimate of the hazard ratio, and the error bars indicate the location of the hazard ratio with 95% probability given the observed data. If the error bars overlap the dotted vertical line (at 1 on the horizontal axis), then this is insufficient (i.e. <95%) evidence of a difference between the comparator and atezolizumab in terms of OS/PFS hazard.

For the OS and PFS analyses based on fractional polynomial (FP) approach, each set of results presents a figure showing the relative hazard ratios over time, comparing atezolizumab to the respective comparator (Figure 19, Figure 22). The figure consists of several panels, each showing the results of comparing atezolizumab to a particular comparator. The fractional polynomial model allows the hazard ratio of progression or death to change over time depending on the treatment received. Therefore, the graph shows a black centreline that indicates how the best estimate (calculated using the median posterior estimate) of the hazard ratio changes with increasing follow-up time. The grey region around the black line indicates the location of the true hazard ratio curve with 95% probability, given the observed data. If this grey region is completely above or below 1 for some part of the follow-up time, that is sufficient evidence (≥95%) of a difference in hazard ratio during that particular period. In addition, a table of HR comparing atezolizumab to the respective comparators at specific time-points during the time horizon considered is also presented. Finally, a forest plot is presented (Figure 20,Figure 23) showing the median OS/PFS difference in months between atezolizumab to the respective comparators and 95% credible intervals for the time-horizon considered.

In appendix D.1.4, for the random effects base case of OS and PFS following fractional polynomial (FP) approach, a plot with predicted survival curves overlaid to the observed KM curves is presented by study and treatment. In the same appendix, for the ORR and AE analyses, forest plots are presented showing the odds ratio for each comparator compared with atezolizumab. The black dots indicate the best estimate of the odds ratio, and the error

bars indicate the location of the odds ratio with 95% probability given the observed data. If the error bars overlap the dotted vertical line (at 1 on the horizontal axis), then this is insufficient (i.e. <95%) evidence of a difference between the comparator and atezolizumab in terms of odds of achieving ORR / having a safety event.

For estimates of survival over time and expected survival, which are absolute rather than relative effect measures such as hazard ratio, we used IMpower110 as the reference study.

For OS and PFS analysed using the FP approach, results are based on model estimates extrapolated to 60 months.

B.2.9.7 NMA results – OS and PFS

For OS, the analysis using hazard ratios data indicated that there was insufficient evidence of a difference between atezolizumab and pembrolizumab. Figure 18 below shows the forest plot based on the IMpower CCOD February 2020 data cut. Using the 2018 data cut the conclusion of the NMA would not change, although the point estimate for OS would (HR 0.88 (0.49, 1.57)) (60).

Similarly, the random effects FP model indicated that there was insufficient evidence of a difference compared to atezolizumab in terms of hazard ratios (Figure 19 and Table 19), and expected OS (Figure 20).

For PFS, analysis using hazard ratio data indicated that there was insufficient evidence to conclude that the PFS hazard were different between atezolizumab and pembrolizumab (see Figure 21). The analysis using the random effects FP model likewise did not show any differences, either for the hazard over time, or for the expected PFS up to 60 months (see Figure 22, Table 20 and Figure 23).

Figure 18: OS hazard ratio based on hazard ratio data for pembrolizumab relative to atezolizumab, using the random effects model

The extent of the line indicates the 95% posterior credible interval, while the dots indicates the median posterior estimate.

Figure 19: OS hazard ratios of atezolizumab relative to pembrolizumab between 1 and 60 months, for the random effects FP model, order 1, P1=0 (Weibull)

Grey shaded region indicates the 95% posterior credible interval, while the black line indicates the median posterior estimate.

Table 19: OS hazard ratios of atezolizumab relative to pembrolizumab, between 3 and 60 months, for the random effects FP model, order 1, P1=0 (Weibull)

Time (months)	OS; HR of PEMB relative to ATZ (95% CrI); HR < 1 favours ATZ
3	
6	
12	
18	
24	
36	
48	
60	

The first number indicates the median posterior estimate, while the numbers in brackets indicate the 95% posterior credible interval.

Figure 20: Forest plot of expected OS difference for atezolizumab versus pembrolizumab up to a time horizon of 60 months, for the random effects FP model, order 1, P1=0 (Weibull)

The extent of the line indicates the 95% posterior credible interval, while the dot indicates the median posterior estimate.

Figure 21: PFS hazard ratio based on hazard ratio data for pembrolizumab relative to atezolizumab, using the random effects model

The extent of the line indicates the 95% posterior credible interval, while the dots indicates the median posterior estimate.

Figure 22: PFS hazard ratios of atezolizumab relative to pembrolizumab between 1 and 60 months, for the random effects FP model, order 1, P1=0 (Weibull)

Grey shaded region indicates the 95% posterior credible interval, while the black line indicates the median posterior estimate.

Table 20: PFS hazard ratios of atezolizumab relative to pembrolizumab, between 3 and 60 months, for the random effects FP model, order 1, P1=0 (Weibull)

Time (months)	PFS; HR of PEMB to ATZ (95% CrI); HR < 1 favours ATZ
3	0.55 (0.16, 1.97)
6	0.81 (0.23, 2.88)
12	1.19 (0.34, 4.50)
18	1.49 (0.41, 5.80)
24	1.74 (0.46, 7.06)
36	2.19 (0.54, 9.39)
48	2.58 (0.61, 11.41)
60	2.91 (0.66, 13.34)

The first number indicates the median posterior estimate, while the numbers in brackets indicate the 95% posterior credible interval.

Figure 23: Forest plot of expected PFS difference for atezolizumab versus pembrolizumab up to a time horizon of 60 months, for the random effects FP model, order 1, P1=0 (Weibull)

The extent of the line indicates the 95% posterior credible interval, while the dots indicates the median posterior estimate.

B.2.9.8 Heterogeneity and inconsistency evaluation

We conducted a heterogeneity analysis for all treatment comparisons informed by two or more studies. For outcomes where KM data were available, this took the form of a visual inspection of the KM curves based on the reconstructed individual patient data (IPD). For

outcomes where a summary measure was available e.g. odds ratio or hazard ratio, these were compared using forest plots, and summarised quantitatively using the I-squared statistic (61).

In general, for the network links where it was feasible to make the assessment, heterogeneity was low, as shown by the plots in Appendix D.1.6. The exception to this were for the data informing the pembrolizumab versus chemotherapy comparison for the hazard ratio analysis of PFS. In this case, the estimates from KN024 and KN042 trials exhibited substantial heterogeneity.

There were no loops within the networks, and therefore no inconsistency assessment was performed.

B.2.9.9 Evaluating whether the data supports a proportional hazard assumption

Log cumulative hazard plots were produced as recommended by NICE TSD 14 (62) to evaluate the behaviour of the observed hazards under different treatments. For the KEYNOTE studies, the reconstructed individual patient survival data was used for this.

The proportional hazards (PH) assumption was assessed through visual inspection of the log cumulative hazard plots (see Figure 24 and Figure 25). If the lines are straight and parallel then this suggests an exponential model would be most appropriate. If the lines are only parallel then this suggests an assumption of proportional hazards is valid. If the lines are not parallel, then this suggests assuming non-proportional hazards would be most appropriate. The plots indicate that in the three studies, the lines for the included treatments cross at between 1 and 6 months, meaning that the hazard ratio may differ between the early and the later part of the follow-up. However, for the second half, the lines for all three studies settle into a roughly parallel relationship. Together, this indicates that a non-proportional hazard approach may be the most exact method, but that assuming PH is unlikely to cause issues when extrapolating over longer periods of follow-up.

Figure 24: Log-cumulative hazard plot for OS

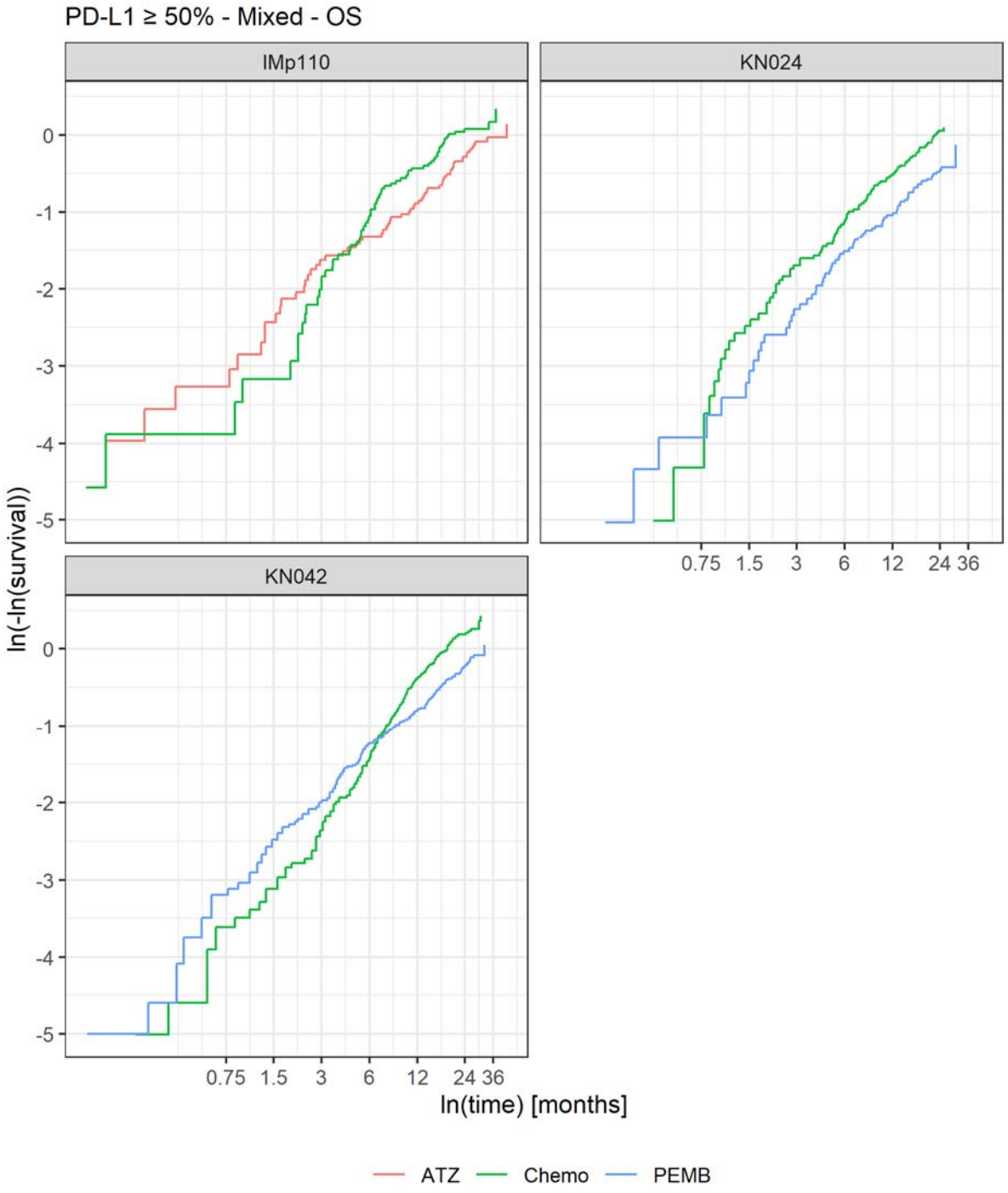
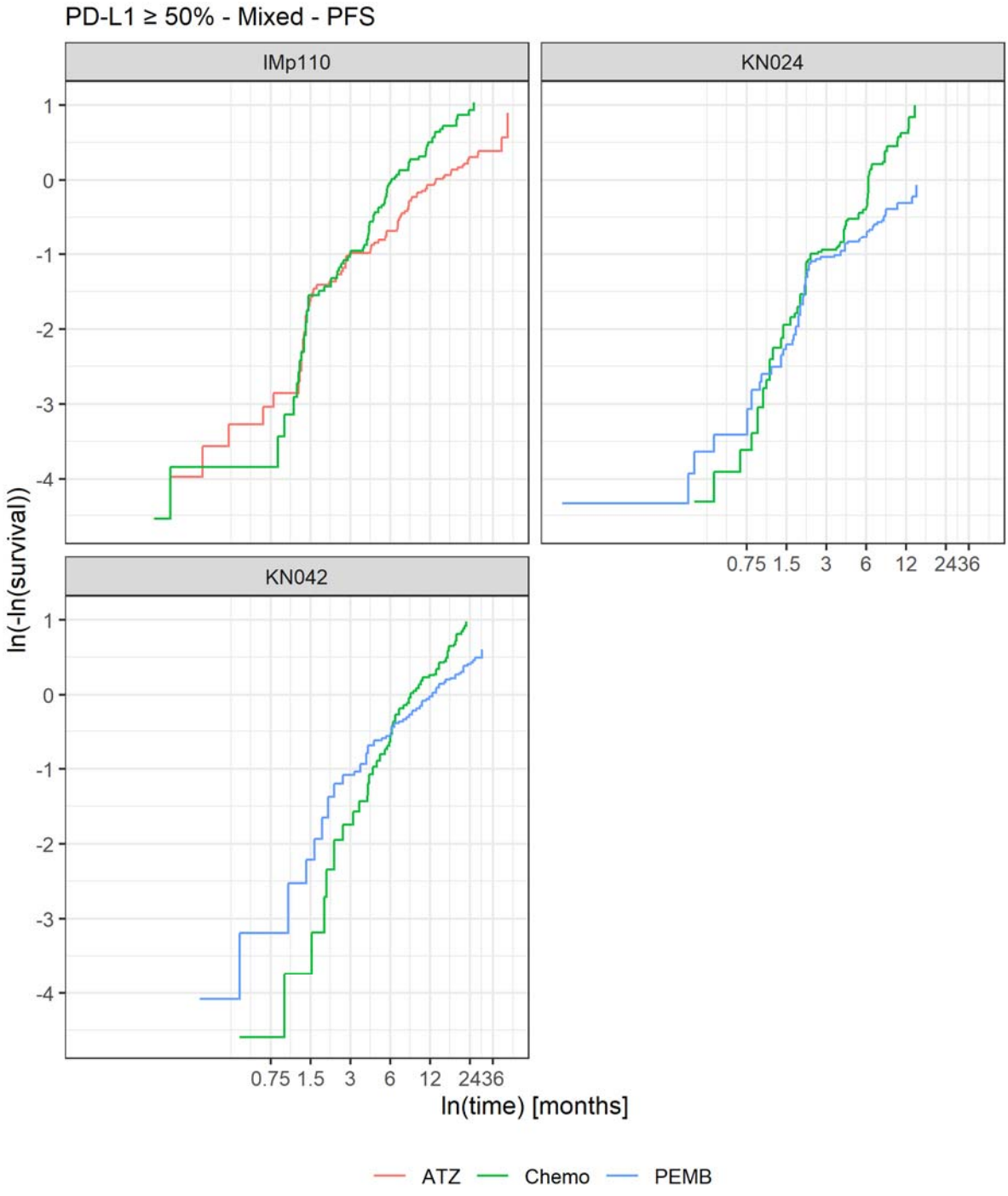


Figure 25: Log-cumulative hazard plot for PFS



B.2.9.10 Uncertainties in the indirect and mixed treatment comparisons

Data availability

For studies other than IMpower110, only published data were available. Individual patient-level data would be preferred to aggregate data as it would require fewer assumptions

regarding censoring times for the data re-constructed from the digitised Kaplan-Meier curves.

Evidence base

Treatment comparisons were informed by few studies, limiting the means to quantitatively evaluate between-study heterogeneity. As such, informative priors for the between-study variance were used to fit random effects models.

Inconsistency could not be evaluated due to an absence of closed loops in the network.

In order to create a connected network, chemotherapy arms in the different studies were treated as exchangeable, and assigned to the same network node. This may be an additional source of heterogeneity in the analysis, and may have resulted in undetected biases when estimating the different treatment effects.

PFS definition

The PFS data from the IMpower110 study was based on investigator assessment, whereas other studies' PFS data was based on independent review committee (IRC) assessment. In this analysis the methods are assumed to be equivalent; a possible source of bias.

B.2.9.11 Summary conclusion

The results of the NMA demonstrate that there is no evidence of a difference between atezolizumab and pembrolizumab in terms of either OS or PFS for treating stage IV squamous or non-squamous NSCLC in patients who have not received prior chemotherapy treatment for stage IV NSCLC and express PD-L1. This conclusion is consistent whether using HR or time-to-event data. NMAs are not powered to demonstrate statistical significance however, and the lack of evidence does not constitute evidence by itself. Indeed no evidence of difference in terms of OS for treating stage IV squamous or non-squamous NSCLC in patients who have not received prior chemotherapy treatment for stage IV NSCLC and express PD-L1 applies to comparisons not relevant to this appraisal.

The results of this NMA should be interpreted together with the topline results of the NMA based on the IMpower110 CCOD September 10th 2018 data cut (60) and the knowledge of the effect that subsequent therapy had on the longer follow-up of the CCOD 4th February 2020. This can indeed be seen in the RPSFT adjusted analysis (see B.2.13.1 and Appendix L).

B.2.10 Adverse reactions

Both the safety results from the primary and exploratory analysis are presented below. The safety data from the exploratory analysis was comparable to the primary analysis with no new safety signals.

B.2.10.1 Safety results – primary analysis

Safety analysis was performed on all treated patients, including patients who received any amount of atezolizumab (n=286) and those who received chemotherapy only (n=263). This included patients with a sensitising EGFR mutation or ALK translocation. The full safety population analysis is presented here to provide a comprehensive overview of the safety profile of atezolizumab.

Median treatment duration for atezolizumab was 5.3 months. In the chemotherapy arm, median treatment duration was 2.1 months for cisplatin, 2.3 months for carboplatin, 2.6 months for gemcitabine and 3.5 months for pemetrexed (44).

Safety summary

The majority of patients in either treatment arm had an adverse event (AE) (atezolizumab, 90.2%; chemotherapy, 94.7%) (Table 21) (44). AEs with a >5% difference in incidence between treatment arms are described in Figure 26.

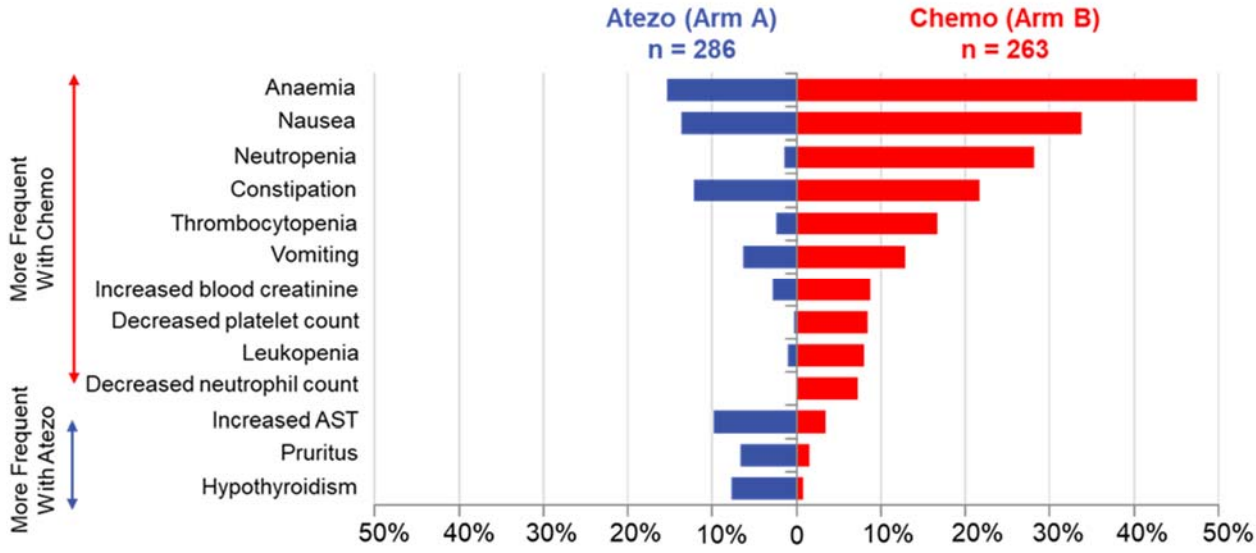
Table 21: Safety summary

	Atezolizumab n=286	**Chemotherapy n=263**			
Median treatment duration (range), months	5.3 (0-33)	Pem	Gem	Carb	Cis
		3.5 (0-20)	2.6 (0-5)	2.3 (0-5)	2.1 (0-5)
Any-cause AE, n (%)	258 (90.2)	249 (94.7)			
Related AE	173 (60.5)	224 (85.2)			
Grade 3-4 AE, n (%)	91 (31.8)	141 (53.6)			
Related Grade 3-4 AE	37 (12.9)	116 (44.1)			
Serious AE, n (%)	81 (28.3)	75 (28.5)			
Related serious AE	24 (8.4)	41 (15.6)			
Grade 5 AE, n (%)	11 (3.8)	11 (4.2)			

Related Grade 5 AE	0	1 (0.4)
AE leading to any treatment withdrawal, n (%)	18 (6.3)	43 (16.3)
Immune-mediated AE, n (%)	115 (40.2)	44 (16.7)
Grade 3-4 immune-mediated AE	19 (6.6)	4 (1.5)
Immune-mediated AE requiring use of corticosteroids, n (%)	[redacted]	[redacted]

AE: adverse events; carbo: carboplatin; cis: cisplatin; gem: gemcitabine; pem: pembrolizumab

Figure 26: All-cause AEs with a >5% difference in incidence between study arms (44)



AST: aspartate aminotransferase; atezo: atezolizumab; chemo: chemotherapy

Treatment-emergent adverse events

Treatment-emergent adverse events were reported in 90.2% of patients receiving atezolizumab and 94.7% of those receiving chemotherapy (Table 21). Grade 3-4 treatment-emergent adverse events occurred in 30.1% and 52.5% of patients in the atezolizumab and chemotherapy arms, respectively (Table 22).

Table 22: Treatment-emergent adverse events (63)

	Atezolizumab n=286			Chemotherapy n=263		
n (%)	**All Grades**	**Grade 3-4**	**Grade 5**	**All Grades**	**Grade 3-4**	**Grade 5**
Any treatment-emergent adverse event	258 (90.2)	86 (30.1)	11 (3.8)	249 (94.7)	138 (52.5)	11 (4.2)
Anemia	44 (15.4)	5 (1.7)	0	125 (47.5)	48 (18.3)	0
Decreased appetite	44 (15.4)	2 (0.7)	0	50 (19.0)	0	0
Dyspnea	4 (14.0)	2 (0.7)	0	26 (9.9)	0	0
Nausea	39 (13.6)	1 (0.3)	0	89 (33.8)	5 (1.9)	0
Asthenia	37 (12.9)	2 (0.7)	0	46 (17.5)	5 (1.9)	0
Fatigue	37 (12.9)	2 (0.7)	0	46 (17.5)	6 (2.3)	0
Constipation	35 (12.2)	3 (1.0)	0	57 (21.7)	2 (0.8)	0
Pyrexia	39 (13.6)	0	0	23 (8.7)	1 (0.4)	0
Cough	34 (11.9)	1 (0.3)	0	25 (9.5)	0	0
Diarrhea	32 (11.2)	0	0	31 (11.8)	2 (0.8)	0
Increased alanine aminotransferase	30 (10.5)	5 (1.7)	0	15 (5.7)	1 (0.4)	0
Increased aspartate aminotransferase	28 (9.8)	5 (1.7)	0	9 (3.4)	1 (0.4)	0
Vomiting	18 (6.3)	1 (0.3)	0	34 (12.9)	2 (0.8)	0
Hyponatremia	17 (5.9)	6 (2.1)	0	12 (4.6)	6 (2.3)	0
Pneumonia	14 (4.9)	7 (2.4)	0	17 (6.5)	9 (3.4)	1 (0.4)
Respiratory tract infection	14 (4.9)	2 (0.7)	0	9 (3.4)	1 (0.4)	1 (0.4)
Hyperglycemia	12 (4.2)	1 (0.3)	0	13 (4.9)	4 (1.5)	0
Hyperkalemia	12 (4.2)	6 (2.1)	0	8 (3.0)	3 (1.1)	0
Chronic obstructive pulmonary disease	11 (3.8)	4 (1.4)	1 (0.3)	2 (0.8)	0	0
Pulmonary embolism	9 (3.1)	4 (1.4)	1 (0.3)	3 (1.1)	2 (0.8)	0

Urinary tract infection	8 (2.8)	1 (0.3)	0	10 (3.8)	3 (1.1)	0
Hypercalcemia	7 (2.4)	4 (1.4)	0	2 (0.8)	0	0
Thrombocytopenia	7 (2.4)	1 (0.3)	0	44 (16.7)	19 (7.2)	0
Hypertension	5 (1.7)	2 (0.7)	0	9 (3.4)	3 (1.1)	0
Hypokalemia	4 (1.4)	0	0	10 (3.8)	3 (1.1)	0
Neutropenia	4 (1.4)	2 (0.7)	0	74 (28.1)	46 (17.5)	0
Decreased white blood cell count	3 (1.0)	0	0	14 (5.3)	5 (1.9)	0
Leukopenia	3 (1.0)	1 (0.3)	0	21 (8.0)	4 (1.5)	0
Lower respiratory tract infection	3 (1.0)	1 (0.3)	0	6 (2.3)	3 (1.1)	0
Death	2 (0.7)	0	2 (0.7)	3 (1.1)	0	3 (1.1)
Sepsis	2 (0.7)	1 (0.3)	1 (0.3)	2 (0.8)	2 (0.8)	0
Acute myocardial infarction	1 (0.3)	0	1 (0.3)	0	0	0
Aspiration	1 (0.3)	0	1 (0.3)	0	0	0
Cardiac arrest	1 (0.3)	0	1 (0.3)	2 (0.8)	0	2 (0.8)
Cerebral infarction	1 (0.3)	0	1 (0.3)	0	0	0
Decrease platelet count	1 (0.3)	0	0	22 (8.4)	11 (4.2)	0
Device occlusion	1 (0.3)	0	1 (0.3)	0	0	0
Melena	1 (0.3)	0	0	0	0	0
Pancytopenia	1 (0.3)	1 (0.3)	0	4 (1.5)	2 (0.8)	1 (0.4)
Acute pulmonary edema	0	0	0	2 (0.8)	1 (0.4)	1 (0.4)
Cardiac failure	0	0	0	1 (0.4)	0	1 (0.4)
Decreased neutrophil count	0	0	0	19 (7.2)	10 (3.8)	0
Febrile neutropenia	0	0	0	9 (3.4)	9 (3.4)	0
Tuberculosis	0	0	0	1 (0.4)	0	1 (0.4)

Note: Treatment-emergent adverse events with an incidence of ≥10% in any arm, grade 3-4 severity with incidence of ≥1% in any arm, or grade 5 severity in any arm.

Adverse events of special interest

The adverse event of special interest (AESIs) represent risks with an established or potential causal association of atezolizumab use and are grouped by medical concepts. A higher proportion of patients in the atezolizumab (40%) vs. the chemotherapy arm (17%) experienced at least one AESI, with the most common (≥5% in any treatment arm) by medical concept being hepatitis (diagnosis and lab abnormality), rash, and hypothyroidism.

Overall, [redacted] AESIs were Grade 1-2 in maximum intensity (Table 24). There were [redacted] reported Grade 5 AESIs. A [redacted] of patients on atezolizumab compared with chemotherapy had AESIs that were reported as [redacted]. Overall, AESIs were [redacted] atezolizumab/chemotherapy treatment, respectively, due to an AESI.

Table 23: Overview of AESIs

	Atezolizumab (n=286)	Chemotherapy (n=263)
AESI (any grade)	115 (40.2%)	44 (16.7%)
Grade 1-2	[redacted]	[redacted]
Grade 3-4	[redacted]	[redacted]
Grade 5	[redacted]	[redacted]
Serious AESIs	[redacted]	[redacted]
AESIs leading to any study drug withdrawal	[redacted]	[redacted]
AESIs leading to any study drug modification/interruption	[redacted]	[redacted]
AESIs requiring systemic corticosteroids[a]	[redacted]	[redacted]

Immune-mediated adverse events

Immune-mediated AEs (imAEs) occurred in 40.2% and 16.7% of patients in the atezolizumab and chemotherapy arms, respectively; Grade 3-4 imAEs occurred in 6.6% and 1.5% of patients, respectively (Table 21). There were no grade 5 imAEs. Hepatic laboratory abnormalities, rash, and hypothyroidism were the most commonly reported imAEs (≥5% in either arm; (Table 24). ImAEs requiring systemic corticosteroid treatment are reported in Table 25.

Table 24: Immune-Mediated Adverse Events* (46)

	Atezolizumab n=286		Chemotherapy n=263	
n (%)	**All Grades**	**Grade 3-4**	**All Grades**	**Grade 3-4**
Hepatitis	46 (16.1)	12 (4.2)	22 (8.4)	1 (0.4)
Laboratory abnormalities	45 (15.7)	12 (4.2)	22 (8.4)	1 (0.4)
Diagnosis	1 (0.3)	0	1 (0.4)	0

Rash	44 (15.4)	3 (1.0)	19 (7.2)	2 (0.8)
Hypothyroidism	27 (9.4)	0	4 (1.5)	0
Hyperthyroidism	13 (4.5)	0	2 (0.8)	0
Pneumonitis	11 (3.8)	2 (0.7)	1 (0.4)	0
Infusion-related reaction	4 (1.4)	0	0	0
Colitis	3 (1.0)	2 (0.7)	0	0

* With an overall incidence of ≥1% in either study arm.

Table 25: Immune-Mediated Adverse Events requiring systemic corticosteroids (46)

	Atezolizumab n=286		**Chemotherapy n=263**	
n (%)	**All Grades**	**Grade 3-4**	**All Grades**	**Grade 3-4**
Hepatitis	12 (4.2)	8 (2.8)*	1(0.4)	0
Pneumonitis	10 (3.5)	2 (0.7)	1 (0.4)	0
Rash	10 (3.5)	3 (1.0)	1 (0.4)	1 (0.4)
Colitis	2 (0.7)	2 (0.7)	0	0
Vasculitis	1 (0.3)	1 (0.3)	0	0
Adrenal insufficiency	1 (0.3)	0	0	0
Diabetes mellitus	1 (0.3)	0	0	0
Infusion-related reaction	1 (0.3)	0	0	0
Hypothyroidism	1 (0.3)	0	0	0
Nephritis	1 (0.3)	0	0	0

* Includes only Grade 3-4 laboratory abnormalities.

B.2.10.2 Safety results – exploratory analysis

Presented in Table 26 is a summary of the safety results from the exploratory analysis.

Table 26: Summary safety profile – exploratory analysis

All treated patients	**Final Analysis (CCOD: 04 February 2020)**

	Atezolizumab (n=286)	Chemotherapy (n=263)
All Grade AE, any cause	[redacted]	[redacted]
Related AE	[redacted]	[redacted]
Grade 3-4 AE	[redacted]	[redacted]
Treatment-related Grade 3-4 AE	[redacted]	[redacted]
Serious Adverse Event	[redacted]	[redacted]
Treatment-Related SAE	[redacted]	[redacted]
Grade 5 AE	[redacted]	[redacted]
Treatment-related Grade 5 AE	[redacted]	[redacted]
AE leading to any treatment withdrawal	[redacted]	[redacted]
Atezo AESI		
All Grade Atezo AESI	[redacted]	[redacted]
Grade 3-4 Atezo AESI	[redacted]	[redacted]
All Grade Atezo AESI requiring use of corticosteroids	[redacted]	[redacted]

CCOD: clinical cut off date; AESI: adverse event of special interest; SAE: serious adverse event

*One more Grade 5 AE (pulmonary oedema) in the atezo arm since the primary analysis

B.2.11 Ongoing studies

Atezolizumab monotherapy showed a significant improvement in OS in the TC3 or IC3 subpopulation as presented in this submission; no further analysis is planned. The [redacted] for patients with lower levels of PD-L1 expression (TC2/3 or IC 2/3 subpopulation and the TC1/2/3 or IC1/2/3 population) [redacted] (51).

B.2.12 Innovation

Atezolizumab monotherapy is a new first-line treatment option in patients with PD-L1–high NSCLC. It is the first PD-L1 inhibitor to demonstrate efficacy in a treatment-naive, high PD-L1 NSCLC population, with an OS HR of 0.59 versus standard chemotherapy and an OS HR of [redacted] versus standard chemotherapy after an additional 15 month follow up (exploratory analysis).

Atezolizumab is a humanised monoclonal antibody immunoglobulin IgG1 that binds directly and selectively to PD-L1 immune checkpoint protein, thus preventing it from binding to receptors PD-1 and B7.1. This prevents down-regulation of T cell activity, allowing for the priming of new T cells to facilitate anticancer immune responses. In parallel, the PD-L2/PD-1 interaction is left intact, potentially preserving peripheral immune homeostasis (64).

Atezolizumab monotherapy provides healthcare professionals and PD-L1-selected, chemotherapy-naïve patients with advanced squamous or non-squamous NSCLC another choice of treatment. In addition, atezolizumab offers flexible dosing options with the option of administration every two, three or four weeks. Patients who benefit from atezolizumab monotherapy may also benefit from treatment beyond 2 years, as demonstrated in IMpower110.

B.2.13 Interpretation of clinical effectiveness and safety evidence

B.2.13.1 Summary of findings

Atezolizumab vs chemotherapy

The IMpower110 trial met its primary endpoint, demonstrating statistically significant and clinically meaningful OS improvement in the TC3 or IC3 (PD-L1–high) subpopulation and a well tolerated safety profile. In addition, a [redacted] was observed in the exploratory analysis with an [redacted]. Therefore, atezolizumab is a new first-line treatment option in patients with PD-L1–high NSCLC. Furthermore, the IMpower110 trial provides the first direct comparison of the different commercialised PD-L1 IHC assays, supporting the benefit observed with atezolizumab monotherapy independent of the assay used, hence facilitating clinical practice.

In the primary analysis, atezolizumab reduced the risk of death by 41% in the TC3 or IC3 subpopulation, providing 7.1 months improvement in OS vs chemotherapy (median OS: 20.2 versus 13.1 months; HR=0.59 [95% CI: 0.40, 0.89]; p=0.0106). Although PFS could not be tested for significance at this point due to the hierarchical testing, there was a clinically meaningful improvement with atezolizumab compared with chemotherapy in the TC3 or IC3 subpopulation (median PFS: 8.1 vs 5.0 months; HR 0.63 [95% CI: 0.45, 0.88]).

In the exploratory analysis, atezolizumab reduced the risk of death by [redacted] in the TC3 or IC3 subpopulation, providing [redacted] in OS vs chemotherapy ([redacted]). Although the p-value is descriptive only, there was a [redacted] with atezolizumab compared with chemotherapy in the TC3 or IC3 subpopulation ([redacted]).

The [redacted] can in part be explained by the [redacted] of the chemotherapy arm to an immunotherapy ([redacted] in the chemotherapy arm at CCOD 4th February 2020, Section B.2.7.2) and the length of time between the primary and exploratory

analysis ([redacted] additional follow-up time). Furthermore, the RPSFT adjustment method demonstrated the impact of the crossover, resulting in a reduced HR of [redacted].

IMpower110 evaluated how different PD-L1 scoring methodologies perform to predict atezolizumab activity vs. chemotherapy. OS results were consistently in favour of atezolizumab in the PD-L1–high subgroups, as defined by the three PD-L1 IHC assays (SP142, 22C3 and SP263). This OS benefit was [redacted] in the exploratory analysis. These results complement the OAK trial of atezolizumab in previously-treated NSCLC (65) and the IMpower150 trial of atezolizumab plus bevacizumab and chemotherapy in first-line metastatic non-squamous NSCLC (66) to show similar benefit with atezolizumab irrespective of the PD-L1 biomarker assay used. We found through clinical expert engagement[6] that all three assays are used in the UK to varying degrees, with 22C3 being the most prevalent (22C3 [21 centres], SP263 [5 centres], and SP142 [one centre]). This analysis supports the survival benefit of atezolizumab monotherapy treatment in patients with high PD-L1 expression across all PD-L1-IHC assays.

Confirmed ORR was numerically improved with atezolizumab compared with chemotherapy in the TC3 or IC3 subpopulation (38.3% vs 28.6%). Median DOR for atezolizumab was not estimable at this data cut-off, and consequently is likely to be considerably longer than the median DOR for chemotherapy (6.7 months).

Assessment of PROs evaluating treatment-related symptoms, HRQoL, and the functional impact of treatment provided evidence of the patient experience with atezolizumab. QLQ-C30 and QLQ-LC13 completion rates were high at baseline and most study visits. Time-to-deterioration of lung cancer–related symptoms was similar in both arms, indicating that patients' low symptom burden at baseline was maintained for a similar duration in both treatment arms. Patients receiving atezolizumab sustained numerical improvements in physical functioning through Week 42 relative to baseline and no worsening in lung cancer–related symptoms compared with chemotherapy.

Overall, atezolizumab demonstrated a favourable safety profile compared with chemotherapy, as reflected by the lower incidence of treatment-related AEs, Grade 3-4 AEs, AEs leading to treatment discontinuation and AEs leading to dose modification and/or interruption. The incidence of deaths was comparable between treatment arms. There were no treatment-related deaths reported in the atezolizumab arm. The incidence of SAEs was also comparable between treatment arms. As expected, the incidence of atezolizumab

[6] Insights were collected from (32 consultants) Lung Cancer Consultants from UK NHS hospitals between October-March 2020.

specific AESIs was higher in the atezolizumab arm than chemotherapy arm. The majority of AESIs were Grade 1-2, with no Grade 5 AESIs reported. The difference in incidence was mainly driven by more events of hepatic lab abnormalities, rash and hypothyroidism in the atezolizumab arm.

The observed safety profile was consistent with prior experience of atezolizumab monotherapy across indications, histology and lines of therapy and no new safety signals were identified. In addition, the safety profile was [redacted].

Atezolizumab vs pembrolizumab

The IMpower110 trial has demonstrated that atezolizumab is efficacious as a monotherapy in chemotherapy-naïve, PD-L1–high selected advanced NSCLC.

Pembrolizumab monotherapy has demonstrated an OS improvement versus chemotherapy in PD-L1 selected NSCLC in two studies: TPS ≥50% in KEYNOTE-024 (67) and TPS ≥1% in KEYNOTE-042 (68).

There are no head-to-head studies between atezolizumab and pembrolizumab monotherapy in lung cancer, and cross-trial comparisons should be interpreted with caution due to differences in study design, stratification factors, size, patient population and data maturity. However, as noted in Section B.2.9.11, there is no evidence of a difference between atezolizumab and pembrolizumab in terms of either OS or PFS for treating stage IV squamous or non-squamous NSCLC in patients who have not received prior chemotherapy treatment for stage IV NSCLC and express PD-L1.

The notable differences between IMpower110, KEYNOTE-042 and KEYNOTE-024 are as follows:

- PD-L1 expression in KEYNOTE-024 and KEYNOTE-042 was determined on TCs using the 22C3 assay, whereas PD-L1 expression in IMpower110 was determined on TCs and ICs using the SP142 assay.
- KEYNOTE-024 only recruited patients whose tumours had the highest level of PD-L1 expression (TPS ≥50%), whereas IMpower110 and KEYNOTE-042 both recruited patients whose tumours had any PD-L1 expression.
- In both KEYNOTE-024 and KEYNOTE-042, treatment with pembrolizumab was for uo to 35 cycles (2 years)

Overall, atezolizumab monotherapy in IMpower110 is comparable to pembrolizumab monotherapy in both KEYNOTE-024 and KEYNOTE-042.

B.2.13.2 Strengths and limitations of IMpower110

The IMpower110 trial is a robust Phase III RCT, with statistically significant primary OS data, and consistent positive efficacy results for the PD-L1–high population across three PD-L1 biomarker assays.

A limitation of the IMpower110 trial is that the direct comparator of chemotherapy is no longer a current standard of care, therefore indirect comparisons are included in this submission. Furthermore, the pre-specified OS subgroup analyses using the SP263 and 22C3 IHC assays were conducted within the enrolled SP142-selected TC1/2/3 or IC1/2/3 patients. These results need to be interpreted with caution, as it represents a "double-selected" population (i.e., ITT patient population were initially selected with SP142 IHC assay and then selected with either SP263 or 22C3 IHC assays).

B.3 Cost effectiveness

B.3.1 Published cost-effectiveness studies

An SLR was conducted to identify published cost-effectiveness studies in the first-line treatment of patients with NSCLC. Detailed descriptions of the search strategy and extraction methods, as well as an overview of the identified studies are provided in Appendix H.

B.3.1.1 Summary of identified studies and results

Overall, 103 eligible economic evaluations were identified. Of these, 57 were presented as full publications (69-125) (of which two were foreign language publications with an English abstract (92, 93), and 39 were presented as conference abstracts only (126-164). A total of seven National Institute for Health and Care Excellence (NICE) Health Technology Assessment (HTA) submissions were also identified (165-171). Due to limited reporting, the current report focuses on the analyses presented as full publications. It is important to note that no economic evaluations assessing atezolizumab monotherapy for untreated patients with advanced NSCLC were identified.

The economic data were derived primarily from the US, Canada and European countries, and the majority of studies presented cost-utility analyses reporting an incremental cost per quality adjusted life year (QALY) for the treatment strategies considered. The most common

treatment comparisons were targeted therapies (including tyrosine kinase inhibitors [TKIs]) versus best supportive care (BSC) or standard of care (SOC) (most often doublet chemotherapy).

With regard to the approaches to modelling, the majority of studies employed decision analytic modelling techniques; Markov models and partitioned survival models were most commonly utilised. Progression free, progressed disease, and death were the most common health states, but some models also incorporated additional health states, for example, states representing stable disease, response to treatment, the impact of adverse events (AEs), and remission with or without dose reduction in treatment. Model time horizons ranged from 6 months to a lifetime (up to 20 years), and model cycle length ranged from 1 week to 1 month. Discounting of both costs and health outcomes ranged from 3.0% to 5.0%; only four studies discounted both costs and health outcomes at 3.5% in line with the requirements of the National Institute for Health and Care Excellence (NICE) reference case. A number of studies did not apply a discount rate to costs or health outcomes; this was most often justified with reference to a short time horizon (<1 year).

A total of seven NICE HTA submissions were found, all of which were cost-utility analyses. The most common type of model utilised in the NICE submissions was the partitioned survival model (PartSA), although Markov models were also common. All the NICE submissions used a discount rate of 3.5% for costs and benefits and an NHS and Personal Social Services (PSS) perspective.

Generally, the full publications included in the review were assessed to be of a moderate quality. Key methodological details, such as model type and structure, discounting, perspective, and time horizon, as well as results were generally reported well. However, there was a notable absence of justification for key decisions, such as discount rate and choice of variables for sensitivity analysis. Generalisability and study-specific limitations were well discussed, enabling more meaningful assessment of applicability of the results to alternative settings.

Summary tables and further details and results for the identified cost-effectiveness studies can be found in Appendix H.

B.3.2 Economic analysis

The cost-effectiveness studies identified in Section B.3.1 were used to inform the structure for the cost-utility analysis (CUA) model used in the economic analysis, in particular the economic analysis conducted in TA531 (see Table 27). However, none of the identified

literature appraised atezolizumab for the first-line treatment of adult patients with PD-L1-high metastatic NSCLC. Therefore, a *de novo* economic model was built to inform decision-making for this appraisal.

In the patient population relevant to this appraisal, there is no concluding evidence to claim superiority of either atezolizumab or pembrolizumab. The diametrically opposing ITC results based on the two different data cuts of the Impower110 are a further confirmation of this. In fact, the RPSFT analysis provided in appendix L and produced in response to a specific FDA request shows how the prolonged follow-up impacted the OS HR. This confirms that the different follow up length between the KEYNOTE and the Impower110 studies increases the confounding due to subsequent therapies. Given the comparable clinical efficacy, safety and resource use between atezolizumab and its comparator, pembrolizumab, a parallel construction of a cost-comparison analysis model (CCompA) has been conducted, that we believe being a suitable base for decision making. For the CCompA, we assumed the same efficacy for atezolizumab and pembrolizumab and focused purely on the cost differences. There is a strong clinical rationale for a CCompA alone, confirmed by the data, nonetheless, on the advice of NICE, a full CUA was conducted in order to justify the need for a CCompA and mitigate against the risk of a straightforward CCompA being deemed inappropriate at the scrutiny stage. Consequently, while the majority of Section B.3 discusses the methods, inputs and results of the CUA, the results of the CCompA are shown in B.3.7.2 and discussed B.3.11, in the context of the results of the CUA. For completeness, scenario analyses will be run for the CCompA as well.

B.3.2.1 Patient population

The patient population subject to the *de novo* analysis is treatment-naïve patients with advanced NSCLC of any histology without EGFR mutations or ALK alterations, whose tumours have high PD-L1 expression. High PD-L1 expression is defined in the base-case as those patients with a PD-L1 score of TC3 (PD-L1 expression on ≥50% of tumour cells) or IC3 (PD-L1-expressing immune cells being ≥10% of the tumour area) as measured by the SP142 PD-L1 assay used in the IMpower110 trial. This population is consistent with the IMpower110 trial population described in section B.2, the scope of this appraisal and the anticipated licence.

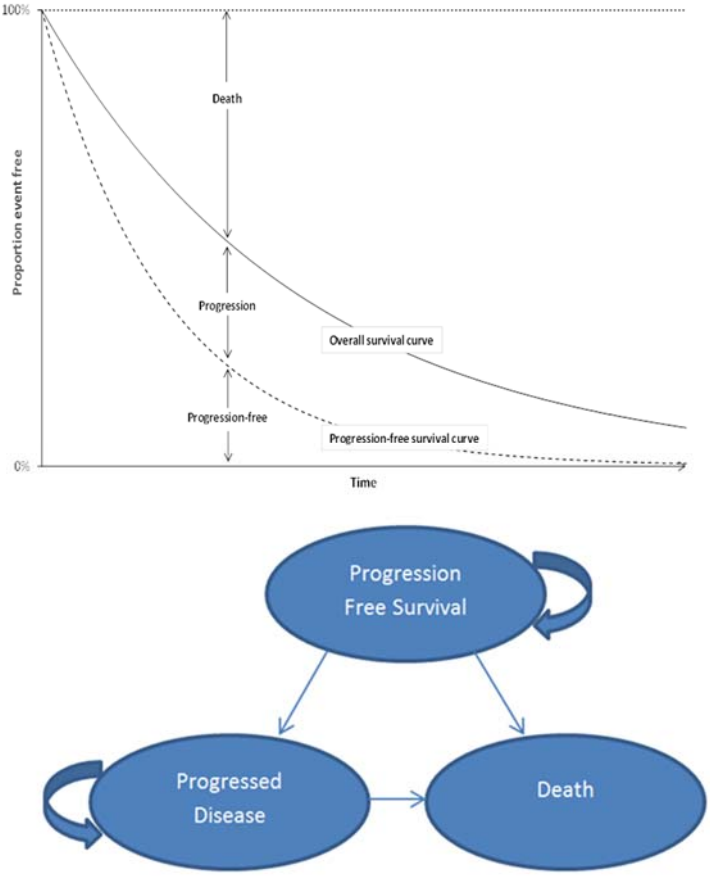
B.3.2.2 Model structure

B.3.2.2.1 Cost effectiveness analysis

The CUA model was developed in Microsoft Excel and is an Area-Under-the-Curve (AUC) or PartSA model. The AUC model structure was selected, as per NICE DSU guidance (172), in order to allow for full use of the PFS and OS study data from IMpower110 and to be able to incorporate external evidence for additional comparators, for which individual patient data is unavailable, in the economic model. In addition, the PartSA approach is relatively simple and intuitive, and allows for multiple predictive extrapolation scenarios to be explored. For these reasons, PartSA is a commonly used approach in oncology appraisals, including that of pembrolizumab monotherapy in treatment-naïve, PD-L1 high NSCLC patients, which involved a similar decision problem to this appraisal (173).

The model includes three mutually exclusive health states, consistent with previous appraisals accepted by NICE for first-line NSCLC, and other metastatic oncology indications (TA531, TA428, TA484, TA520, TA525 (173-177)): “Progression-Free Survival (PFS)”, “Progressed Disease (PD)”, and “Death”. These health states are fully aligned with two of the primary objectives of treatment in NSCLC; delaying disease progression and prolonging life. PFS, PD and death are also the most relevant disease related health states from a patient, clinician and NHS perspective. Further, the direct correspondence between the key endpoints of the IMpower110 trial (i.e. PFS and OS) and the survival functions required to determine state occupancy allows for full use of the IMpower110 data. The model structure is shown in Figure 27.

Figure 27: Cost effectiveness model structure



The health economic model was developed to compare the cost-effectiveness of atezolizumab versus the standard of care in England for the patient population described above (i.e. pembrolizumab monotherapy), in line with its licence and NICE recommendation. The rationale for comparison with pembrolizumab monotherapy alone is provided in Sections B.1.1, B.1.3.2, B.2.13.1, and B.3.2.

Within the AUC model, health states are based on the partitioning of the proportion of patients alive into “PFS” and “PD” at discrete time points, based on the PFS and OS curves from IMpower110 and the relative treatment effects derived from the NMA. The proportion of patients in the “PD” health state is assumed to be the difference between OS and PFS. The three health states in the model represent the primary stages of disease in metastatic NSCLC.

All patients enter the model in the PFS health state and remain in this health state until they progress. At progression, patients either transition into the PD health state or enter the absorbing health state of Death. Patients in the PD health state stay in that health state until

Death. Patients cannot transition to an improved health state (back to PFS), a restriction that is consistent with previous economic modelling in oncology.

Due to the structural form of the model, patient transitions between the health states are not explicitly modelled. The proportion of patients in each health state was estimated using the PartSA method. Rather than transition probabilities, the proportion of patients within each health state was calculated based on the PFS and OS survival curves from IMpower110 for atezolizumab and based on the relative treatment effects derived from the NMA, for relevant comparators. The PartSA approach allows for modelling of OS and PFS based on study-observed events, which is expected to accurately reflect disease progression and the long-term expected survival profile of patients treated with atezolizumab. The primary limitations of this approach are that OS and PFS are modelled as independent endpoints, and since transitions are not explicitly modelled, the model structure is rigid and does not allow for sensitivity or scenario analyses to be explored by altering the transition probability in specific health states only.

The model inputs (efficacy, safety and tolerability) are based on the results of the phase III IMpower110 trial for atezolizumab, and on the indirect treatment comparison with pembrolizumab described in Section B.2.9. In accordance with the decision problem, model results are reported in terms of cost per life years gained (LYG) and costs per quality adjusted life years (QALY) gained.

Costs and health-related utilities are allocated to each health state and multiplied by state occupancy to calculate the weighted costs and QALYs per cycle.

The economic model uses a time horizon of 20 years, which is considered to be appropriate as a lifetime horizon for patients with first-line metastatic NSCLC, taking into account typical age at diagnosis and the advanced nature of disease. This time horizon ensures all benefits and costs accrued by patients are captured, and is consistent with the anticipated survival based on the economic model. The 20-year time horizon is also consistent with TA531, the pembrolizumab appraisal in first-line advanced or metastatic PD-L1 high NSCLC (173).

Costs and health outcomes are discounted at 3.5% and the perspective of the NHS and personal social services (PSS) is assumed, as per the NICE reference case (178).

The model has been designed to use a weekly cycle, with the proportion of patients in each health state calculated each week. Transition between health states can occur at any time within the cycle. To account for the over or under estimation of transitions occurring at the beginning or end of the cycle, half-cycle correction was applied, in line with previous NICE

technology appraisals in this disease area (TA531, TA584, TA428, TA484, TA520, TA525 (173-177, 179)).

An overview of how the economic analysis for atezolizumab compares to the NICE appraisal for pembrolizumab in an equivalent patient population (TA531) is provided in Table 27. TA531 is provided as the key prior example given the similarity with this appraisal in terms of most aspects of the decision problem. There is a high degree of concordance between the two economic analyses.

Table 27: Features of the economic analysis

Factor	Pembrolizumab first line NSCLC (TA531)	Current appraisal	
		Chosen values	Justification
Model structure	Three health state (PFS-PD-Death) PartSA	Three health state (PFS-PD-Death) PartSA	Simple, well-characterised and commonly accepted approach in oncology appraisals. In line with TA531.
Time horizon	Lifetime (20 years)	Lifetime (20 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	1 week	1 week	In line with TA531.
Half-cycle correction	Yes	Yes	In line with previous submissions and to mitigate bias.
Were health effects measured in QALYs? if not, what was used?	Yes	Yes	Aligned with NICE reference case. Only direct health effects related to patients were considered, and no wider societal impact or impact on carers.
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 stopping rule	2 year stopping rule	No stopping rule	The two year stopping rule for pembrolizumab is in accordance with its NICE recommendation. Lack of stopping rule for atezolizumab is aligned with the clinical evidence base, which allows treatment until loss of clinical benefit. It also allows clinicians and patients the option of continuing therapy beyond two

			years in cases where they are still deriving clinical benefit. Feedback from clinical experts and patients themselves supports this approach.
Treatment effect stopping	Considered in NICE Committee decision-making.	Five year treatment effect used in base case for pembrolizumab.	A limited treatment effect on OS is only considered for pembrolizumab in the base case since it is limited by a two-year stopping rule. A five year treatment effect (two years on treatment plus three post-treatment) was chosen as this appeared to be the Committee's preference in previous pembrolizumab appraisals (TA531, TA428, TA557, TA600 (173, 174, 180, 181)). Atezolizumab is continued until loss of clinical benefit in the base case, so limited treatment effect on OS does not apply.
Source of utilities	KEYNOTE-024 EQ-5D individual patient data.	IMpower110 EQ-5D individual patient data	Aligned with NICE reference case
Source of costs	NHS reference costs; PSSRU; BNF; eMIT; published literature, resource utilisation and costs accepted in previous NICE submissions.	NHS reference costs; PSSRU; BNF; eMIT; published literature, resource utilisation and costs accepted in previous NICE submissions, in particular TA584 and TA531.	Widely used and accepted sources of cost and resource use data in UK HTAs.
Adjustment for treatment switching	No	No	Accepted assumption by ERG and NICE Appraisal committee in TA531

EQ-5D: European Quality of Life-5 Dimensions; PSSRU: Personal Social Services Research Unit

B.3.2.2.2 Cost-comparison analysis

For simplicity, we have incorporated a cost comparison model in the cost utility model by adding a functionality that sets efficacy for atezolizumab and pembrolizumab equal: the PFS and OS functions are set equal for both product to atezolizumab's chosen functions. This approach has the advantage of removing almost all the uncertainty linked to estimating the magnitude and the impact on the incremental cost effectiveness ratio (ICER) of supposed very small differential health outcomes (QALYs) and enables focusing the decision on the cost component. Varying the time to treatment discontinuation functions allows exploration of

the cost impact that this part of the modelling entails. We believe this approach would be a better use of NICE's limited resources.

B.3.2.2.3 Intervention technology and comparators

The intervention technology atezolizumab and the comparator pembrolizumab are consistent with the final NICE scope outlined in Section B.1.1.

Within the base case economic model:

- atezolizumab is applied according to its marketing authorisation, i.e. 1200 mg administered intravenously every three weeks until unmanageable toxicity or loss of clinical benefit as defined by the following criteria:
    - Evidence of clinical benefit as assessed by the investigator
    - Absence of symptoms and signs (including worsening of laboratory values [e.g., new or worsening hypercalcemia]) indicating unequivocal progression of disease
    - No decline in ECOG Performance Status that was attributed to disease progression
    - Absence of tumour progression at critical anatomical sites (e.g., leptomeningeal disease) that could not be managed by protocol-allowed medical interventions
    - Patients must have provided written consent to acknowledge deferring other treatment options in favour of continuing study treatment at the time of initial radiographic progression per RECIST v1.1
- Pembrolizumab is applied according to its marketing authorisation, i.e. 200 mg administered intravenously every three weeks. The licence for pembrolizumab specifies treatment until disease progression or unacceptable toxicity, though it should be noted that, similar to atezolizumab, it is recommended to continue treatment for clinically stable patients with initial evidence of disease progression until disease progression is confirmed (182). However, the NICE recommendation for pembrolizumab in this indication limits the maximum treatment duration to two years of uninterrupted treatment, in line with the evidence available at the time of assessment.

Treatment duration with atezolizumab is modelled according to its marketing authorisation for the following reasons:

- It is consistent with the evidence base – all atezolizumab NSCLC trial protocols with specify treatment until loss of clinical benefit or unmanageable toxicity.
- There is a lack of evidence or rationale to support stopping treatment with atezolizumab at an arbitrary time point such as two years.
- There is evidence that patients commonly relapse or progress after stopping treatment at an arbitrary point of one or two years with re-challenge, which is not permitted in clinical practice in England, only being partially successful (183-185).
- It is therefore important to allow clinicians and patients who are continuing to benefit from treatment to continue therapy beyond two years, should they wish.
- UK clinicians support the option to be able to continue treating patients beyond two years, in the absence of an option to re-challenge.

B.3.3 Clinical parameters and variables

B.3.3.1 Incorporation of clinical data into the economic model

The primary data source for the atezolizumab arm of the economic model is the exploratory long-term follow-up of the IMpower110 trial (CCOD 4th February 2020). This study is also the data source for adverse events for atezolizumab and quality of life (utilities).

As pembrolizumab was not included in IMpower110, and there were no head-to-head trials comparing it to atezolizumab, an indirect treatment comparison (ITC) was conducted to estimate its relative effectiveness. Survival estimates for pembrolizumab were then generated by applying the hazard ratios generated by the ITC to survival data from the IMpower110 study in the economic model (Section B.2.9).

PFS and OS results from IMpower110 were extrapolated to the 20-year time-horizon of the model, as life-time results are not available from the IMpower110 trial. This analysis has a follow up of [redacted]. Guidance from the NICE DSU was followed to identify parametric survival models for OS, PFS and time to treatment discontinuation (TTD) in the base-case of the model (186).

Standard parametric functions were fitted and Kaplan-Meier curves with a parametric tails are made available in the model. The cut-off point for switching from KM to parametric

extrapolation is when 20% of patients remain at risk (187), to ensure robustness in terms of patient numbers whilst the KM data being utilised.

All parametric models were assessed against the Akaike Information Criterion (AIC) and Bayesian Information Criterion (BIC) for statistical fit to the observed data. Curves were visually inspected and validated against relevant long-term data sources available to help identify the most plausible survival model. Clinical expert opinion[7] was also sought to validate the extrapolation approach taken and determine which of the extrapolations better represent UK clinical practice.

B.3.3.2 OS extrapolation

Table 28 provides the AIC and BIC goodness of fit results for the functions used to model OS for atezolizumab from IMpower110. As we can notice the AIC and BIC statistics are all in a close range. Table 29 reports the percentage of patients alive projected by different OS functions and Table 30 summarises these statistics with the visual inspection and the clinical validation outputs. As previously mentioned, the comparator curves were constructed using the atezolizumab curve as a reference, applying the time dependent relative treatment effects from the ITC.

Table 28: OS AIC/BIC statistics

Distribution	AIC (rank)	BIC (rank)
EXPONENTIAL	341.8(6)	344.5(5)
WEIBULL	336.3(2)	341.7(2)
LOG-LOGISTIC	336.2(1)	341.5(1)
LOG-NORMAL	337(3)	342.4(3)
GEN-GAMMA	337.7(5)	345.7(6)
GOMPERTZ	337.2(4)	342.6(4)

[7] A total of 3 UK clinicians were consulted for extrapolation validation

Table 29: Percentage of patients alive

Months	Exponential	Weibull	Gamma	Log-logistic	Log-Normal	Gompertz
6	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
12	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
24	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
36	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
48	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
60	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
72	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
84	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
90	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
120	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
126	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
132	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Table 30: Ranking of OS distributions for atezolizumab based on AIC/BIC, visual fit and clinical plausibility

Parametric distribution	Atezo AIC (rank)	Atezo BIC (rank)	Visual fit to KM	Clinical plausibility	Ranking
Exponential	6	6	~	~	-
Weibull	2	2	✓	✓	1
Log-Logistic	1	1	✓	~	~
Log-Normal	3	3	~	×	-
Gen Gamma	5	5	✓	~	2
Gompertz	4	4	✓	×	-

AIC, Akaike Information Criterion; BIC, Bayesian Information Criterion, KM, Kaplan-Meier

The Weibull function (Figure 28) was the parametric extrapolation reaching clinical consensus during clinical expert consultation, and having statistical and visual fit to the data. Hence it was chosen as the base case OS function. Generalized Gamma (Figure 29), a more optimistic option, will be explored in the scenario analyses. The Exponential function, the more pessimistic option, does not fit the data and has only 7% of patients alive at 90 months. The functions not shown here are reported in Appendix N. This is at odd with the available PFS curves values, shown in section B.3.3.3 below.

From the below OS extrapolation figures below we can appreciate the effect of the 2 year stopping rule applied to pembrolizumab, as described previously. Atezolizumab does not have a stopping rule implemented in the model. According to available evidence and licence the treatment benefit is assumed to continue. This causes all the available parametric functions to cross between approximately 100-120 months. The crossing of the curves is minimal and has been described by clinicians as possible and clinically insignificant, although it could arguably be representative of continuing treatment beyond two years.

In a scenario analysis, we will explore capping atezolizumab's OS benefit at 96 months (Figure 30). As this is an arbitrary time point, it should be interpreted with caution, but it allows the two OS curves to be overlapping from 90 months onwards. Capping the treatment effect at the same time point as pembrolizumab (60 months), would imply there is no OS benefit in continuing treatment beyond two years, for any single patient. There is no clinical evidence to support such an assumption. We will test this in a scenario analysis as well.

Given experience with immunotherapies in this patient population is limited by the "two year stopping rule", it is impossible to estimate with a degree of certainty what percentage of patients will be alive beyond 60 months. This degree of uncertainty is overcome by the cost comparison approach that assumes equal efficacy to pembrolizumab.

Figure 28: OS Weibull function - base case

Table 31: Percentage of patients alive atezolizumab vs. pembrolizumab

Months	Atezolizumab	Pembrolizumab	Difference
6	[redacted]	[redacted]	[redacted]
12	[redacted]	[redacted]	[redacted]
18	[redacted]	[redacted]	[redacted]
24	[redacted]	[redacted]	[redacted]
36	[redacted]	[redacted]	[redacted]
42	[redacted]	[redacted]	[redacted]
48	[redacted]	[redacted]	[redacted]
60	[redacted]	[redacted]	[redacted]
66	[redacted]	[redacted]	[redacted]
72	[redacted]	[redacted]	[redacted]
84	[redacted]	[redacted]	[redacted]
90	[redacted]	[redacted]	[redacted]
96	[redacted]	[redacted]	[redacted]
108	[redacted]	[redacted]	[redacted]
120	[redacted]	[redacted]	[redacted]
132	[redacted]	[redacted]	[redacted]

Figure 29: OS Generalised Gamma function

[redacted]

Figure 30: OS Weibull function - atezolizumab treatment effect capped at 96 months

B.3.3.2.1 Validation

Roche engaged with NHS practicing oncologists and key opinion leaders in the field[8] to ensure the most suitable functions were chosen. As stated, for the base case the Weibull function was chosen, as it fits the data well and was the function achieving clinical consensus of delivering realistic outcomes. It is worth noticing how unadjusted Flatiron data for pembrolizumab show at 36 months an OS of [redacted] While the atezolizumab projection is on the high end, but within this range [redacted] the pembrolizumab function is more optimistic and projects 0.42 patients alive at the 36 months landmark (188). The crossing of the curves has been defined as clinically marginal given the low numbers of patients involved. The clinicians we engaged expressed consensus that the two products can be assumed as clinically equivalent for the relevant indication. This does not mean some patients would benefit from treatment beyond two years with either product. In fact, choosing an arbitrary cut-off point for atezolizumab's OS benefit was not favoured by clinicians.

It was also pointed out that the Generalised Gamma and Log-Logistic functions are aligned with the real world evidence data available from Garon et al. at 60 months (189), who found that approximately 30% of the population relevant to this submission were still alive at that time points on pembrolizumab. The hazard rate after that time point could be seen as

[8] A total of 3 UK clinicians were consulted for extrapolation validation

optimistic however. The Log-Normal and Gompertz functions were also excluded, as deemed too optimistic beyond 120 months.

B.3.3.3 PFS extrapolation

The AIC and BIC goodness of fit results for the functions used to model PFS for atezolizumab in IMpower110 can be seen in Table 32. Similarly to the approach for OS, the comparator curves were then constructed using the atezolizumab curve as a reference, applying the time dependent relative treatment effects from the ITC.

Table 32: PFS AIC/BIC statistics

Distribution	AIC (rank)	BIC (rank)
Exponential	387.8(6)	390.4(6)
Weibull	376.6(5)	381.9(5)
Log-logistic	369.1(2)	374.4(2)
Log-normal	367.8(1)	373.1(1)
Gen-gamma	369.6(3)	377.6(4)
Gompertz	370.2(4)	375.5(3)

From the AIC/BIC statistics we can see that the Log-Logistic, the Log-Normal, the Gamma and the Gompertz function are all in a tight statistical range and could be options. Weibull and Exponential do have higher values however, above 5 points difference.

From Table 33 we notice that the Log-Normal, Log-Logistic and Gamma functions are all very similar in patient numbers at landmarks, while the Gompertz function is more optimistic. The curves fitting the data less well were also the most pessimistic ones. As reported in Table 34, the Exponential and the Weibull functions have a particularly poor statistical and visual fit to the data.

Table 33: Projected PFS for atezolizumab based on different extrapolation functions

Months	Log-Normal	Log-Logistic	Gamma	Gompertz	Exponential	Weibull
6	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
12	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
24	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
36	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
48	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
60	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
72	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
84	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
90	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Table 34: Ranking of PFS distributions for atezolizumab based on AIC/BIC, visual fit and clinical plausibility

Parametric distribution	Atezo AIC (rank)	Atezo BIC (rank)	Visual fit to KM	Clinical plausibility	Ranking
Exponential	6	6	×		×
Weibull	5	5	×		×
Log-Logistic	2	2	✓	✓	3
Log-Normal	1	1	✓	✓	2
Gen Gamma	3	4	✓	✓	1
Gompertz	4	3	✓	×	×

AIC, Akaike Information Criterion; BIC, Bayesian Information Criterion, KM, Kaplan-Meier

Of the four remaining functions, the Gompertz was excluded based on clinical opinion, as it was considered too optimistic beyond 60 months.

The Log-Normal, Log-Logistic and Generalised Gamma functions are very close to each other in terms of patient numbers in the progression free health state and statistical and

visual fit to the data. While the Log-Normal and the Log-Logistic function will be explored in scenario analyses, the Generalised Gamma function was chosen for the base case. The reason being to seek consistency with the available Time to Treatment Discontinuation (TTD) functions described later. The chosen PFS function can be seen in Figure 31 to Figure 33 and assumes the continuation of treatment benefit beyond 60 months for both products. Figure 34 shows the effect of capping the treatment effect for both products at 60 months.

Figure 31: PFS Generalised Gamma function - atezolizumab and pembrolizumab - base case

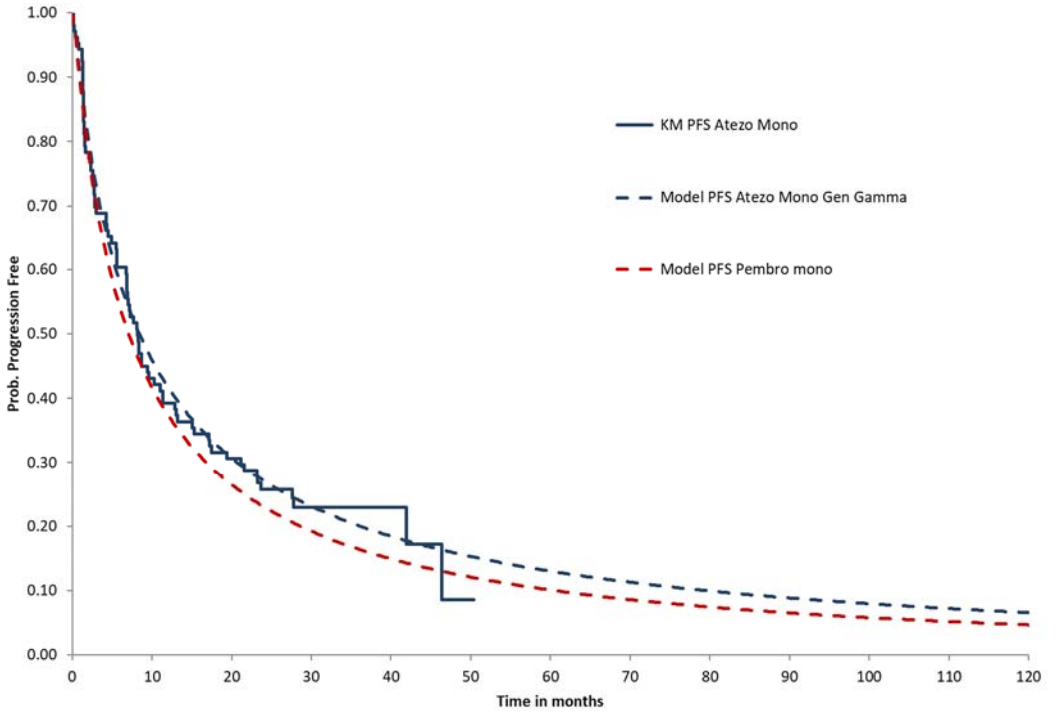


Table 35: Percentage of patients in the progression free health state

Months	Atezo Mono	Pembro mono	Inc. Atezo Mono vs. Pembro mono
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]

[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]

Figure 32: PFS Log-Normal function – atezolizumab and pembrolizumab

Figure 33: PFS Log-Logistic function – atezolizumab and pembrolizumab –

Figure 34: PFS Generalised Gamma function – atezolizumab and pembrolizumab – capped treatment effect for both at 60 months

B.3.3.4 Treatment duration extrapolation

Data on time to treatment discontinuation (TTD) are available for atezolizumab in IMpower110, however not all patients had discontinued treatment in IMpower110. As such, it was necessary to extrapolate the study results so that treatment duration could be estimated beyond the trial period. Parametric distributions were fitted to the TTD Kaplan–Meier curves and assessed for their goodness of fit to the data using the AIC/BIC statistics, visual assessment and clinical plausibility of each of the extrapolations.

Table 36 below provides the AIC and BIC goodness of fit results for the functions used to model TTD. The Weibull, Gamma and Log-logistic functions have similar AIC/BIC statistics. The values for the Log-Normal function are higher, and the Gompertz and Exponential function don't seem to have a good statistical fit to the data. Table 37 shows the numbers of patients expected to be on treatment at different time points, while Table 38 ranks the parametric distributions based on all available information.

Table 36: TTD AIC/BIC statistics

Distribution	AIC (rank)	BIC (rank)
Exponential	477.3(6)	480(6)
Weibull	432.2(1)	437.5(1)
Log-logistic	436.5(3)	441.8(2)
Log-normal	440.6(4)	445.9(4)
Gen-gamma	434.1(2)	442.1(3)
Gompertz	452.7(5)	458(5)

Table 37: Percentage of patients on treatment for atezolizumab

Months	Weibull	Gen Gamma	Log-Logistic	Log-Normal	Gompertz	Exponential
6	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
12	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
24	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
36	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
48	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
54	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
60	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
66	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
72	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
78	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
84	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
90	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Table 38: Ranking of TTD distributions for atezolizumab based on AIC/BIC, visual fit and clinical plausibility

Parametric distribution	Atezo AIC (rank)	Atezo BIC (rank)	Visual fit to KM	Clinical plausibility	Ranking
Exponential	6	6	x	x	-
Weibull	1	1	✓	✓	2
Log-Logistic	3	2	~	x	-
Log-Normal	4	4	x	×	-
Gen Gamma	2	3	✓	✓	1
Gompertz	5	5	✓	×	-

AIC, Akaike Information Criterion; BIC, Bayesian Information Criterion, KM, Kaplan-Meier

The clinical experts consulted by Roche highlighted that it would be reasonable to expect about or below 10% of patients to still be on treatment at 60 months and that anything above

that value could be an overestimation. Clinicians also mentioned how UK clinical experience at that time point is limited, particularly given the two year stopping rule with pembrolizumab.

As such, Log-Logistic, Log-Normal and Gompertz can be excluded as they overestimate the numbers of patients on treatment. The Exponential and the Log-Normal functions have particularly poor visual fit to the data and can also be excluded. All the excluded functions can be seen in Appendix N and can be found in the economic model.

The Generalised Gamma function (Figure 35) was chosen for the base case, allowing for consistency with the PFS extrapolation. This function overestimates the number of patients on atezolizumab comparing to the IMpower110 Kaplan-Meier curve, from 20 months onwards and crosses the KM data again when the numbers of events becomes smaller. The use of the Weibull function (Figure 36) will be explored in a scenario analysis.

TTD data for pembrolizumab are not publicly available. The decision was therefore taken to use pembrolizumab PFS as a proxy for TTD. Treatment on pembrolizumab is stopped after two years of continuous treatment (182).

Figure 35: TTD Generalised Gamma function – atezolizumab – base case

Figure 36: TTD Weibull function – atezolizumab

B.3.3.5 Summary and comparison of the base case time to event functions

For OS, the Weibull function seems to represent the best available option taking into account statistical, visual fit and clinical opinion. While the OS parametric extrapolations cross at the tail end, this could reflect the clinical benefit a very small number of patients may derive from continuing treatment beyond two years. The crossing is marginal, only involving about 1% of patients. To impede the curves from crossing, we will explore, in a scenario anlaysis, the effect of an arbitrary capping the clinical benefit of atezolizumab. As we heard from clinical experts, there is no evidence to suggest one product is superior to another for this patient population, beyond the potential benefit some patients might derive by not stopping the treatment.

For PFS, the Generalised Gamma Function was chosen as the base case taking into account statistical and visual fit, clinical validation and interdependency of outcomes, allowing for consistency with the TTD function.

For TTD, the Generalised Gamma function was the best available option, although it probably still overestimates the patients on treatment, particularly beyond 60 months. This was confirmed by the UK practicing oncologists we consulted. As such, it is a conservative estimate on the most influential time to event parameter. Pembrolizumab has the stopping rule implemented at 24 months limiting TTD, with the treatment effect lasting up to 60

months for both PFS and OS. At that time point, the efficacy defaults back to the chemotherapy efficacy (pemetrexed plus platinum).

After about four years, the model projects slightly more patients in the progression free health state than on treatment. We heard from clinicians that this is likely to happen, as patients with persistent response often exhibit frequent and varied reasons for treatment discontinuation. It is hypothesized that the response might be persistent in many cases nonetheless, if the patient has been on treatment long enough. At the moment it is unknown if two years treatment is long enough to trigger what has been described as persistent “immunological memory” however. The biggest unmet clinical need was highlighted for patients who relapse after stopping treatment and do not have further immunotherapy options available. This is not in licence and out of scope for this submission. For some patients it could be very important to continue treatment beyond two years, however the numbers of patients needing to continue treatment beyond that time point was described by clinicians as very small.

We have been guided by clinical validation and have taken into account the interdependency of outcomes to our best efforts to choose the most realistic base case. Figure 37 below shows the base case functions, Table 39 summarises the percentage of patients derived from each function at different time points.

Figure 37: Base case functions

Table 39: Percentage of patients projected by the different time to event (TTE) functions

Months	TTD Gen Gamma	PFS Gen Gamma	OS Weibull
6	[redacted]	[redacted]	[redacted]
12	[redacted]	[redacted]	[redacted]
18	[redacted]	[redacted]	[redacted]
24	[redacted]	[redacted]	[redacted]
30	[redacted]	[redacted]	[redacted]
36	[redacted]	[redacted]	[redacted]
42	[redacted]	[redacted]	[redacted]
48	[redacted]	[redacted]	[redacted]
54	[redacted]	[redacted]	[redacted]
60	[redacted]	[redacted]	[redacted]
72	[redacted]	[redacted]	[redacted]
84	[redacted]	[redacted]	[redacted]
96	[redacted]	[redacted]	[redacted]
108	[redacted]	[redacted]	[redacted]
120	[redacted]	[redacted]	[redacted]

B.3.3.6 Time to event endpoints in the cost comparison analysis

The only time to event endpoint that has a meaningful impact on costs in the cost comparison is time to treatment discontinuation. For the base case, we have chosen the same TTD function as for the cost utility analysis, Generalised Gamma. PFS and OS extrapolations affect the cost comparison to little extent mainly by marginally impacting the treatment costs and the costs associated to post-progression.

The assumptions needed to optimize the choice of the PFS and OS extrapolations and the fact that this analysis is based on an exploratory data cut highlight, once more, how the cost comparison analysis is more appropriate for decision making.

B.3.4 Measurement and valuation of health effects

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

Health-related quality of life (HRQoL) data were collected in the IMpower110 study directly from first line metastatic NSCLC patients via the European Quality of Life-5 Dimensions 3 level (EQ-5D-3L) questionnaire. Measurement and valuation of HRQoL using EQ-5D-3L directly from patients is consistent with the NICE reference case, hence HRQoL from IMpower110 is used in our base case analysis.

EQ-5D-3L data were collected in IMpower110 in alignment with the tumour assessment schedule during the study treatment period (i.e., every 6 weeks (± 7 days) for 48 weeks following Cycle 1, Day 1, and every 9 weeks (± 7 days) thereafter after the completion of the Week 48 tumour assessment, until radiographic disease progression per RECIST v1.1 (or loss of clinical benefit for atezolizumab-treated patients who had continued treatment with atezolizumab after radiographic disease progression according to RECIST v1.1). During survival follow-up the EQ-5D-3L was completed at 3 and 6 months following disease progression (or loss of clinical benefit for atezolizumab-treated patients). The EQ-5D-3L index scores were calculated using UK tariffs.

Overall, there were 1,793 utility measurements (baseline and post baseline) from 193 patients, of which 102 in the Atezolizumab treatment arm and 91 in the Chemotherapy treatment arm. A total of 184 patients (97 for Atezolizumab and 87 for Chemotherapy) had a baseline utility value and 163 patients (84 for Atezolizumab and 79 for Chemotherapy) had both a baseline and post-baseline utility measurements. The summary of the baseline utilities is presented in Table 40.

Table 40: Summary of baseline utilities

N	Min.	1st Qu.	Median	Mean	3rd Qu.	Max.
184	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

In the following analyses, the post-baseline utilities from patients with available baseline were considered. Overall, 1528 utilities were analysed from 163 patients. The baseline utility value was included in the models, since it was always relevant and statistically significant. The randomisation stratification factors (ECOG, Sex, Histology) were also considered in exploratory models, but were not retained, since they were not statistically significant. Likewise, there was no statistically significant effect of time.

Three different approaches for applying the utility values derived from IMpower110 were considered: the proximity to death approach, the pre-/post-progression approach, and the on-/off-treatment approach. However, the proximity to death approach was subsequently disregarded due to wide, overlapping confidence intervals and counter-intuitive results between groups, possibly due insufficient numbers of measurements in some groups (see below). The pre/post progression approach was chosen for the base case and the alternative options will be explored in scenario analyses. This is in line with two previous studies that were found to have been used in most of the economic evaluations published in NSCLC (190, 191).

B.3.4.1.1 Utilities by progression status

Progression data from the IMpower110 trial was used to estimate utilities by progression status (pre-progression and after progression). Using this approach, utilities were classified according to whether patients experienced a progression event as assessed by RECIST v1.1 criteria by the investigator in IMpower110 (post-progression) or not (pre-progression). Utilities were analysed by arm and progression status to see whether there are any differences observed by treatment arm using a linear mixed-effects model with random subject intercept including baseline utility (mean subtracted), progression status (pre/post), treatment arm and progression status by treatment arm interaction. The number of observations by treatment arm and progression status are shown in Table 41.

Table 41: Number of patients and observations per treatment arm included in pre/post progression model

Treatment arm	Number of patients	Number of observations
Pre-progression	[redacted]	[redacted]
Atezo (Arm A)	[redacted]	[redacted]
Chemo (Arm B)	[redacted]	[redacted]
Post-progression	[redacted]	[redacted]
Atezo (Arm A)	[redacted]	[redacted]
Chemo (Arm B)	[redacted]	[redacted]

The utilities by progression status and treatment arm are shown in Table 42. Pre-progression utilities were very similar in the two treatment arms, and although it appears that post-progression utilities were higher for atezolizumab arm compared to the chemotherapy arm, utilities were estimated from a model that included progression status with pooled treatment arms, in order to be conservative given the small number of post-progression observations.

Table 42: Health state utility values by progression status

Label	Estimate	SE	Lower limit 95% CI	Upper limit 95% CI
Pre progression				
Atezo (Arm A)	[redacted]	[redacted]	[redacted]	[redacted]
Chemo (Arm B)	[redacted]	[redacted]	[redacted]	[redacted]
Arm A and B pooled	[redacted]	[redacted]	[redacted]	[redacted]
Post progression				
Atezo (Arm A)	[redacted]	[redacted]	[redacted]	[redacted]
Chemo (Arm B)	[redacted]	[redacted]	[redacted]	[redacted]
Arm A and B pooled	[redacted]	[redacted]	[redacted]	[redacted]

SE: standard error

Additional models aiming at estimating utilities in case of treatment-related grade 3 or higher or serious adverse events were explored, but did not show any relevant differences.

B.3.4.1.2 Utilities on/off treatment

Time on treatment from the IMpower110 trial was used to implement the on/off treatment approach. Health state utility value (HSUV) were estimated during the time patients received therapy (on treatment) and after treatment's discontinuation (off treatment) using a linear mixed-effects model with random subject intercept including baseline utility (mean subtracted), on/off treatment, treatment arm and on/off treatment by treatment arm interaction. Utilities were analysed by arm and on/off treatment to see whether there are any

differences by treatment arm. The number of patients and observations by on/off treatment and treatment arm are presented in Table 43 . The utilities estimated by treatment arm and on/off treatment are shown in Table 44. There were small differences on-treatment between the two arms and 95% confidence intervals (CI) overlap, and although it appears that off-treatment utilities were higher for atezolizumab arm compared to chemotherapy arm, utilities were estimated from a model that included on/off treatment with pooled treatment arms, in order to be conservative given the small number of observations off-treatment.

Table 43: Number of patients and observations on/off treatment by treatment arm

Treatment arm	Number of patients	Number of observations
On-treatment	[redacted]	[redacted]
Atezo (Arm A)	[redacted]	[redacted]
Chemo (Arm B)	[redacted]	[redacted]
Off-treatment	[redacted]	[redacted]
Atezo (Arm A)	[redacted]	[redacted]
Chemo (Arm B)	[redacted]	[redacted]

Table 44: Health state utility values on/off treatment

Label	Estimate	SE	Lower limit 95% CI	Upper limit 95% CI
On treatment				
Atezo (Arm A)	[redacted]	[redacted]	[redacted]	[redacted]
Chemo (Arm B)	[redacted]	[redacted]	[redacted]	[redacted]
Arm A and B pooled	[redacted]	[redacted]	[redacted]	[redacted]
Off treatment				
Atezo (Arm A)	[redacted]	[redacted]	[redacted]	[redacted]
Chemo (Arm B)	[redacted]	[redacted]	[redacted]	[redacted]
Arm A and B pooled	[redacted]	[redacted]	[redacted]	[redacted]

B.3.4.1.3 Utilities by time to death

The ‘proximity to death’ approach using HRQoL data derived directly from the IMpower110 trial was explored. This approach is based on patients’ ‘proximity to death’ at the time of the utility assessment. This method was preferred in previous NICE assessments (173, 174, 192-194), since it captured the reduction in utility experienced by patients approaching death.

A mixed-effects model with random subject intercept including baseline utility (mean subtracted), proximity to death group, treatment arm and proximity to death group by treatment arm. Utility observations from all patients who died and the observations more than 211 days before censoring for censored patients were included. The following proximity to death groups were used, as in previous submissions (176):

- Group 1: less than 35 days before death; Group 2: more than 34 and less than 75 days before death; Group 3: more than 74 and less than 210 days before death; Group 4: more than 211 days before death / censoring

A total of 929 utilities were considered from 145 patients. The number of patients and observations by proximity to death group and treatment arm are presented in Table 45 and the results are displayed in Figure 38. Given that the estimated utilities and their 95% CI overlap between treatment arms and most of the proximity to death groups, this approach was not considered further. Additional exploratory analyses in the subset of patients who died provided similar results. The same analysis was also performed considering the proximity to death groups used for the submission of Pembrolizumab in 1L NSCLC to NICE (173), but the results did not show substantial differences for the groups closer to death. Finally, visual assessment of the scatter plot (Figure 39) of utilities by proximity to death did not highlight other meaningful time-intervals that could be considered.

Table 45: Number of patients and observations per treatment arm included in pre/post progression model

Treatment arm	Number of patients	Number of observations
Group 1		
Atezo (Arm A)	[redacted]	[redacted]
Chemo (Arm B)	[redacted]	[redacted]
Group 2		
Atezo (Arm A)	[redacted]	[redacted]
Chemo (Arm B)	[redacted]	[redacted]
Group 3		
Atezo (Arm A)	[redacted]	[redacted]
Chemo (Arm B)	[redacted]	[redacted]
Group 4		
Atezo (Arm A)	[redacted]	[redacted]
Chemo (Arm B)	[redacted]	[redacted]

Figure 38: Estimated utilities by proximity to death group and treatment arm

Figure 39: Scatter plot of utility score by proximity to death

B.3.4.2 Mapping

HRQoL was collected using the EQ-5D-3L questionnaire in the IMpower110 study, consistent with the NICE reference case. As such, no mapping techniques were required.

B.3.4.3 Health-related quality-of-life studies

An SLR was conducted to identify HRQoL evidence in the first-line treatment of patients with NSCLC. Detailed descriptions of the search strategy and extraction methods, as well as an overview of the identified studies are provided in Appendix I.

Summary of identified studies and results

A total of 42 publications were identified reporting health state utility values (HSUVs) associated with advanced or metastatic wild-type NSCLC (i.e. excluding studies reporting HSUVs in populations with oncogenic driver mutations such as EGFR mutations or ALK rearrangements). Of these, five reported utilities in graph format only. The remaining 37 studies reported unique, original HSUV data for the population of interest (71, 96, 191, 195-230). Of these 37 studies, 21 were presented as full publications (71, 96, 191, 197, 200, 201, 203, 207, 211-215, 217, 219-222, 224-226, 229), and 16 were presented as conference abstracts only (195, 196, 198, 199, 202, 204-206, 208-210, 216, 218, 227, 228, 230, 231).

Commonly reported health states across the identified studies included progression status (progression free/progressive disease/stable disease), impact of adverse events (AEs), time to death/survival, patient characteristics and demographics (e.g. age, gender, smoking status, Eastern Cooperative Oncology Group [ECOG] performance score [PS]), line of treatment, recurrence status, disease stage, and presence/absence of metastases. Four full publications and ten conference abstracts reported intervention-specific utilities for the population of interest.

In line with HTA body requirements, the EQ-5D was the most commonly used instrument for measuring HRQoL in the study populations. Other instruments used to derive utilities included the direct standard gamble (SG) method and time trade off (TTO) method, visual analogue scale (VAS), the 15D, and the quality of life utility (QLU)-C10D (derived from the European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire [EORTC-QLQ-C30]). In all studies, patients directly described health states, with the exception of the two studies by Nafees et al (201, 215). In these studies, members of the general public were used to value a series of vignette health states, developed to reflect metastatic NSCLC. With regard to health state valuation, a range of societal tariffs were used including the UK and Canadian tariffs. Overall, only six full publications fully met the requirements of the NICE reference case; that is, utilities were derived directly from patients

using the preferred EQ-5D and health states were valued using UK societal preference elicited using the direct TTO method (96, 191, 197, 200, 212, 217). An assessment of suitability was conducted on the identified studies to establish which, if any, of them may be suitable for use in the economic model. This assessment was based on how closely they adhered to the NICE reference case and the validity of the parameters to the appraisal decision problem and model, such as study location, line of therapy and which health states were valued. The two studies selected to be included in the model were the results from the KEYNOTE-024 study (TA531) and Chouaid et al (191). It should be noted that the values reported by Huang *et al* (196) are those from the KEYNOTE-024 study, which were used in TA531. Huang *et al* valued the health states according to the geographic locations of the patients within the study; consequently, values from the TA531 submission documents were used instead, since these values are based on UK valuation.

B.3.4.4 Adverse reactions

Two approaches for the inclusion of the impact of AEs on HRQoL were considered:

1. The assumption that any disutility has already been incorporated in to the base case health state utilities through the trial derived EQ-5D utilities, and incorporating an additional disutility could be considered double counting;
2. The assumption that averaged trial-derived utilities underestimate disutilities associated with adverse events, and therefore an additional disutility must be applied.

Consistent with previous appraisals in NSCLC the base case analysis takes the former assumption and does not include any disutility for AEs (168, 174, 176, 179). Furthermore, additional models aimed at estimating utilities in treatment-related grade 3 or higher, or serious AEs were explored, but did not show any significant differences between patients with grade 3 AEs and those without.

B.3.4.5 Health-related quality-of-life data used in the cost-effectiveness analysis

The utility values used in the cost-effectiveness analysis are presented in Table 46*.*

Table 46: Summary of utility values for cost-effectiveness analysis

Category	Utility	95% CI	Reference in submission	Justification
IMpower110 utilities – Pre-/post-progression – base case				
Pre-progression	[redacted]	[redacted]	Section B.3.4.1	Derived from EQ-5D data collected during IMpower110 study.
Post-progression	[redacted]	[redacted]		
IMpower110 utilities – On-/off-treatment – scenario analysis				
On-treatment	[redacted]	[redacted]	Section B.3.4.1	Derived from EQ-5D data collected during IMpower110 study.
Off-treatment	[redacted]	[redacted]		
Pembrolizumab utilities - Pre- and post-progression – TA531 – scenario analysis				
Pre-progression	0.778	0.763-0.793	Section B.3.4.3	Identified from published literature
Post-progression	0.668	0.629-0.707		
Utilities from Chouaid et al – scenario analysis				
Progression free	0.71†	Calculated based on utility model coefficients	Section B.3.4.3	Identified from published literature
Progressed disease	0.67†			

CI: confidence interval

*Value capped at population norm (value from study was 0.808). NB CI relates to study value

†Calculated based on reported regression coefficients

B.3.4.5.1 Consistency of literature utility values with values derived from IMpower110

Progression-free utility estimates from the literature are broadly in line with the progression-free and on-treatment utility values from IMpower110 [redacted], which lie in between Chouaid et al (0.71) and the KEYNOTE-024 value (0.778). This suggests a high degree of plausibility for the IMpower110 value.

The post-progression value from IMpower110 [redacted] is higher than values reported by Chouaid et al (0.67) and in KEYNOTE-024 (0.668), though still represents a decline from on-treatment/progression-free, reflecting loss of clinical benefit. The comparatively smaller decline may be explained by a lower number of observations in these health states.

B.3.4.5.2 Base case rationale

Initially, on-/off-treatment HSUVs were considered for the base case analysis, since these account for the use of cancer immunotherapies beyond disease progression defined by RECIST v1.1 criteria, until loss of clinical benefit, which allows for non-classical response patterns observed with immunotherapies. However, this approach has a key limitation in the current model due to the implementation of the 2-year stopping rule for pembrolizumab, which results in a cohort of patients arbitrarily transitioning to the lower off-treatment HSUV at two years. This scenario is not clinically plausible and results in a bias against pembrolizumab. Consequently, the IMpower110 utility values for pre- and post-progression are used in the base case since they are derived directly from trial patients using the EQ-5D-3L as per the NICE reference case. In addition, the difference between PFS and TTD results in the IMpower110 trial is small, suggesting that there would be minimal difference between pre-/post-progression and on-/off-treatment in the absence of a stopping rule. The impact of using different utility values from IMpower110 or from the literature is explored in scenario analyses.

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

Due to the volume of recent NSCLC appraisals conducted by NICE, in particular the appraisal of pembrolizumab in PD-L1-high first-line NSCLC patients (TA531), a new SLR to identify costs and healthcare resource use for this appraisal was not conducted. In lieu of a new SLR, a review that was previously provided by Roche in a relevant submission (atezolizumab in first-line non-squamous NSCLC, TA584) is provided in appendix J. This review resulted in a total of nine records representing seven unique studies. Where relevant, costs such as NHS reference costs have been updated to the most recent values (eg. the 2018/19 National Schedule of NHS Costs).

B.3.5.1 Intervention and comparators' costs and resource use

Drug acquisition costs and dosing for the treatments considered in the model are presented in Table 47. As atezolizumab and pembrolizumab are both branded medicines, unit costs were taken from the British National Formulary (BNF) (232). Net prices for atezolizumab based on a currently-approved Patient Access Scheme (PAS) are also included. It should also be noted that pembrolizumab is also subject to an undisclosed PAS.

Table 47: Acquisition costs of the intervention and comparator technologies

	Atezolizumab	Pembrolizumab	Source
Pharmaceutical formulation	1,200mg/20ml concentrate for solution for infusion; 840mg/14ml concentrate for solution for infusion	100mg/4ml concentrate for solution for infusion; 50mg powder for concentrate for solution for infusion	**SmPC**
Care setting	Secondary care	Secondary care	**SmPC**
Acquisition cost (excluding VAT) at list price (PAS price)	Atezolizumab 1,200mg/20ml concentrate for solution for infusion vials list price: £3,807.69 ([redacted])	Pembrolizumab 100mg/4ml concentrate for solution for infusion vials list price: £2,630.00	**BNF**
	Atezolizumab 840mg/14ml concentrate for solution for infusion vials list price: £2,665.38 ([redacted])	Pembrolizumab 50mg powder for concentrate for solution for infusion vials list price: £1,315.00	**BNF**
Cost per mg	£3.17 ([redacted])	£26.30	**Calculation**
Cost per Q2W cycle	£2,665.38 ([redacted])	N/A	**Calculation**
Cost per Q3W cycle	£3,807.69 ([redacted])	£5,260.00	**Calculation**
Cost per Q4W cycle	£5,330.76 ([redacted])	N/A	**Calculation**
Cost per Q6W cycle	N/A	£10,520.00	**Calculation**
Cost per month	Q3W: £5,514.08 [redacted] Q4W: £5,787.68 ([redacted])	£7,614.48	**Calculation**
Method of administration	Intravenous infusion	Intravenous infusion	**SmPC**
Doses	840mg, 1,200mg, 1,680mg	200mg, 400mg	**SmPC**
Dosing frequency	840mg Q2W, 1,200mg Q3W, 1,680mg Q4W	200mg Q3W, 400mg Q6W	**SmPC**
Dose adjustments	None	None	**SmPC**

Atezolizumab is administered until loss of clinical benefit (as defined in Section B.3.2.2.3) or unmanageable toxicity. Pembrolizumab is administered until disease progression or unacceptable toxicity, though it should be noted that the pembrolizumab SmPC states that treatment may be continued for clinically stable patients until disease progression is confirmed. In addition, as stated in Section B.3.2.2.3, the NICE recommendation limits the

maximum treatment duration of pembrolizumab in this setting to two years of uninterrupted treatment.

Both drugs use flat dosing regardless of patient weight or size. The base case uses a once every three week (Q3W) administration schedule, for both treatments. A scenario analysis comparing atezolizumab's Q4W vs. pembrolizumab's Q6W will be performed.

B.3.5.1.1 Subsequent therapies costs and resource use

The costs of subsequent lines of therapy are included in the progressed disease health state of the model. Although data on the treatment and duration of subsequent lines of therapy after discontinuation of atezolizumab were collected in the IMpower110 study, these are not fully representative of UK clinical practice, as some patients treated with atezolizumab in IMpower110 received subsequent cancer immunotherapy or targeted therapies such as bevacizumab, ramucirumab and erlotinib (see Section B.2.6.3).

In order to account for this in the model base case, an adjustment was made with respect to subsequent therapies. This approach is in line with UK clinical practice and was accepted by the NICE committee and the evidence review group (ERG) in the NICE appraisal of pembrolizumab in first-line NSCLC (TA531). As such, in the model base-case, all patients treated with atezolizumab are assumed to receive platinum-doublet chemotherapy second-line, in accordance with clinical practice and the recommendations summarised on the NICE Pathways website (233). Since both atezolizumab and pembrolizumab are immunotherapies, identical subsequent therapy assumptions are applied to both treatments. The specific regimens and proportions of patients treated with each regimen are presented in Table 48. These are based on the histology proportions in IMpower110 (76% non-squamous), with an arbitrary 50:50 split between cisplatin and carboplatin and the partner drug for non-squamous (pemetrexed) and squamous histology (gemcitabine).

The dosing for each of the subsequent therapies considered in the model is outlined below:

- Cisplatin: in line with its marketing authorisation and use in UK clinical practice, i.e. 75 mg/m^2 Q3W up to 6 cycles
- Carboplatin: in line with its marketing authorisation and use in UK clinical practice i.e. 6 mg/mL/min (AUC) for four or six cycles Q3W
- Pemetrexed: in line with its marketing authorisation and use in UK clinical practice, i.e. 500 mg/m^2 Q3W up to 6 cycles
- Gemcitabine: in line with its marketing authorisation and use in UK clinical practice, i.e. 1250 mg/m^2 Q3W up to 6 cycles

The average weight (68.74 kg) and body surface area (BSA; 1.78 m^2 using the Dubois formula) from the IMpower110 study were utilised to estimate the average cost per dose per patient for the treatments with dosing according to weight or BSA. The drug costs of the combination therapies were assumed to be equal to the sum of individual drug's costs included in a combination therapy (e.g., the drug costs for the combination pemetrexed/cisplatin therapy per administration is the sum of drug costs for pemetrexed per administration plus the drug costs for cisplatin per administration).

The base case of the economic model assumes full vial sharing (i.e., no wastage) for the administration of all weight/BSA-based drugs in the model.

Table 48: Subsequent therapies after discontinuation – base case

Post-discontinuation therapy	Treatments after atezolizumab or pembrolizumab	Duration of therapy (weeks)
Cisplatin + pemetrexed	37.4%	18
Carboplatin + pemetrexed	37.4%	18
Cisplatin + gemcitabine	12.6%	18
Carboplatin + gemcitabine	12.6%	18

Table 49: Drug acquisition costs – subsequent therapies

Drug	Vial/pack concentration	Vial/pack volume	Dose per vial/pack	Cost per vial/pack	Cost per mg	Source
Cisplatin	100 mg/ml	100 ml	100 mg	£6.66	£0.07	eMIT
Carboplatin	10 mg/ml	5 ml	50 mg	£28.22	£0.05	eMIT
Pemetrexed	100 mg powder			£150.00	£1.50	BNF
Pemetrexed	500 mg powder			£450.00	£0.90	BNF
Gemcitabine	10 mg/ml	20 ml	200	£23.23	£0.01	eMIT

eMIT: 12 month period until 31st December 2019

Table 50: Dosing schedule and dose per administration – subsequent therapies

Drug	Dosing per administration	Frequency of administration	Total dose	Reference for dosing
Cisplatin	75 mg/m^2	Q3W	133.5 mg	SmPC
Carboplatin	400 mg/m^2	Q3W	712 mg	SmPC
Pemetrexed	500 mg/m^2	Q3W	890 mg	SmPC
Gemcitabine	1250mg/m^2	Q3W	2,225 mg	SmPC

Q3W, every three weeks; Q4W, every four weeks; AUC, area under the curve

It should be noted that, while subsequent therapies are accounted for in the model, identical subsequent therapy assumptions are applied to both atezolizumab and pembrolizumab; consequently subsequent therapies have a neutral impact on cost-effectiveness. There is however a discrepancy in subsequent therapy costs between atezolizumab and pembrolizumab) when the stopping rule is applied to pembrolizumab; this is due to relative front-loading of subsequent therapy costs brought about by the stopping rule, meaning total discounting is lower.

B.3.5.1.2 Drug administration costs

The costs of administration used in the economic model for atezolizumab and pembrolizumab are shown in Table 51. The administration costs for both drugs is assumed to be that of outpatient simple parenteral chemotherapy, in accordance with TA531.

Table 51: Drug administration costs

Drug	Type of administration		NHS reference code	Cost per administration	Source
Atezolizumab and pembrolizumab	Deliver simple parenteral chemotherapy at first attendance	Outpatient setting	SB12Z (outpatient)	£183.54	NICE TA531, NHS reference costs 2018-19 (234)

The administration costs of subsequent therapies are shown in Table 52.

Table 52: Drug administration costs – subsequent therapies

Drug	Type of administration		NHS reference code	Cost per administration	Source
Cisplatin/ carboplatin + pemetrexed/ gemcitabine	Deliver Complex Chemotherapy, at First Attendance	Daycase and Reg Day/Night	SB14Z	£385.28	NICE TA584, NHS reference costs 2018-19
Cisplatin/ carboplatin + pemetrexed/ gemcitabine	Deliver Complex Chemotherapy, at First Attendance	Outpatient	SB14Z	£317.73	NICE TA584, NHS reference costs 2018-19

B.3.5.2 Health-state unit costs and resource use

Supportive care costs are applied for both PFS, and PD health states. The types of resource and frequency of use are derived from previous NICE technology appraisals, published sources and the SLR. Input from UK clinicians was not sought on this topic due to the number of recent prior appraisals in this area from which resource use can be drawn. Unit costs were derived from NHS reference costs (234) and PSSRU published costs (235). Table 53 details the resource use for the PFS and PD health state and Table 54 presents the unit cost for each element of resource use.

Table 53: Resource use for PFS and PD health state

Resource	PFS	PD	Unit	Source
Outpatient visit	9.61	7.91	per annum	NICE TA531
Chest Radiography	6.79	6.5	per annum	NICE TA531
CT scan (chest)	0.62	0.24	per annum	NICE TA531
CT scan (other)	0.36	0.42	per annum	NICE TA531
ECG	1.04	0.88	per annum	NICE TA531
Community nurse visit	8.7	8.7	visits (20 minutes) per patient	Appendix 1 of NICE Guideline CG121 (236) Marie Curie report (237)
Clinical nurse specialist	12	12	hours contact time per patient	Appendix 1 of NICE Guideline CG121 (236)
GP surgery	12	0	consultations per patient	Appendix 1 of NICE Guideline CG121(236)
GP home visit	0	26.09	per annum (fortnightly)	Marie Curie report (237)
Therapist visit	0	26.09	per annum (fortnightly)	Appendix 1 of NICE Guideline CG121 (236)

PFS, progression free state; PD, progressed disease state; GP, general practitioner; CT, computerised tomography; ECG, electrocardiogram; NICE, The National Institute for Health and Care Excellence; CG, clinical guidance

Table 54: Unit costs (PFS and PD health states)

Resource	Unit cost	Unit	Source
Outpatient follow-up visit	£148.95	per visit	NHS Reference Costs 2018-2019, Outpatient attendance data, Consultant Led, Service code 800, Clinical Oncology
Chest Radiography	£27.82	per case	NICE technology appraisal TA199; (£24.04 in 2009 - inflated to 2019-2020 using the PSSRU HCHS index)
CT scan (chest)	£103.61	per case	NHS Reference Costs 2018-2019, Diagnostic Imaging,

			Outpatient, HRG code RD24Z (two areas with contrast)
CT scan (other)	£102.82	per case	NHS Reference Costs 2018-2019, Diagnostic Imaging, Outpatient, HRG code RD24Z (two areas with contrast)
ECG	£136.11	per case	NHS Reference Costs 2018-2019, Complex ECG, HRG code EY51Z
Community nurse visit	£64.00	per hour	PSSRU 2019; pg 117; cost per hour Band 8A
Clinical nurse specialist	£76.00	per hour	PSSRU 2019; pg 117; cost per hour Band 8B
GP surgery visit	£39.00	per visit	PSSRU 2019; pg 120; cost per patient contact lasting 9.22 minutes; including direct care staff costs; with qualification costs
GP home visit	£96.45	per visit	PSSRU 2015 pg 177-78; cost per home visit including 11.4 mins for consultations and 12 mins for travel-inflated from TA531 to 2018/19 using the PSSRU HCHS index
Therapist visit	£48.00	per visit	PSSRU 2019; pg 133; cost per hour for community occupational therapist (including training)

GP, general practitioner; CT, computerised tomography; ECG, electrocardiogram; NHS, National Health Service; PSSRU, Personal Social Services Research Unit; NICE, The National Institute for Health and Care Excellence; HRG, Healthcare Resource Groups; HCHS, hospital and community health services

The resulting health state costs for PFS and PD are a product of the resource use (Table 53) multiplied by the unit costs (Table 54). For the total supportive care cost per week in PD, the distribution of subsequent therapies and the associated costs are also taken into account. The total cost per week in the PFS health state is £65.71 and for the PD state £122.91.

Cost of terminal care

An end of life / terminal care cost is applied to patients who enter the death state as a one off cost, in line with previous appraisals in NSCLC. The terminal care cost reflects the resource consumption in various care settings, and is weighted by the proportion of patients treated in each setting. This cost is assumed equal for all treatments in the economic model. Resource use and costs are shown in Table 55. The total cost of end of life is £4,598.01.

Table 55: Resource use and unit costs for terminal care/end of life

Resource	Unit cost	Number of consumption	% of patients	Assumptions / Source

			in each setting	
Community nurse visit	£64.00 per hour	28.00 hours	27%	PSSRU 2019; pg 117; cost per hour Band 8A
GP Home visit	£96.45 per visit	7.00 visits	27%	PSSRU 2015 pg 177-78; cost per home vist inlcuding 11.4 mins for consultations and 12 mins for travel-inflated from TA531 to 2018/19 using the PSSRU HCHS index
Macmillan nurse	£42.69 per hour	50.00 hours	27%	Assumed to be 66.7% of community nurse cost
Drugs and equipment	£578.56 per patient	Average drug and equipment usage	27%	NICE TA531, inflated to 2018/19 costs using PSSRU NHSCII index
Terminal care in hospital	£4,003.46 per episode	1 episode (9.66 days)	56%	NICE TA531, inflated to 2018/19 using the PSSRU HCHS index (238)
Terminal care in hospice	£5,173.59 per episode	1 episode (9.66 days)	17%	NICE TA531, assumed 25% increase on hospital inpatient care
Total cost	£4,598.01 per episode			

B.3.5.3 Adverse reaction unit costs and resource use

Adverse event data used in the model for atezolizumab were taken directly from the IMpower110 study. Previous appraisals within this therapy area have incorporated Grade ≥3 treatment related AEs with an incidence of ≥2% - ≥5% in either treatment arm into the economic model. In order to ensure a more robust assessment of the safety profile of the treatment regimens being compared all Grade ≥3 treatment-related AEs with an incidence of ≥2% in the atezolizumab arm of the IMpower110 trial are included in the base case analysis (Table 56). The AE for atezolizumab are based on the TC3/IC3 WT population data of the exploratory February 2020 data cut. The respective Grade ≥3 treatment-related AEs for pembrolizumab were sourced from “Grade ≥3 treatment-related AEs occurring in >10% of patients in either arm - Table 2” from the Updated KEYNOTE-024 publication (239). This is a conservative estimate that attributes more AEs to atezolizumab than to pembrolizumab in the model. This is due to the insufficient granularity of data for pembrolizumab to extract individual Grade ≥3 treatment-related AEs with an incidence of ≥2%.

Table 56: Numbers of adverse events included in the base case

Adverse Event	Atezo (n=107)	Pembro (n=154)
Diarrhoea	[redacted]	6
Hyponatraemia	[redacted]	0
Pneumonitis	[redacted]	0
Hyperkalaemia	[redacted]	0
Pyrexia	[redacted]	0

The unit costs related to the management of AEs were mainly derived from TA531. When unit costs were not available, an assumption was applied, and when AE management costs were trivial, they were assumed to be zero. All unit costs were inflated to 2018/19 prices using the hospital and community health services (HCHS) index published by PSSRU for 2019 (235). Table 57 presents the unit costs per AE for which costing was applied in the cost-effectiveness model.

Table 57: Unit cost per AE used in the economic model

Adverse Event	Unit Cost	Reference
Diarrhoea	£1,032.62	TA447 inflated to 2018-19 values from 2015/16 values using PSSRU NHSCII index
Hyponatraemia	£1,201.43	NHS reference costs 2018-2019: Total NHS reference costs 2018-2019 total HRG's KC05G-N fluid or electrolyte disorders with/without interventions Weighted cost of non-elective long stay, short stay and day case. TA 592
Pneumonitis	493.63	NHS reference costs 2018-2019 total HRG's Non-elective short stay weighted average DZ11K-V lobar, atypical or viral pneumonia with single, multiple or no interventions (cc score 0-14+) (TA10181)
Pyrexia and Hyperkalaemia	£0.00	Trivial cost, assumed to be 0

In the base case, the impact of AEs was incorporated by estimating weighted average costs per patient, applied as a one-off cost. These were then applied in the first cycle of the model for each treatment arm.

B.3.5.4 Miscellaneous unit costs and resource use

All elements of resource use and cost have been outlined in previous sections.

UK clinical experts have confirmed that PD-L1 testing is now considered standard clinical practice in the UK. As such, it is excluded from the analysis.

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

B.3.6.1 Summary of base-case analysis inputs

Table 58: Summary of base case analysis inputs

General Parameters and demographic	**Value**
Discount rate (costs)	3.5%
Discount rate (efficacy)	3.5%
Time horizon	20
Demographic data	
Patient weight	68.74
Patient BSA	1.78
Utilities	**Value**
Health State Utility	IMpower110 (Pre/Post progression)
Time to event end points	**Value**
NMA selection	NMA - HR (RE)
TTD Treatment duration Pembrolizumab	Until progression, up to 24 months
TTD - Atezolizumab parametric distribution	Gen Gamma
PFS - Atezolizumab parametric distribution	Gen Gamma
Duration of treatment effect - Atezo Mono	Effect is maintained
Duration of treatment effect - Pembro mono	Effect is maintained
OS – Atezolizumab parametric distribution	Weibull
Duration of treatment effect - Atezo Mono	Effect is maintained
Duration of treatment effect - Pembro mono	No more effect after cut-off point
Cut-off point of treatment effect (months)	60.00
Dosing	**Value**
Drug dosing assumption	Planned dose w. vial sharing
Vial sharing assumption	5%
Amount of vial needed to justify its use	5%
Administration Cost - £	**Value**
First cycle - Atezo Mono	183.54
First cycle - Pembro mono	183.54
Subsequent cycle - Atezo Mono	183.54
Subsequent cycle - Pembro mono	183.54
AE management cost - £	**Value**
Atezo Mono	0.93
Pembro mono	0.61
Weekly supportive care cost - £	**Value**

Health state costs - PFS	65.71
Health state costs - PD	122.91

B.3.6.2 Summary of key assumptions

Table 59: Key assumptions used in the economic model (base case)

Area	Assumption	Justification
Time horizon	20 years	The average age of patients in the model is 64. The 20-year model horizon is in line with NICE reference case, and also long enough to reflect the difference in costs and outcomes between the interventions being compared in this submission. Also consistent with previous NICE appraisals in this indication.
Comparators considered in the economic model	Pembrolizumab	See Section B.1.1. Pembrolizumab is the only clinically relevant, non-CDF comparator based on the recommended NICE pathway (233) and clinical expert opinion.
Resource use utilisation	Resource use utilisation is assumed to be the same for both atezolizumab and pembrolizumab.	Similar patient populations requiring identical healthcare resource use.
PD-L1 testing cost	Not included in base case	UK clinical experts have confirmed that PD-L1 testing in first-line NSCLC is now standard clinical practice in the UK. As such, since including PD-L1 testing cost would not have a differential impact on the comparators being considered, it was excluded from the analysis.
Subsequent therapy	100% of patients progressing on either atezolizumab or pembrolizumab received platinum doublet subsequent therapy.	In accordance with recommended NICE pathway (233) and clinical practice.
Atezolizumab: clinical efficacy and safety	IMpower110 study data (February 2020, exploratory data cut) were used for atezolizumab. Efficacy and safety results from IMpower110 are transferable to the UK population.	Advice from UK clinical experts suggested that the outcomes seen from the study are expected in UK patients given the similarity of patient characteristics between the trial and patients in the UK.
Pembrolizumab: clinical efficacy and safety	There is no head-to-head trial of atezolizumab vs pembrolizumab. A random	As per NICE guide to the methods of technology appraisal, and based on

	effects NMA was therefore conducted.	availability and limitations of published evidence for pembrolizumab.
Administration frequency	Q3W administration is assumed as the standard administration frequency for both atezolizumab and pembrolizumab.	In line with product SmPCs. Commonly adopted treatment regimen.
Extrapolation of time-to-event endpoints	TTD: Generalised Gamma For pembrolizumab assumed treatment until progression PFS: Generalised Gamma OS: Weibull Among the best fitting parametric extrapolations and those with visual fit to the available data, the functions were chosen that better would represent long-term clinical plausibility. In order to validate long-term OS for pembrolizumab, UK published estimates, precedent from NICE committee-preferred assumptions and the Flatiron Health database were used. For atezolizumab, UK clinical expert opinion was used to validate long-term OS estimates.	Based on NICE DSU recommendation (186).
Treatment stopping rule	No treatment stopping rule is applied to atezolizumab in the base case. A 2 year stopping rule is applied to pembrolizumab' OS model.	The clinical evidence base for atezolizumab allows treatment until loss of clinical benefit and does not have any stopping rule evidence. It also allows clinicians and patients the option of continuing therapy beyond two years in cases where they are still deriving clinical benefit. Feedback from clinical experts and patients themselves supports this approach. The two year stopping rule for pembrolizumab is in accordance its NICE recommendation.
Duration of treatment effect	Treatment effect for pembrolizumab stopping at 5 years (i.e. 3 years after	Ensures consistency with previous NICE decisions for pembrolizumab (TA531, TA428, TA557, TA600 (168, 174, 180, 181)).

	treatment discontinuation at 2 years). As atezolizumab is continued until loss of clinical benefit, no limitation on treatment effect should be applied in the base case on the OS function (as with atezolizumab appraisal for TNBC, TA639 (240)). We have however capped the treatment benefit of atezolizumab in scenario analyses.	The capping of atezolizumab's OS benefit, not allowing the OS functions to cross is a conservative assumption and relies on our clinical understanding that the two product are comparable in terms of efficacy in this patient population.
HRQoL	Based on EQ-5D data collected in IMpower110. Pre-/post-progression utility values used in the base-case analysis.	In line with NICE reference case. See rationale in section B.3.4.5. Pre-/post-progression represents a pragmatic compromise between approaches, and mitigates against artificial drops in utility values caused treatment stopping rules, as seen in on-treatment/off-treatment models. A limitation is that it does not account for treatment beyond progression until loss of clinical benefit. EQ-5D data were pooled to ensure a more robust sample size and a more plausible utility value. Insufficient data was collected to inform robust time-to-death approach.
Safety	Grade ≥3 treatment related adverse events experienced by ≥2% of patients in the atezolizumab arm of IMpower110 were included. The respective Grade ≥3 treatment-related AEs for pembrolizumab were sourced from "Grade ≥3 treatment-related AEs occurring in >10% of patients in either arm - Table 2" from the Updated KEYNOTE-024 publication. This is a conservative estimate due to lack of granularity in the available data.	The threshold of 2% for AE inclusion is a pragmatic and conservative approach. No disutility from AEs in base-case analysis to avoid double-counting; disutility associated with AEs was assumed to have been captured in the EQ-5D responses in IMpower110.

	No disutility from AEs considered in base-case analysis.	

B.3.7 Base-case results

Key information and limitations for economic results sections

- Over the time horizon of the model, the QALY difference is trivial and clinically meaningless (less than 0.1 QALY difference) and the 95% confidence intervals (C.I.) from the PSA are wide and cross zero: QALY difference: -0.08 (PSA C.I.: -0.88; 1.41).

- Due to the extremely small QALY difference based on the Impower110 exploratory data cut, the deterministic ICERs of atezolizumab at PAS price vs. pembrolizumab at list price now fall in the southwest quadrant of the incremental cost-effectiveness plane. For ease of interpretation, reverting the perspective of the analysis and setting the product with lowest costs at origin was preferred. For this reason, at PAS price we will **present ICERs of pembrolizumab vs. atezolizumab**, not vice versa. PAS price only ICERs are presented here.

- Whether through a complex decision making process based on the cost-utility analysis, or through a simpler cost comparison model, the analysis reach similar conclusions. Atezolizumab can be considered cost effective up to a discount of [redacted] for pembrolizumab at a WTP of £20,000 and [redacted] at £30,000 WTP threshold, based on the base case deterministic ICER.

- These results take into account continued therapy with atezolizumab versus a two-year stopping rule with pembrolizumab:
    - This is a key consideration, as the reimbursement of atezolizumab according to its licence and trial treatment duration will provide an important treatment option to clinicians and some patients in need of continuing treatment beyond two years.

B.3.7.1 Base-case incremental cost-effectiveness analysis results

Base case model results at list price are presented in Table 60.

Over the time horizon of the model, the QALY difference is trivial and clinically meaningless (less than 0.1 QALY difference) and the 95% confidence intervals (C.I.) from the partitioned survival analysis (PSA) are wide and cross zero: QALY difference: -0.08 (PSA C.I.: -0.88; 1.41); LY difference: -0.14 (PSA C.I.: (-1.21; 1.97)

The IMpower 110 exploratory data cut has a longer follow up ([redacted]) compared to the KEYNOTE studies (KEYNOTE-024: 25.2 months (241) and KEYNOTE-042: 14 months (242)). This consequently affects the OS HR in the ITC given the increased confounding due to subsequent lines of therapy. The RPSFT adjusted analysis [redacted] and attached in the appendix L explores the impact on the IMpower110 trial results described above.

[redacted] However, the ICERs at list price are not relevant for decision making given the confidential patient access schemes for both atezolizumab and pembrolizumab.

Due to the extremely small QALY difference based on the Impower110 exploratory data cut, the deterministic ICERs of atezolizumab at PAS price vs. pembrolizumab at list price now fall in the southwest quadrant of the Incremental Cost-Effectiveness Plane.

These ICERs are not intuitive to interpret and alternative ways of presenting the results were considered. Initially the Net Monetary Benefit (NMB) approach was taken into considertation. This approach has the benefit of clearly showing if the result is above or below the willingness to pay (WTP) threshold. How the NMB results translate into ICERs and how close these are to the chosen threshold is not easy to understand.

As such, reverting the perspective of the analysis and setting the product with lowest costs at origin was preferred. This allows looking at incremental costs per incremental benefits and sets the ICERs back in the North East Quadrant of the Incremental Cost-Effectiveness Plane, which can be easily understood. **For this reason, we will present ICERs of pembrolizumab vs. atezolizumab, not vice versa**. If pembrolizumab's ICER is above the WTP threshold, it means atezolizumab can be considered a cost-effective use of NHS resources.

Table 60 and Table 61 show the results of pembrolizumab versus atezolizumab and pembrolizumab's ICER.

Atezolizumab can be considered cost effective up to a discount [redacted] for pembrolizumab at a WTP of £20,000 [redacted] at £30,000 WTP threshold, based on the base case deterministic ICER. These findings are not very distant from the Cost Comparison findings reported in Table 62 and Table 63.

Table 60: Base case results of pembrolizumab vs. atezolizumab* (list price)

	Total costs (£)	Total LY	Total QALYs	Incr. costs (£)	Incr. LY	Incr. QALYs	ICER (£/QALY)
Pembro	[redacted]	3.19	[redacted]	[redacted]	0.14	0.08	[redacted]
Atezo	[redacted]	3.06	[redacted]				
ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years, *pembro versus atezo: high ICER indicates atezo is worth funding							

List price ICERs would show mainly a list of dominant or dominated. Given the impossibility of presenting interpretable figures, we will only present PAS price results from here onwards. List price results can be found in Appendix M.

Table 61: Base case results of pembrolizumab versus atezolizumab * (PAS price)

	Total costs (£)	Total LY	Total QALYs	Incr. costs (£)	Incr. LY	Incr. QALYs	ICER (£/QALY)
Pembro	[redacted]	3.19	[redacted]	47,059	0.14	0.08	560,832*
Atezo	[redacted]	3.06	[redacted]				
ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years, *pembro versus atezo: high ICER indicates atezo is worth funding							

B.3.7.2 Base-case cost-comparison results

As discussed in section B.3.2, a CCompA was also conducted due to the fundamental similarities in clinical efficacy, safety and resource use between atezolizumab. The CCompA is further supported by the trivial and clinically meaningless QALY difference in the CUA (less than 0.1 QALY difference). This analysis showed that at PAS price and without a stopping rule for atezolizumab, compared to pembrolizumab with a two year stopping rule in place, atezolizumab is worth funding up to a discount for pembrolizumab of [redacted] At that level of discount, pembrolizumab with the two year stopping rule in place, is cost neutral compared to atezolizumab without a stopping rule.

Table 62 shows the result at list price (incremental costs of [redacted]), Table 63 compares the results of atezolizumab at PAS price with pembrolizumab at list price (cost savings: [redacted]

Table 62 Cost comparison analysis (list price)

	Atezolizumab	Pembrolizumab
Mean cost of PFS	[redacted]	[redacted]
Mean cost of progression	[redacted]	[redacted]
Terminal/palliative care cost	[redacted]	[redacted]
Mean total cost	[redacted]	[redacted]
Incremental total costs	[redacted]	

Table 63 Cost comparison analysis (PAS price)

	Atezolizumab	Pembrolizumab
Mean cost of PFS	[redacted]	[redacted]
Mean cost of progression	[redacted]	[redacted]
Terminal/palliative care cost	[redacted]	[redacted]
Mean total cost	[redacted]	[redacted]
Incremental total costs	(£52,078)	

B.3.8 Sensitivity analyses

B.3.8.1 Probabilistic sensitivity analysis

A probabilistic sensitivity analysis was undertaken to explore the uncertainty of the model parameters and their associated impact on cost-effectiveness results. Three thousand iterations were used. The total costs, LYs and QALYs were recorded for each iteration and averaged.

PSA results for the comparison of pembrolizumab to atezolizumab are presented in Table 64. The probabilistic ICER for pembrolizumab (list price) versus atezolizumab at PAS price is £266,587.

Table 64: Probabilistic sensitivity analysis results: pembrolizumab vs. atezolizumab* (PAS price)

	Total costs (£)	Total LY	Total QALYs	Incr. costs (£)	Incr. LY	Incr. QALYs	ICER (£/LY)	ICER (£/QALY)
Pembro	[redacted]	3.32	[redacted]	45,800	0.24 (-1.24; 2.17)	0.17 (-0.89; 1.55)	192,055	266,587*
Atezo	[redacted]	3.08	[redacted]	-	-	-	-	-

ICER, incremental cost-effectiveness ratio; LYG, life years gained; PAS, patient access scheme; QALY, quality-adjusted life year, *pembro versus atezo: high ICER indicates atezo is worth funding

Cost-effectiveness planes (Figure 40) and the cost effectiveness acceptability curves (Figure 41) are presented below. Looking at the distribuitons of the scatters along the x-axis of Figure 40 we can appreciate how atezolizumab and pembrolizumab mainly demonstrated very similar, overlapping clinical benefit in terms of QALYs. The broader scatter of iterations for pembrolizumab are due to the higher uncertainty in the pembrolizumab data, likely from the lack of patient level data and the broad confidence intervals of the ITC. The probabilistic ICER is also affected by this uncertainty.

Figure 40: Cost-Effectiveness Plane - (PAS price)

[redacted]

Figure 41: Cost-Effectiveness Acceptability Curves - (PAS price)

B.3.8.2 Deterministic sensitivity analysis

A one-way sensitivity analysis (OWSA) was performed to investigate key drivers of the cost-effectiveness model. Each input parameter was set to its respective upper or lower bound and the deterministic results for the model recorded. The upper and lower bounds around the mean value for each input parameter were based upon the 10% and 90% percentile values obtained from the PSA input distribution. Where percentile estimates were not available, the input parameter was varied by ±20%.

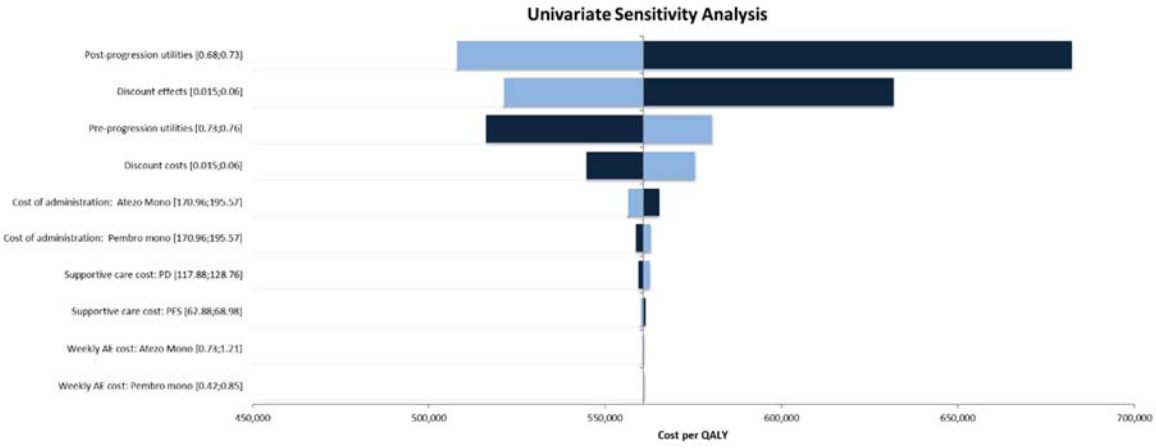
Table 65 shows the parameter values for the univariate sensitivity analysis. The tornado diagram for pembrolizumab versus atezolizumab at PAS price is presented in Table 44.

Based on the deterministic sensitivity analyses at PAS price, the most influential parameters appear to be the post-progression utilities, the discount rate for health outcomes, the pre-progression utilities, the discount rate for costs, the administration cost for atezolizumab, supportive care costs in the PD health state and the administration cost for pembrolizumab.

Table 65: Parameter values for univariate sensitivity analysis

Parameter	Base case value	Lower value	Higher value
Discount costs	3.5%	1.50%	6.00%
Discount effects	3.5%	1.50%	6.00%
Supportive care cost: PFS	65.71	62.88	68.98
Supportive care cost: PD	122.91	117.88	128.76
Weekly AE cost: Atezo Mono	0.93	0.73	1.21
Weekly AE cost: Pembro mono	0.61	0.42	0.85
Cost of administration: Atezo Mono	183.54	170.96	195.57
Cost of administration: Pembro mono	183.54	170.96	195.57
Pre-progression utilities	0.75	0.73	0.76
Post-progression utilities	0.71	0.68	0.73

Figure 42: Tornado diagram – (atezolizumab PAS price)



B.3.8.3 Scenario analysis

B.3.8.3.1 Scenario analyses: cost effectiveness analysis

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

- Alternative plausible OS Extrapolations (see B.3.3.4)
- Alternative plausible PFS Extrapolations (see B.3.3.5)
- Alternative plausible TTD Extrapolations (see B.3.3.6)

- Alternative utility values (see B.3.4.5)
- Alternative administration schedule (pembrolizumab Q6W vs. atezolizumab Q4W) (see B.3.5.1)
- Using atezolizumab's TTD data for pembrolizumab up to two years (see B.3.3.6)
- NMA Fixed Effect model HR (B.2.9)
- Capping OS benefit at 96 months for atezolizumab, as presented in Figure 30
- Capping OS benefit at 60 months for atezolizumab

Scenario analyses results at PAS price are presented below. It should be noted that not all scenario analyses are appropriate to consider for decision-making.

Table 66: Scenario analyses <u>results pembrolizumab vs. atezolizumab* (PAS price)</u>

Parameter	Value	Atezo Mono			Pembro mono			Pembro Mono vs. Atezo Mono		
		Life Years	QALYS	Costs	Life Years	QALYS	Costs	Inc. QALYs	Inc. Costs	ICER
Base case		[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	0.08	47,059	560,832*
Distribution OS	Exponential	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	0.10	48,475	476,303*
	Log-normal	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	0.12	47,481	401,488*
	Gen Gamma	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	0.09	47,186	536,154*
	Log-logistic	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	0.12	47,445	405,563*
	Gompertz	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	0.29	48,869	170,602*
	KM with Exponential tail	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	0.10	48,235	461,996*
	KM with Weibull tail	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	0.08	47,010	565,197*
	KM with Log-normal tail	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	0.12	47,386	392,050*
	KM with Gamma tail	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	0.09	47,090	538,405*
	KM with Log-logistic tail	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	0.12	47,358	402,037*

	KM with Gompertz tail	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	0.29	48,746	170,678*
Distribution PFS	Exponential	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	0.09	59,018	645,357*
	Weibull	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	0.09	51,166	576,877*
	Log-normal	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	0.08	47,451	561,842*
	Log-logistic	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	0.08	46,549	552,459*
	Gompertz	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	0.08	46,559	563,118*
	KM with Exponential tail	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	0.09	45,394	507,668*
	KM with Weibull tail	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	0.09	45,574	523,873*
	KM with Log-normal tail	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	0.08	45,866	552,201*
	KM with Gamma tail	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	0.08	45,883	553,930*
	KM with Log-logistic tail	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	0.08	45,885	554,118*
	KM with Gompertz tail	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	0.08	45,925	558,277*
Distribution TTD	Exponential	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	0.08	55,120	656,895*
	Weibull	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	0.08	46,041	548,696*
	Log-normal	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	0.08	35,726	425,770*

	Log-logistic	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	0.08	35,866	427,431*
	Gompertz	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	0.08	37,358	445,211*
	KM with Exponential tail	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	0.08	57,250	682,279*
	KM with Weibull tail	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	0.08	46,510	554,282*
	KM with Log-normal tail	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	0.08	37,683	449,090*
	KM with Gamma tail	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	0.08	47,536	566,506*
	KM with Log-logistic tail	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	0.08	38,132	454,439*
	KM with Gompertz tail	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	0.08	36,104	430,267*
Pembro treatment duration assumption	Set it equal to atezo actual treatment duration up to two years, when pemro is discontinued	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	0.08	51,873	618,203*

Utility method	IMpower110 (On/Off treatment)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	0.03	47,059	1,433,902*
	IMpower110 (Proximity to death)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	0.11	47,059	441,166*
	Chouaid et al. 2013	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	0.08	47,059	591,720*
	Nafees et al. 2008	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	0.00	47,059	22,209,162*
	KEYNOTE-024	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	0.05	47,059	864,808*
Time horizon	5 years	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	0.12	55,315	453,856*
	10 years	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	0.14	49,792	363,872*
	15 years	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	0.10	47,830	456,515*
NMA	FE model	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	0.06	37,862	677,054*
Administration schedule	Q6W vs. Q4W atezo	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	0.08	48,555	578,658*
Capping of treatment benefit	Atezo OS treatment effect capped at 96 months	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	0.14	47,464	345,711*
	Atezo OS treatment effect capped at 60 months	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	0.2	48,022	234,870*

ICER, incremental cost-effectiveness ratio; LYs, life years; QALYs, quality-adjusted life years; KM, Kaplan Meier; NMA, network meta-analysis; HR, hazard ratio; FE, fixed effects; *pembro versus atezo: high ICER indicates atezo is worth funding

The scenario analyses demonstrated the robustness of the base case:

From a utilities perspective, the QALY difference remains negligible and clinically insignificant: Using all clinically plausible alternative OS and PFS models, the difference is consistently below 0.1 QALY.

Furthermore, using alternative utility estimates does not change the general conclusion of clinical equivalence: Interestingly using Nafees et al. 2008 the difference in utilities is zero (0.0021) and using the KEYNOTE-024 values from TA531 the QALY difference is 0.05. Both studies have a bigger difference between pre and post- progression utilitites compared to the IMpower110 data. The limitations due to the limited number of observations for the post-progression utilitites from the IMpower110 trail have been highlighted in Section B.3.4.5. The PFS HRs in the IMpower110 and KEYNOTE studies are not affected by subsequent lines of therapy and the HR point estimate derived from the ITC favours atezolizumab. As such, attributing proportionally more weight to pre-progression utilites partially mitigates for the unadjusted confounding effect of the subsequent therapy. Finally, using IMpower110 proximity to death approach, results in a reduction of 0.11 QALY for atezolizumab compared to pembrolizumab.

What could arguably be seen as atezolizumab's clinically plausible worst-case scenario presented here is the "capping of atezolizumab treatment benefit" (OS 96 months), similarly does not detract from what has been observed in the base case. Under this scenario the QALY difference would be 0.14 and atezolizumab is worth funding up to pembrolizumab's discount of between [redacted] Capping atezo OS benefit at 60 months results in a QALY difference of 0.2 and atezolizumab is worth funding up to pembrolizumab's discount of [redacted]

It is worth remembering that with clinically appropriate base case settings, atezolizumab can be considered cost effective up to a discount [redacted] for pembrolizumab (WTP of £20,000) and [redacted] (£30,000 WTP).

These results further feed to the available evidence and clinical opinion that demonstrates clinical equivalence of the two products in the population under appraisal.

In addition, a stable range of economic results were presented, where atezolizumab would be better value for money for the NHS without a stopping rule in place, compared to standard of care with a stopping rule.

Indeed, the cost comparison analysis reached similar conclusions and is believed to be the most appropriate decision making tool for this appraisal, given NICE's limited resources.

B.3.8.3.2 Scenario analysis: Cost comparison analysis

Table 67 shows the key scenario analyses using alternative models or variables that significantly impact the costs. Other scenarions explored can be found in Appendix K.

Table 67: Cost comparison scenario analyses results atezolizumab vs. pembrolizumab (list price)

Parameter	Value	Atezolizumab	Pembrolizumab	Atezolizumab vs. Pembrolizumab
		Costs	Costs	Incremental Costs
Base case	Gen Gamma	[redacted]	[redacted]	[redacted]
TTD distribution	Exponential	[redacted]	[redacted]	[redacted]
	Log-normal	[redacted]	[redacted]	[redacted]
	Weibull	[redacted]	[redacted]	[redacted]
	Log-logistic	[redacted]	[redacted]	[redacted]
	Gompertz	[redacted]	[redacted]	[redacted]
	KM with Exponential tail	[redacted]	[redacted]	[redacted]
	KM with Weibull tail	[redacted]	[redacted]	[redacted]
	KM with Log-normal tail	[redacted]	[redacted]	[redacted]
	KM with Gamma tail	[redacted]	[redacted]	[redacted]
	KM with Log-logistic tail	[redacted]	[redacted]	[redacted]
	KM with Gompertz tail	[redacted]	[redacted]	[redacted]
Pembro treatment duration assumption	Actual atezo treatment duration	[redacted]	[redacted]	[redacted]
Administration schedule	Q4W vs Q6W	[redacted]	[redacted]	[redacted]

Table 68 Cost comparison scenario analyses results atezolizumab vs. pembrolizumab (PAS price)

Parameter	Value	Atezolizumab	Pembrolizumab	Atezolizumab vs. Pembrolizumab
		Costs	Costs	Incremental savings
Base case	Gen Gamma	[redacted]	[redacted]	(52,078)
TTD distribution	Exponential	[redacted]	[redacted]	(60,139)
	Weibull	[redacted]	[redacted]	(51,060)
	Log-normal	[redacted]	[redacted]	(40,745)
	Log-logistic	[redacted]	[redacted]	(40,884)
	Gompertz	[redacted]	[redacted]	(42,376)
	KM with Exponential tail	[redacted]	[redacted]	(62,269)
	KM with Weibull tail	[redacted]	[redacted]	(51,529)
	KM with Log-normal tail	[redacted]	[redacted]	(42,702)
	KM with Gamma tail	[redacted]	[redacted]	(52,554)
	KM with Log-logistic tail	[redacted]	[redacted]	(43,151)
	KM with Gompertz tail	[redacted]	[redacted]	(41,122)
Pembro treatment duration assumption	Actual atezo treatment duration	[redacted]	[redacted]	(49,996)
Administration schedule	Q4W vs Q6W	[redacted]	[redacted]	(53,555)

The results compare costs of continuous treatment with atezolizumab to pembrolizumab having a 2 year treatment stopping rule.

Also the cost comparison scenario analyses confirmed the robustness of the base case. Using the Weibull TTD function for atezolizumab does not change the picture: atezolizumab is cost saving up to [redacted] discount for pembrolizumab

If we consider pembrolizumab's 6 weekly administration schedule versus atezolizumab's 4 weekly schedule, atezolizumab is cost saving to the NHS up to a discount for pembrolizumab of [redacted] delivering an important option without a stopping rule in place.

B.3.8.4 Summary of sensitivity analyses results

B.3.8.4.1 Cost Utility analysis

Based on the deterministic sensitivity analyses at PAS price, the most influential parameters appear to be the post-progression utilities, the discount rate for health outcomes, the pre-progression utilities, the discount rate for costs, the administration cost for atezolizumab, supportive care costs in the PD health state and the administration cost for pembrolizumab. Alternative utility values have been explored in the scenario anlysis.

The probabilistic sensitivity analysis showed in the scatter plots how atezolizumab and pembrolizumab have highly comparable QALYs. The ICER reflects the uncertainty in the indirect treatment comparison.

The scenario analyses demonstrated the robustness of the base case. The QALY difference remains insignificant, mostly below or around 0.1 QALY. On the other hand, considering pembrolizumab's 6 weekly administration schedule versus atezolizumab's 4 weekly schedule increases pembrolizumab's costs.

What could be arguably seen as atezolizumab's worst case scenario presented, "capping atezolizumab's OS treatment benefit", does not detract from what seen in the base case: Summarising all clinically meaningful scenario analyses atezolizumab is worth funding up to pembrolizumab's discount of between [redacted]

The scenario analyses for the cost comparison demonstrated similar outputs: atezolizumab is worth funding up to circa [redacted] pembrolizumab discount, as it is cost saving to the NHS.

The small difference between the cost effectiveness and cost utility analysis is driven by the very small difference in QALY between the two products in the cost utility analisis.

B.3.9 Subgroup analysis

No subgroup analyses are presented as part of this submission.

B.3.10 Validation

Selection of the appropriate distributions for time-to-event endpoints was driven by statistical fit to the data, visual fit to the KM curves, clinical plausibility of t the outcomes.All outcomes of the economic model have been extensively compared to and validated against all available evidence, as well as clinical expert opinion, to assess the accuracy of the modelled survival (See Section B.3.3).

The economic model was developed specifically from the UK NHS and PSS perspective. The structure is consistent with other cancer immunotherapy models and previous NSCLC submissions to NICE and all costs are sourced from UK published sources. In particular, the model adheres closely to the precedents of TA531 and TA584, which in turn were extensively clinically validated. In addition, the model approach was validated by UK clinical experts to ensure the model is reflective of clinical practice. This includes, but is not limited to: health state inclusion, relevant comparators, OS and PFS projections and extrapolation techniques.

Internal quality control and validation of the model was conducted by an external consultancy. Cell by cell validation was conducted which included formula checking, cell references and all aspects of model functionality. A number of pressure tests were also conducted, often using extreme values. The results of the model using these values were then compared to expected outputs to assess functional accuracy.

Finally, all clinical experts consulted by Roche saw the cost comparison analysis as the most appropriate tool for decision making in this instance, given the lack of meaningful cinical difference between atezolizumab and pembrolizumab in this indication.

B.3.11 Interpretation and conclusions of economic evidence

B.3.11.1 Comparison with published economic literature

This is the first economic evaluation focused on assessing the cost-effectiveness of atezolizumab monotherapy as a first-line treatment of adult patients with metastatic NSCLC.

No study assessing the cost-effectiveness of atezolizumab for the target population was identified from the SLR. It was therefore not possible to compare the results of the economic model developed in this submission with any available publication.

B.3.11.2 Relevance of the economic evaluation for all patient groups

The population included in the economic evaluation is consistent with the population in our pivotal study IMpower110 and our anticipated licence. As mentioned previously (see section B.3.3), efficacy and safety data from IMpower110 were used for atezolizumab, and results of the indirect treatment comparison outlined in Section B.2.9 were used to inform relative efficacy and safety for pembrolizumab.

B.3.11.3 Generalisability of the analysis to clinical practice in England

The analysis is directly applicable to clinical practice in England.

The patient population in IMpower110 and the de novo economic evaluation are reflective of first-line patients with metastatic NSCLC in the UK. Advice from UK clinical experts suggested that the patient population in IMpower110 is broadly consistent with UK patients treated in clinical practice. Despite the post-progression therapies in IMpower110 being somewhat inconsistent with UK clinical practice, the outcomes seen from the study are expected in UK patients.

- The economic model structure is consistent with other oncology models and previous NICE submissions in NSCLC.
- 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, incorporating the feedback provided by the ERGs in recent NICE appraisals. These cost inputs are considered most appropriate to model the cost-effectiveness of atezolizumab.
- Since pembrolizumab was not included as a comparator in IMpower110, an ITC was conducted to enable atezolizumab to be compared to pembrolizumab, making use of all available evidence and the appropriate methodologies.
- Extensive scenario and sensitivity analyses were conducted in the economic model, considering alternative approaches to the extrapolation of time-to-event endpoints, alternative parameter inputs and data sources.
- The landmark OS projections from the model were validated against all available UK sources and UK clinical expert opinion to ensure the clinical plausibility of the model and its applicability to UK clinical practice.

- The results from the IMpower110 trial are considered by UK clinicians to be highly comparable to the published data for pembrolizumab in the same patient population, lending credibility and validity to a cost-comparison approach.

B.3.11.4 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:

- Efficacy and safety data from IMpower110 were used to model OS, PFS and TTD for atezolizumab.
- Utility values were obtained directly from EQ-5D-3L IMpower110 data.
- Resource utilisation used in the analysis is derived from recent, directly relevant NICE appraisals. Unit costs used in the analysis are reflective of UK clinical practice and were mainly derived from UK published sources, accounting for the feedback provided by NICE and ERGs in the most recent submissions.
- The ITC implemented enabled a comparison between atezolizumab and pembrolizumab, by applying appropriate methodology and making use of all available evidence.
- The model accounts for the two-year stopping rule governing the use of pembrolizumab in this indication, and the associated treatment effect duration applied in previous NICE appraisals.
- Extensive sensitivity and scenario analyses were conducted in the economic model to inform the uncertainty around the parameters used and help understand what key variables and assumptions potentially have a major impact on cost-effectiveness results.
- The economic evaluation accounts for the clinically-validated similarities between atezolizumab and pembrolizumab by considering a cost-comparison approach in addition to a cost-utility analysis.

Nevertheless, the economic analysis is also associated with limitations:

- Pembrolizumab was not included as a comparator in IMpower110 and as such, we had to implement an ITC to enable a comparison between atezolizumab and pembrolizumab. The base case network for the ITC is associated with limitations, primarily resulting from the different levels of detail available for the studies included and the censoring of OS outcomes.
- Time-to-event endpoints such as PFS, TTD and OS are not fully mature and extrapolation of these endpoints is subject to uncertainty. Nevertheless, by following a robust and comprehensive approach for the survival extrapolation, best efforts have been taken to ensure the methods were statistically sound, clinically plausible, and reflective of real-

world clinical practice. Extensive sensitivity and scenario analyses were conducted to inform the impact of alternative extrapolation models and assess the long-term plausibility and appropriateness of each scenario.

- In prior appraisals of cancer immunotherapies, the on-treatment/off-treatment model structure has frequently been used to account for treatment beyond progression. However, the two year stopping rule applied to pembrolizumab in clinical practice in England makes the use of an on-treatment/off-treatment model structure flawed, due to arbitrary transition to the lower off-treatment utility value. Results from this scenario analysis should therefore be interpreted with caution.

B.3.11.5 Conclusions

IMpower110 is the first trial of a PD-L1 inhibitor, atezolizumab, to demonstrate a statistically significant OS benefit over platinum chemotherapy in treatment-naïve, PD-L1-high NSCLC patients, with an OS HR of 0.59 in the 2018 final analysis and a HR of [redacted] in the February 2020 exploratory analysis. Particularly, the longer follow-up of the exploratory analysis compared to the KEYNOTE studies impacts the HR of the ITC due to the effect of subsequent therapies, as shown by the RPSFT analysis (Appendix L). The results of the primary analysis are comparable to the primary analyses of two key pembrolizumab trials in a similar population, KEYNOTE-024 and KEYNOTE-042, which demonstrated OS HRs versus platinum chemotherapy of 0.60 and 0.68, respectively. The comparability of atezolizumab and pembrolizumab in this population is confirmed by the NMA, which, in the 2018 primary analysis, showed a marginal benefit in favour of atezolizumab though with confidence intervals crossing 1, demonstrating an HR [redacted] (see Section B.2.9.7 NMA results – OS and PFS. This latter, unadjusted HR is used as the base of the cost effectiveness model. The available evidence, together with the outcomes of this cost utility analysis validate the clinical opinion about the two products being of comparable efficacy in the patient population evaluated in this appraisal.

In fact, over the lifetime horizon of the model, the QALY difference is mostly <0.1, which can be seen as negligible and too weak to justify NICE resources needed for a full cost utility assessment. Hence, it seems appropriate to base the funding decision on the cost comparison provided. The equivalence in QALY generated by the two products can also be observed in the cost effectiveness planes.

Nonetheless, in light of the trivial QALY difference, both the cost utility and the cost minimisation analyses come to very similar conclusions:

In the cost utility base case, whether we use any meaningful scenario, the presented base case or cap atezolizumab's OS benefit at 60 months, atezolizumab without a stopping rule shows value for money for the NHS up to a discount of pembrolizumab of between approximately [redacted] (WTP £20,000).

In the same ball park are the figures for the cost minimisation analysis, where atezolizumab is worth funding up to a discount of pembrolizumab of [redacted]

The cost utility analysis results support the conclusion that atezolizumab is likely to provide similar or the same benefits at similar or lower cost to the NHS than pembrolizumab in first line patients with metastatic, PD-L1-high NSCLC. In fact, Document C, the budget impact assessment, demonstrates how atezolizumab without a stopping rule in place, is cost saving in the first five years compared to standard of care with a two year stopping rule, [redacted]

These results take into account continued therapy with atezolizumab versus a two-year stopping rule with pembrolizumab. This is a key consideration due to the lack of robust data supporting a two-year stopping rule in the NSCLC setting, and increasing concern from clinicians and patients who are approaching the stopping rule and may consequently wish to continue therapy. The reimbursement of atezolizumab according to its licence and trial treatment duration (i.e. until loss of clinical benefit or unmanageable toxicity with no arbitrary cut-off) will therefore provide an important treatment option to these clinicians and patients and possibly cost savings to the NHS. Of note, several prior NICE appraisals of atezolizumab have resulted in recommendations in the absence of a stopping rule: monotherapy in untreated PD-L1-positive locally advanced or metastatic urothelial cancer when cisplatin is unsuitable (TA492 (243)), in combination with carboplatin and etoposide for untreated extensive-stage small-cell lung cancer (TA638 (244)) and in combination with nab-paclitaxel for treating PD-L1-positive, triple-negative, advanced breast cancer (TA639 (240)).

B.4 References

1. Meng X, Huang Z, Teng F, Xing L, Yu J. Predictive biomarkers in PD-1/PD-L1 checkpoint blockade immunotherapy. Cancer treatment reviews. 2015;41(10):868-76.
2. Chen DS, Mellman I. Oncology meets immunology: the cancer-immunity cycle. Immunity. 2013;39(1):1-10.
3. Herbst RS, Soria JC, Kowanetz M, Fine GD, Hamid O, Gordon MS, et al. Predictive correlates of response to the anti-PD-L1 antibody MPDL3280A in cancer patients. Nature. 2014;515(7528):563-7.
4. Kowanetz M, Zou W, Gettinger SN, Koeppen H, Kockx M, Schmid P, et al. Differential regulation of PD-L1 expression by immune and tumor cells in NSCLC and the response to treatment with atezolizumab (anti-PD-L1). Proceedings of the National Academy of Sciences of the United States of America. 2018;115(43):E10119-e26.
5. Ohaegbulam KC, Assal A, Lazar-Molnar E, Yao Y, Zang X. Human cancer immunotherapy with antibodies to the PD-1 and PD-L1 pathway. Trends in molecular medicine. 2015;21(1):24-33.
6. Santini FC, Rudin CM. Atezolizumab for the treatment of non-small cell lung cancer. Expert Rev Clin Pharmacol. 2017;10(9):935-45.
7. Inman BA, Longo TA, Ramalingam S, Harrison MR. Atezolizumab: A PD-L1-Blocking Antibody for Bladder Cancer. Clinical cancer research : an official journal of the American Association for Cancer Research. 2017;23(8):1886-90.
8. Electronic Medicines Consortium. Tecentriq 1,200 mg concentrate for solution for infusion 2019 [Date Accessed 18th February 2020]. Available from: https://www.medicines.org.uk/emc/product/8442/smpc.
9. Electronic Medicines Consortium. Tecentriq 840 mg concentrate for solution for infusion 2019 [Date Accessed 18th February 2020]. Available from: https://www.medicines.org.uk/emc/product/10697/smpc.
10. Torre LA, Bray F, Siegel RL, Ferlay J, Lortet-Tieulent J, Jemal A. Global cancer statistics, 2012. CA: A Cancer Journal for Clinicians. 2015;65(2):87-108.
11. Cancer Research UK. Lung cancer statistics 2020 [Date Accessed 17th February 2020]. Available from: https://www.cancerresearchuk.org/health-professional/cancer-statistics/statistics-by-cancer-type/lung-cancer#heading-Zero.
12. Molina JR, Yang P, Cassivi SD, Schild SE, Adjei AA. Non-small cell lung cancer: epidemiology, risk factors, treatment, and survivorship. Mayo Clin Proc. 2008;83(5):584-94.
13. National Lung Cancer Audit. NLCA annual report 2018 - information sheet 2018 [Date Accessed 17th January 2020]. Available from: https://www.rcplondon.ac.uk/projects/outputs/nlca-annual-report-2018.
14. Travis WD, Rekhtman N. Pathological diagnosis and classification of lung cancer in small biopsies and cytology: strategic management of tissue for molecular testing. Seminars in respiratory and critical care medicine. 2011;32(1):22-31.
15. Langer CJ, Besse B, Gualberto A, Brambilla E, Soria JC. The evolving role of histology in the management of advanced non-small-cell lung cancer. Journal of clinical oncology : official journal of the American Society of Clinical Oncology. 2010;28(36):5311-20.
16. Zappa C, Mousa SA. Non-small cell lung cancer: current treatment and future advances. Transl Lung Cancer Res. 2016;5(3):288-300.
17. National Institute for Health and Care Excellence. Lung cancer in adults - Quality Standard 17 2012 [Date Accessed 27th March 2020]. Available from: https://www.nice.org.uk/guidance/qs17/resources/lung-cancer-in-adults-pdf-2098490350021.
18. Grigg C, Rizvi NA. PD-L1 biomarker testing for non-small cell lung cancer: truth or fiction? Journal for ImmunoTherapy of Cancer. 2016;4(1):48.
19. National Institute for Health and Care Excellence. Pembrolizumab for untreated PD-L1 positive metastatic non-small-cell lung cancer (CDF Review of TA447) [ID1349] 2018 [Available from: https://www.nice.org.uk/guidance/ta531/documents/committee-papers.

20. Dietel M, Savelov N, Salanova R, Micke P, Bigras G, Hida T, et al. Real-world prevalence of programmed death ligand 1 expression in locally advanced or metastatic non-small-cell lung cancer: The global, multicenter EXPRESS study. Lung Cancer. 2019;134:174-9.
21. Edge SB, Compton CC. The American Joint Committee on Cancer: the 7th edition of the AJCC cancer staging manual and the future of TNM. Annals of surgical oncology. 2010;17(6):1471-4.
22. UyBico SJ, Wu CC, Suh RD, Le NH, Brown K, Krishnam MS. Lung cancer staging essentials: the new TNM staging system and potential imaging pitfalls. Radiographics : a review publication of the Radiological Society of North America, Inc. 2010;30(5):1163-81.
23. National Lung Cancer Audit. National Lung Cancer Audit Annual report 2018 (for the audit period 2017) 2019 [Date Accessed 17th February 2020]. Available from: https://www.rcplondon.ac.uk/projects/outputs/national-lung-cancer-audit-nlca-annual-report-2018.
24. Cancer Research UK. Lung cancer survival statistics 2018 [Available from: https://www.cancerresearchuk.org/health-professional/cancer-statistics/statistics-by-cancer-type/lung-cancer/survival#heading-Three.
25. American Cancer Society. Lung Cancer Survival Rates 2019 [Date Accessed 21st April 2020]. Available from: https://www.cancer.org/cancer/lung-cancer/detection-diagnosis-staging/survival-rates.html.
26. Cancer Network (Oncology Journal). Non-Small-Cell Lung Cancer 2005 [Date Accessed 17th February 2020]. Available from: https://www.cancernetwork.com/view/non-small-cell-lung-cancer.
27. Blandin Knight S, Crosbie PA, Balata H, Chudziak J, Hussell T, Dive C. Progress and prospects of early detection in lung cancer. Open Biol. 2017;7(9):170070.
28. Tishelman C, Degner LF, Rudman A, Bertilsson K, Bond R, Broberger E, et al. Symptoms in patients with lung carcinoma: distinguishing distress from intensity. Cancer. 2005;104(9):2013-21.
29. Cooley ME. Symptoms in adults with lung cancer. A systematic research review. Journal of pain and symptom management. 2000;19(2):137-53.
30. de Marinis F, Pereira JR, Fossella F, Perry MC, Reck M, Salzberg M, et al. Lung Cancer Symptom Scale outcomes in relation to standard efficacy measures: an analysis of the phase III study of pemetrexed versus docetaxel in advanced non-small cell lung cancer. Journal of thoracic oncology : official publication of the International Association for the Study of Lung Cancer. 2008;3(1):30-6.
31. Shi Y, Sun Y, Yu J, Ding C, Wang Z, Wang C, et al. China experts consensus on the diagnosis and treatment of advanced stage primary lung cancer (2016 version). Asia-Pacific journal of clinical oncology. 2017;13(1):87-103.
32. Muers MF, Round CE. Palliation of symptoms in non-small cell lung cancer: a study by the Yorkshire Regional Cancer Organisation Thoracic Group. Thorax. 1993;48(4):339-43.
33. National Institute for Health and Care Excellence. Lung cancer: diagnosis and management (NICE guideline NG122) 2019 [Date Accessed 6th February 2020]. Available from: https://www.nice.org.uk/guidance/ng122.
34. Peters S, Gettinger S, Johnson ML, Janne PA, Garassino MC, Christoph D, et al. Phase II Trial of Atezolizumab As First-Line or Subsequent Therapy for Patients With Programmed Death-Ligand 1-Selected Advanced Non-Small-Cell Lung Cancer (BIRCH). Journal of clinical oncology : official journal of the American Society of Clinical Oncology. 2017;35(24):2781-9.
35. Costa EC, Felip E, Reck M, Patel J, Heist RB, A. , Chow LQ, et al., editors. Updated Efficacy Results From the BIRCH Study: First-Line Atezolizumab Therapy in PD-L1–Selected Patients With Advanced NSCLC. IASLC 18th World Conference on Lung Cancer October 15-18, 2017; 2017; Yokohama, Japan.
36. Spigel DR, Chaft JE, Gettinger S, Chao BH, Dirix L, Schmid P, et al. FIR: Efficacy, Safety, and Biomarker Analysis of a Phase II Open-Label Study of Atezolizumab in PD-L1-

Selected Patients With NSCLC. Journal of thoracic oncology : official publication of the International Association for the Study of Lung Cancer. 2018;13(11):1733-42.
37. Garassino M, Rizvi N, Besse B, Jänne P, Christoph D, Peters S, et al. OA03.02 Atezolizumab as 1L Therapy for Advanced NSCLC in PD-L1 Selected Patients: Updated ORR, PFS and OS Data from the BIRCH Study. Journal of Thoracic Oncology. 2017;12(1):S251-S2.
38. Herbst RS, De Marinis F, Jassem J, Lam S, Mocci S, Sandler A, et al. PS01.56: IMpower110: Phase III Trial Comparing 1L Atezolizumab with Chemotherapy in PD-L1–Selected Chemotherapy-Naive NSCLC Patients: Topic: Medical Oncology. Journal of Thoracic Oncology. 2016;11(11, Supplement):S304-S5.
39. Herbst RS, de Marinis F, Giaccone G, Reinmuth N, Vergnenegre A, Barrios CH, et al. LBA1 Clinical efficacy of atezolizumab (atezo) in biomarker subgroups by SP142, SP263 and 22C3 PD-L1 immunohistochemistry (IHC) assays and by blood tumour mutational burden (bTMB): Results from the IMpower110 study. Annals of Oncology. 2019;30(Supplement_11).
40. Vennapusa B, Baker B, Kowanetz M, Boone J, Menzl I, Bruey J-M, et al. Development of a PD-L1 Complementary Diagnostic Immunohistochemistry Assay (SP142) for Atezolizumab. Appl Immunohistochem Mol Morphol. 2019;27(2):92-100.
41. Fehrenbacher L, Spira A, Ballinger M, Kowanetz M, Vansteenkiste J, Mazieres J, et al. Atezolizumab versus docetaxel for patients with previously treated non-small-cell lung cancer (POPLAR): a multicentre, open-label, phase 2 randomised controlled trial. Lancet (London, England). 2016;387(10030):1837-46.
42. Rittmeyer A, Barlesi F, Waterkamp D, Park K, Ciardiello F, von Pawel J, et al. Atezolizumab versus docetaxel in patients with previously treated non-small-cell lung cancer (OAK): a phase 3, open-label, multicentre randomised controlled trial. Lancet (London, England). 2017;389(10066):255-65.
43. Scagliotti GV, Parikh P, von Pawel J, Biesma B, Vansteenkiste J, Manegold C, et al. Phase III study comparing cisplatin plus gemcitabine with cisplatin plus pemetrexed in chemotherapy-naive patients with advanced-stage non-small-cell lung cancer. Journal of clinical oncology : official journal of the American Society of Clinical Oncology. 2008;26(21):3543-51.
44. Spigel D, De Marinis F, Giaccone G, Reinmuth N, Vergnenegra A, Barrios C, et al. IMpower110: Interim overall survival (OS) analysis of a phase III study of atezolizumab (atezo) vs platinum-based chemotherapy (chemo) as first-line (1L) treatment (tx) in PD-L1–selected NSCLC. Annals of oncology. 2019;30(Suppl 5):v915.
45. Liu YL, Zhou Q, Iasonos A, Emengo VN, Friedman C, Konner JA, et al. Subsequent therapies and survival after immunotherapy in recurrent ovarian cancer. Gynecologic Oncology. 2019;155(1):51-7.
46. F. Hoffman-La Roche Ltd. Primary CSR Study GO29431, (IMpower 110). 2019.
47. Osoba D, Rodrigues G, Myles J, Zee B, Pater J. Interpreting the significance of changes in health-related quality-of-life scores. Journal of clinical oncology : official journal of the American Society of Clinical Oncology. 1998;16(1):139-44.
48. Marinis Fd, Giaccone G, Herbst RS, Oprean C-M, Szczesna A, Boukovinas I, et al. Patient-reported outcomes (PROs) in the randomized, phase III IMpower110 study of atezolizumab (atezo) vs chemotherapy in 1L metastatic NSCLC. Journal of Clinical Oncology. 2020;38(15_suppl):9594-.
49. Fayers P, Aaronson NK, Bjordal K, Groenvold M, Curran D, A. B. EORTC QLQ-C30 Scoring Manual. 3rd ed. Brussels: European Organisation for Research and Treatment of Cancer Brussels: European Organisation for Research and Treatment of Cancer; 2001 [Date Accessed 2nd September 2020]. Available from: https://qol.eortc.org/manuals/.
50. F. Hoffman-La Roche Ltd. IMpower110 Summary of Clinical Efficacy - A phase III, open-label, randomized study of atezolizumab (anti–PD-L1 antibody) compared with a platinum agent (cisplatin or carboplatin) in combination with either pemetrexed or gemcitabine for PD-L1–selected, chemotherapy-naive patients with stage IV non-squamous or squamous non–small cell lung cancer 2019.

51. Data on File (Greco). IMpower110 - Final Analysis. 2020.
52. Guyot P, Ades A, Ouwens MJ, Welton NJ. Enhanced secondary analysis of survival data: reconstructing the data from published Kaplan-Meier survival curves. BMC medical research methodology. 2012;12(1):9.
53. Dias S, Welton NJ, Sutton AJ, Ades A. NICE DSU technical support document 2: a generalised linear modelling framework for pairwise and network meta-analysis of randomised controlled trials. 2011.
54. Jansen JP. Network meta-analysis of survival data with fractional polynomials. BMC medical research methodology. 2011;11(1):61.
55. Turner RM, Jackson D, Wei Y, Thompson SG, Higgins JP. Predictive distributions for between-study heterogeneity and simple methods for their application in Bayesian meta-analysis. Statistics in medicine. 2015;34(6):984-98.
56. Team RC. R: A language and environment for statistical computing 2013 [Date Accessed 2nd September 2020]. Available from: https://www.gbif.org/tool/81287/r-a-language-and-environment-for-statistical-computing.
57. Plummer M. rjags: Bayesian graphical models using MCMC. R package version. 2013;3(10).
58. Plummer M, editor JAGS: A program for analysis of Bayesian graphical models using Gibbs sampling. Proceedings of the 3rd international workshop on distributed statistical computing; 2003: Vienna, Austria.
59. Gelman A, Rubin DB. Inference from Iterative Simulation Using Multiple Sequences. Statist Sci. 1992;7(4):457-72.
60. Data on File (2018 NMA). 2020.
61. Higgins JP, Wells GA. Cochrane handbook for systematic reviews of interventions. 2019. p. i-xxviii.
62. Latimer N. NICE DSU technical support document 14: survival analysis for economic evaluations alongside clinical trials-extrapolation with patient-level data. Sheffield: Report by the Decision Support Unit. 2011.
63. Herbst RS, Giaccone G, de Marinis F, Reinmuth N, Vergnenegre A, Barrios CH, et al. Atezolizumab for First-Line Treatment of PD-L1–Selected Patients with NSCLC. New England Journal of Medicine. 2020;383(14):1328-39.
64. F. Hoffman-La Roche Ltd. Draft Summary of Product Characteristics - Confidential. 2020.
65. S. Gadgeel, M. Kowanetz, W. Zou, F.R. Hirsch, K.M. Kerr, D.R. Gandara, et al. Clinical efficacy of atezolizumab (atezo) in PD-l1 subgroups defined by SP142 and 22C3 ihc assays in 2l+ NSCLC: Results from the randomized OAK study 2017 [Date Accessed 31st March 2020]. Available from: https://oncologypro.esmo.org/meeting-resources/esmo-2017-congress/Clinical-Efficacy-of-Atezolizumab-Atezo-in-PD-L1-Subgroups-Defined-by-SP142-and-22C3-IHC-Assays-in-2L-NSCLC-Results-From-the-Randomized-OAK-Study.
66. Kowanetz M, Socinski MA, Zou W, McCleland M, Yang N, Lopez Chavez A, et al., editors. IMpower150: Efficacy of Atezolizumab Plus Bevacizumab and Chemotherapy in 1L Metastatic Nonsquamous NSCLC Across Key Subgroups. American Association for Cancer Research; 2018.
67. Reck M, Rodríguez-Abreu D, Robinson A, Hui R, Cs?szi T, Fülöp A, et al. Pembrolizumab versus Chemotherapy for PD-L1-Positive Non-Small-Cell Lung Cancer. New England journal of medicine. 2016;375(19):1823-33.
68. 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.
69. Ahn MJ, Tsai CM, Hsia TC, Wright E, Chang JWC, Kim HT, et al. Cost-effectiveness of bevacizumab-based therapy versus cisplatin plus pemetrexed for the first-line treatment of advanced non-squamous NSCLC in Korea and Taiwan. Asia-Pacific journal of clinical oncology. 2011;7:22-33.

70. Annemans L, Giaccone G, Vergnenègre A. The cost-effectiveness of paclitaxel (Taxol®) + cisplatin is similar to that of teniposide + cisplatin in advanced non-small cell lung cancer: A multicountry analysis. Anti-Cancer Drugs. 1999;10(6):605-15.
71. Dooms CA, Lievens YN, Vansteenkiste JF. Cost-utility analysis of chemotherapy symptomatic advanced nonsmall cell cancer. European Respiratory Journal. 2006;27(5):895-901.
72. Earle CC, Evans WK. A comparison of the costs of paclitaxel and best supportive care in stage IV non-small-cell lung cancer. Cancer Prevention and Control. 1997;1(4):282-8.
73. Evans WK, Chevalier T. The cost-effectiveness of navelbine alone or in combination with cisplatin in comparison to other chemotherapy regimens and best supportive care in stage IV non-small cell lung cancer (Structured abstract). European Journal of Cancer [Internet]. 1996b; 32a(13):[2249-55 pp.]. Available from: http://onlinelibrary.wiley.com/o/cochrane/cleed/articles/NHSEED-21997000202/frame.html.
74. Giuliani G, Grossi F, de Marinis F, Walzer S. Cost-effectiveness analysis of bevacizumab versus pemetrexed for advanced non-squamous NSCLC in Italy. Lung Cancer. 2010;69:S11-S7.
75. Goulart B, Ramsey S. A trial-based assessment of the cost-utility of Bevacizumab and chemotherapy versus chemotherapy alone for advanced non-small cell lung cancer. Value in Health. 2011a;14(6):836-45.
76. Hillner BE, Smith TJ. Cost-effectiveness analysis of three regimens using vinorelbine (Navelbine) for non-small cell lung cancer (Structured abstract). Seminars in Oncology [Internet]. 1996; 23(2 Supplement 5):[25-30 pp.]. Available from: http://onlinelibrary.wiley.com/o/cochrane/cleed/articles/NHSEED-21996000539/frame.html.
77. Kennedy W, Reinharz D, Tessier G, Contandriopoulos AP, Trabut I, Champagne F, et al. Cost utility of chemotherapy and best supportive care in non-small cell lung cancer. Pharmacoeconomics. 1995;8(4):316-23.
78. Klein R, Muehlenbein C, Liepa AM, Babineaux S, Wielage R, Schwartzberg L. Cost-effectiveness of pemetrexed plus cisplatin as first-line therapy for advanced nonsquamous non-small cell lung cancer. Journal of Thoracic Oncology. 2009;4(11):1404-14.
79. Le Lay K, Myon E, Hill S, Riou-Franca L, Scott D, Sidhu M, et al. Comparative cost-minimisation of oral and intravenous chemotherapy for first-line treatment of non-small cell lung cancer in the UK NHS system. Eur J Health Econ. 2007;8(2):145-51.
80. Lees M, Aristides M, Maniadakis N, McKendrick J, Botwood N, Stephenson D. Economic evaluation of gemcitabine alone and in combination with cisplatin in the treatment of nonsmall cell lung cancer. PharmacoEconomics. 2002a;20(5):325-37.
81. Maniadakis N, Fragoulakis V, Pallis A, Prezerakos P, Georgoulias V. Economic evaluation of docetaxel/gemcitabine versus docetaxel as frontline treatment of patients with advanced/metastatic non-small cell lung cancer in Greece. Lung Cancer. 2007;58(2):275-81.
82. Maniadakis N, Fragoulakis V, Pallis AG, Simou E, Georgoulias V. Economic evaluation of docetaxel-gemcitabine versus vinorelbine-cisplatin combination as front-line treatment of patients with advanced/metastatic nonsmall-cell lung cancer in Greece: A cost-minimization analysis. Annals of Oncology. 2010;21(7):1462-7.
83. Matter-Walstra K, Joerger M, Khnel U, Szucs T, Pestalozzi B, Schwenkglenks M. Cost-effectiveness of maintenance pemetrexed in patients with advanced nonsquamous-cell lung cancer from the perspective of the swiss health care system. Value in Health. 2012;15(1):65-71.
84. Ramsey SD, Moinpour CM, Lovato LC, Crowley JJ, Grevstad P, Presant CA, et al. Economic analysis of vinorelbine plus cisplatin versus paclitaxel plus carboplatin for advanced non-small-cell lung cancer. Journal of the National Cancer Institute. 2002a;94(4):291-7.
85. Rubio-Terrés C, Luis Tisaire J, Kobina S, Moyano A. Cost-minimisation analysis of three regimens of chemotherapy (docetaxel-cisplatin, paclitaxel-cisplatin, paclitaxel-carboplatin) for advanced non-small-cell lung cancer. Lung Cancer. 2002;35(1):81-9.

86. Schiller J, Tilden D, Aristides M, Lees M, Kielhorn A, Maniadakis N, et al. Retrospective cost analysis of gemcitabine in combination with cisplatin in non-small cell lung cancer compared to other combination therapies in Europe. Lung Cancer. 2004;43(1):101-12.
87. Smith TJ, Hillner BE, Neighbors DM, McSorley PA, Chevalier T. Economic evaluation of a randomized clinical trial comparing vinorelbine, vinorelbine plus cisplatin, and vindesine plus cisplatin for non-small-cell lung cancer (Structured abstract). Journal of Clinical Oncology [Internet]. 1995a; 13(9):[2166-73 pp.]. Available from: http://onlinelibrary.wiley.com/o/cochrane/cleed/articles/NHSEED-21995001054/frame.html.
88. Touchette DR, Stevenson JG, Jensen G. Cost-effectiveness analysis of amifostine (Ethyol®) in patients with non-small cell lung cancer. Journal of Aging and Pharmacotherapy. 2007a;13(2):109-26.
89. Walleser S, Ray J, Bischoff H, Vergnenègre A, Rosery H, Chouaid C, et al. Maintenance erlotinib in advanced nonsmall cell lung cancer: Cost-effectiveness in EGFR wild-type across Europe. ClinicoEconomics and Outcomes Research. 2012;4(1):269-75.
90. Wu B, Chen H, Shen J, Ye M. Cost-Effectiveness of Adding Rh-Endostatin to First-Line Chemotherapy in Patients With Advanced Non-Small-Cell Lung Cancer in China. Clinical Therapeutics. 2011;33(10):1446-55.
91. Yalcin Balcik P, Sahin B. Cost-effectiveness analysis of pemetrexed and gemcitabine treatment for advanced nonsmall cell lung cancer in Turkey. Turk J Med Sci. 2016;46(1):152-8.
92. Inage S, Ise Y, Obayashi M, Katayama S, Gemma A. Cost-effectiveness analysis comparing carboplatin and weekly paclitaxel with cisplatin and docetaxel in the treatment of advanced non-small cell lung carcinoma. Japanese Journal of Cancer and Chemotherapy. 2010;37(11):2093-100.
93. Le Lay K, Riou-França L, Launois R. Cost-effectiveness analysis of oral chemotherapy in ambulatory care: The example of vinorelbine. Journal d'Economie Medicale. 2002;20(7):379-400.
94. Gilden DM, Kubisiak JM, Pohl GM, Ball DE, Gilden DE, John WJ, et al. Treatment patterns and cost-effectiveness of first line treatment of advanced non-squamous non-small cell lung cancer in Medicare patients. J Med Econ. 2017;20(2):151-61.
95. Gonzalez Garcia J, Gutierrez Nicolas F, Nazco Casariego GJ, Valcarcel Nazco C, Batista Lopez JN, Oramas Rodriguez J. Cost-effectiveness of pemetrexed in combination with cisplatin as first line treatment for patients with advanced non-squamous non-small-cell lung cancer in Spain. Farm. 2017;41(n01):3-13.
96. Huang M, Lou Y, Pellissier J, Burke T, Liu FX, Xu R, et al. Cost Effectiveness of Pembrolizumab vs. Standard-of-Care Chemotherapy as First-Line Treatment for Metastatic NSCLC that Expresses High Levels of PD-L1 in the United States. Pharmacoeconomics. 2017;35(8):831-44.
97. Lu Y, Cheng J, Lin Z, Chen Y, Xuan J. Pharmacoeconomic analysis for pemetrexed as a maintenance therapy for NSCLC patients with patient assistance program in China. J Med Econ. 2018;21(1):60-5.
98. Shi Q, Hu S, Furnback WE, Guzauskas GF, Shen J, Wang BC. The cost-effectiveness of a NSCLC patient assistance program for pemetrexed maintenance therapy in people's republic of China. ClinicoEconomics and Outcomes Research. 2017;9:99-106.
99. Taipale K, Winfree KB, Boye M, Basson M, Sleilaty G, Eaton J, et al. A cost-effectiveness analysis of first-line induction and maintenance treatment sequences in patients with advanced nonsquamous non-small-cell lung cancer in France. ClinicoEconomics and Outcomes Research. 2017;9:505-18.
100. Zheng H, Xie L, Zhan M, Wen F, Xu T, Li Q. Cost-effectiveness analysis of the addition of bevacizumab to chemotherapy as induction and maintenance therapy for metastatic non-squamous non-small-cell lung cancer. Clinical and Translational Oncology. 2017:1-8.
101. Chouaid C, Bensimon L, Clay E, Millier A, Levy-Bachelot L, Huang M, et al. Cost-effectiveness analysis of pembrolizumab versus standard-of-care chemotherapy for first-line

treatment of PD-L1 positive (>50%) metastatic squamous and non-squamous non-small cell lung cancer in France. Lung Cancer. 2019;127:44-52.
102. Criss SD, Mooradian MJ, Watson TR, Gainor JF, Reynolds KL, Kong CY. Cost-effectiveness of Atezolizumab Combination Therapy for First-Line Treatment of Metastatic Nonsquamous Non-Small Cell Lung Cancer in the United States. JAMA Netw Open. 2019;2(9):e1911952.
103. Criss SD, Mooradian MJ, Sheehan DF, Zubiri L, Lumish MA, Gainor JF, et al. Cost-effectiveness and Budgetary Consequence Analysis of Durvalumab Consolidation Therapy vs No Consolidation Therapy After Chemoradiotherapy in Stage III Non-Small Cell Lung Cancer in the Context of the US Health Care System. JAMA Oncol. 2019;5(3):358-65.
104. Georgieva M, da Silveira Nogueira Lima JP, Aguiar P, Jr., de Lima Lopes G, Jr., Haaland B. Cost-effectiveness of pembrolizumab as first-line therapy for advanced non-small cell lung cancer. Lung Cancer. 2018;124:248-54.
105. Giuliani J, Bonetti A. Financial Toxicity and Non-small Cell Lung Cancer Treatment: The Optimization in the Choice of Immune Check Point Inhibitors. Anticancer Res. 2019;39(7):3961-5.
106. Hu X, Hay JW. First-line pembrolizumab in PD-L1 positive non-small-cell lung cancer: A cost-effectiveness analysis from the UK health care perspective. Lung Cancer. 2018;123:166-71.
107. Insinga RP, Vanness DJ, Feliciano JL, Vandormael K, Traore S, Ejzykowicz F, et al. Cost-effectiveness of pembrolizumab in combination with chemotherapy versus chemotherapy and pembrolizumab monotherapy in the first-line treatment of squamous non-small-cell lung cancer in the US. Curr Med Res Opin. 2019;35(7):1241-56.
108. Insinga RP, Vanness DJ, Feliciano JL, Vandormael K, Traore S, Burke T. Cost-effectiveness of pembrolizumab in combination with chemotherapy in the 1st line treatment of non-squamous NSCLC in the US. J Med Econ. 2018;21(12):1191-205.
109. Li X, Li W, Hou L. A Trial-Based Cost-Effectiveness Analysis of Bevacizumab and Chemotherapy Versus Chemotherapy Alone for Advanced Nonsquamous Non-Small-Cell Lung Cancer in China. Value Health Reg Issues. 2019;18:1-7.
110. Liao W, Huang J, Hutton D, Li Q. Cost-effectiveness analysis of first-line pembrolizumab treatment for PD-L1 positive, non-small cell lung cancer in China. J Med Econ. 2019;22(4):344-9.
111. Loong HH, Wong CKH, Leung LKS, Dhankhar P, Insinga RP, Chandwani S, et al. Cost Effectiveness of PD-L1-Based Test-and-Treat Strategy with Pembrolizumab as the First-Line Treatment for Metastatic NSCLC in Hong Kong. Pharmacoecon Open. 2019.
112. Panje CM, Dedes KJ, Matter-Walstra K, Schwenkglenks M, Gautschi O, Siano M, et al. A cost-effectiveness analysis of consolidative local therapy in oligometastatic non-squamous non-small cell lung cancer (NSCLC). Radiother Oncol. 2018;129(2):257-63.
113. Permsuwan U, Thongprasert S, Sirichanchuen B. Cost-Utility Analysis of First-Line Pemetrexed Plus Cisplatin in Non-Small Cell Lung Cancer in Thailand. Value Health Reg Issues. 2019;21:9-16.
114. She L, Hu H, Liao M, Xia X, Shi Y, Yao L, et al. Cost-effectiveness analysis of pembrolizumab versus chemotherapy as first-line treatment in locally advanced or metastatic non-small cell lung cancer with PD-L1 tumor proportion score 1% or greater. Lung Cancer. 2019;138:88-94.
115. Wan X, Luo X, Tan C, Zeng X, Zhang Y, Peng L. First-line atezolizumab in addition to bevacizumab plus chemotherapy for metastatic, nonsquamous non-small cell lung cancer: A United States-based cost-effectiveness analysis. Cancer. 2019;125(20):3526-34.
116. Weng X, Luo S, Lin S, Zhong L, Li M, Xin R, et al. Cost-utility analysis of pembrolizumab versus chemotherapy as first-line treatment for metastatic non-small cell lung cancer with different PD-L1 expression levels. Oncol Res. 2019.
117. Zheng H, Xie L, Zhan M, Wen F, Xu T, Li Q. Cost-effectiveness analysis of the addition of bevacizumab to chemotherapy as induction and maintenance therapy for metastatic non-squamous non-small-cell lung cancer. Clin Transl Oncol. 2018;20(3):286-93.

118. Zhou K, Jiang C, Li Q. Cost-effectiveness analysis of pembrolizumab monotherapy and chemotherapy in the non-small-cell lung cancer with different PD-L1 tumor proportion scores. Lung Cancer. 2019;136:98-101.
119. Goldstein DA, Chen Q, Ayer T, Howard DH, Lipscomb J, Ramalingam SS, et al. Necitumumab in Metastatic Squamous Cell Lung Cancer: Establishing a Value-Based Cost. JAMA oncology. 2015;1(9):1293-300.
120. Grossi F, Bennouna J, Havel L, Hochmair M, Almodovar T. Oral vinorelbine plus cisplatin versus pemetrexed plus cisplatin as first-line treatment of advanced non-squamous non-small-cell lung cancer: cost minimization analysis in 12 European countries. Current Medical Research and Opinion. 2016:1-8.
121. Kanarkiewicz M, Zagańczyk M, Zurawski B, Tujakowski J, Windorbska W, Krysiński J. Cost-effectiveness analysis of advanced stage non-small cell lung cancer treatment with cisplatin-vinorelbine and carboplatin-gemcytabine combination regimens. Nowotwory. 2014b;64(3):217-23.
122. Lairson DR, Parikh RC, Cormier JN, Chan W, Du XL. Cost-utility analysis of treatments for advanced non-small cell lung cancer. American Journal of Pharmacy Benefits. 2015;7(6):271-9.
123. Schluckebier L, Garay OU, Zukin M, Ferreira CG. Carboplatin plus pemetrexed offers superior cost-effectiveness compared to pemetrexed in patients with advanced non-small cell lung cancer and performance status 2. Lung Cancer. 2015;89(3):274-9.
124. Shah M, Winfree KB, Peterson P, Gruschkus SK, Eaddy M, Green MR. Cost effectiveness of first-line pemetrexed plus platinum compared with other regimens in the treatment of patients with nonsquamous non-small cell lung cancer in the US outpatient setting. Lung Cancer. 2013;82(1):121-7.
125. Aguiar P, Jr., Giglio AD, Perry LA, Penny-Dimri J, Babiker H, Tadokoro H, et al. Cost-effectiveness and budget impact of lung cancer immunotherapy in South America: strategies to improve access. Immunotherapy. 2018;10(10):887-97.
126. Baillt S, De Pouvourville G, Morais E, Scharzinger M, Fossella F. Docetaxel in the first-line treatment of non-small-cell lung cancer: A cost-effectiveness analysis versus vinorelbine from the tax 326 trial. Annals of Oncology. 2008;19:viii227.
127. Bucher D, Grossi F. Oral vinorelbine plus cisplatin versus pemetrexed plus cisplatin as first-line treatment for patients with advanced non-squamous non-small cell lung cancer: a cost minimization analysis in twelve European countries. ISPOR 18th Annual European Congress; November 2015; Milan, Italy2015.
128. Capano F, Vavala T, Monica V, Mele T, Filieri A, Lerda C, et al. Cost-effectiveness of chemotherapy based on the tumor genetic profile in elderly patients with advanced non-small-cell lung cancer. Journal of Thoracic Oncology. 2015;10(9):S418.
129. Chouaid C, Le Caer H, Crequit J, Monnet I, Chouabe S, Locher C, et al. Cost-effectiveness of erlotinib in first-line treatment of advanced non-small cell lung cancer (NSCLC) in fit elderly patients: An economical analysis of a prospective phase 2 study (GFPC 0504). Value in Health. 2010;13(7):A267.
130. Cobo M, De Castro J, Isla D, Oyagüez I, Lozano V, Castro-Gomez A. Cost-effectiveness of erlotinib as first-line maintenance therapy for advanced non-small-cell lung carcinoma in patients egfr wt and stable disease after four cycles of chemotherapy. Value in Health. 2012;15(7):A422-A3.
131. Favaretto A, Ciuffreda L, Nicolini M, Camerini A, Melotti B, Berardi R, et al. Oral vinorelbine (NVBo) plus cisplatin (CDDP) versus pemetrexed (PEM) plus CDDP followed by maintenance with single agent NVBo or PEM as first-line treatment of patients (pts) with advanced non-squamous non small cell lung cancer (NS-NSCLC): A cost minimization analysis from the Italian National Health System (NHS) perspective. European Journal of Cancer. 2013;49:S329.
132. Guidi L, Malik S, Valle D, Asukai Y, Taipale K. Cost-effectiveness analysis of pemetrexed/cisplatin in the first-line treatment of non-small cell lung cancer in Italy: Results for the adenocarcinoma histology sub-population. Value in Health. 2009;12(7):A278-A9.

133. Hoverman JR, Pohl G, Gruschkus SK, Marciniak M, Forsyth M, Peltz G. Cost-effectiveness of 1st line chemotherapy regimens in the treatment of non-small cell lung cancer among patients receiving care in the outpatient community setting. Value in Health. 2010;13(3):A1-A2.
134. Kawalec P, Badurak P, Denisso T, Jastrzebski D, Marek M, Pluzanski A, et al. Bevacizumab + paclitaxel + carboplatin (Bev + Pac + Car) vs. pemetrexed + cisplatin (Pem + Cis) in adenocarcinoma non-squamous non-small cell lung cancer (NSCLC): A cost-effectiveness analysis from a Polish public payer's perspective. Value in Health. 2010;13(7):A268.
135. Lim PS, Chan YH, Chew L. Measuring the trend of use of targeted therapy and economic evaluation of gefitinib for advanced non-small cell lung cancer (NSCLC) in Singapore. Value in Health. 2014;17(7):A737.
136. Muehlenbein CE, Klein RW, Liepa AM, Babineaux SM, Wielage RC, Schwartzberg LS. The importance of histology when evaluating the cost-effectiveness of pemetrexed plus cisplatin as first-line therapy for advanced non-small cell lung cancer. Journal of Clinical Oncology. 2009;27(15):e17533.
137. Nguyen TTT, Tran TTH. Cost-utility of bevacizumab with PC regimen in non-small cell lung cancer treatment. Value in Health. 2014;17(7):A725.
138. Pinto CG, Manac¸as M, Miguel LS. Cost-effectiveness of pemetrexed in first line treatment of non-small cell lung cancer in Portugal. Value in Health. 2009;12(7):A222.
139. Roth J, Carlson J. Advanced non-small cell lung cancer (nsclc) cetuximab treatment decision model: Chemotherapy+cetuximab vs. cetuximab treat-to-rash strategy vs. chemotherapy only in first-line treatment of stage IIIB/IV NSCLC. Value in Health. 2010;13(3):A42.
140. Spigel D, Harwin W, Dranitsaris G, Binder G, Weber P, Renschler MF, et al. Nab-paclitaxel in combination with carboplatin as first-line therapy in patients (PTS) with advanced non-small cell lung cancer (NSCLC): An economic analysis. Journal of Thoracic Oncology. 2013;8:S1176-S7.
141. Takahashi TK, Souza FH, Rosa TBC, Castro G, Hoff PM. Maintenance chemotherapy in advanced nonsmall cell lung cancer: Cost utility of pemetrexed and gemcitabine. Annals of Oncology. 2010;21:viii337.
142. Tongpak P. Cost-utility analysis of first-line regimen between cisplatin plus pemetrexed and carboplatin plus paclitaxel in advanced non-squamous non-small-cell lung cancer in Thailand. Value in Health. 2014;17(7):A737.
143. Tran TTH, Nguyen TTT. Cost-effectiveness analysis of bevacizumab-paclitaxel-carboplatin (PC) versus PC in first-line therapy of advanced non-small cell lung cancer from patients' perspective in Vietnam. Value in Health. 2014;17(7):A634-A5.
144. Winfree KB, Shah M, Peterson P, Gruschkus S, Eaddy M, Green M. Cost effectiveness of pemetrexed/cisplatin (PEM/ CIS) in the treatment of advanced, non-squamous, non-small cell lung cancer (NSQNSCLC) patients. Annals of Oncology. 2012;23:ix428.
145. Basson M, Sleilaty G, Taipale KL, Boye M, Winfree KB, Eaton J, et al. Effectiveness of pemetrexed in advanced non-squamous NSCLC and estimation of its impact on public health in France. Journal of Thoracic Oncology. 2017;12 (1 Supplement 1):S1431-S2.
146. Georgieva M, Aguiar P, Lima JP, Haaland B, Lopes G. Cost-effectiveness of pembrolizumab as first-line therapy for advanced non-small cell lung cancer. Journal of Thoracic Oncology. 2017;12 (11 Supplement 2):S2149-S50.
147. Hu X, Goldman DP. First-line pembrolizumab in PD-l1 positive non-small cell lung cancer: A cost-effectiveness analysis from a UK healthcare perspective. Value in Health. 2017;20 (9):A399.
148. Loong H, Huang M, Wong C, Leung L, Burke T, Chandwani S, et al. Cost-effectiveness of PDL1 based test-and-treat strategy with pembrolizumab as the 1st line treatment for NSCLC in Hong Kong. Journal of Thoracic Oncology. 2017;12 (11 Supplement 2):S1913.

149. Pinheiro BA, Alarcao J, Silva Miguel L, Huang M, Chandwani S, Vargas Lopes F, et al. Cost-effectiveness of pembrolizumab for the first-line treatment of metastatic non-small cell lung carcinoma in Portugal. Value in Health. 2017;20 (9):A432.
150. Leandro A, Alcobia A. Cost-efficacy analysis of pemetrexed in first-line treatment of non-small cell lung cancer. Pharmacotherapy. 2011;31(10):407e.
151. Walleser S, Ray JA, Bischoff H, Vergnenegre A, Rosery H, Walzer S. Maintenance erlotinib in stable disease EGFR wildtype advanced non-small-cell lung cancer: A cost-effectiveness analysis for 5 european countries. Journal of Thoracic Oncology. 2011;6(6):S559-S60.
152. Aggarwal H, Muehlenbein CE, Klein T, Winfree KB, Bly CA, Zhu Y, et al. Pcn131 Cost Effectiveness of Pemetrexed in Combination with Pembrolizumab and Platinum Chemotherapy (Pem+Pembro+Plat), for Initial Treatment of Patients with Metastatic Non-Squamous (Nsq) Non-Small Cell Lung Cancer (Nsclc) in the U.S. Value in Health. 2019;22 (Supplement 2):S81.
153. Alkhatib NS, Choi B, Pae E, Babiker HM, Garland LL, Henglefelt A, et al. Economic evaluation of anaplastic lymphoma kinase (ALK) inhibitors brigatinib, alectinib and crizotinib in non-small cell lung cancer (NSCLC): Analysis for intracranial metastasis-related progression free survival (CNSPFS). Journal of Clinical Oncology Conference. 2019;37(Supplement 15).
154. Kim A, Devine B, Roth JA. Cost-effectiveness of first-line pembrolizumab plus chemotherapy for metastatic squamous non-small cell lung cancer (NSCLC). Journal of Clinical Oncology Conference. 2019;37(Supplement 15).
155. Nishiuchi Y, Ueda M, Hirota Y, Moriwaki K. Pcn110 Preliminary Analysis of the Cost-Effectiveness of Necitumumab as First Line Therapy in Patients with Stage Iv Squamous Non Small Cell Lung Cancer in Japan. Value in Health. 2019;22 (Supplement 2):S76.
156. Reyes-Santias F, Cordova-Arevalo O. Analysis Cost / Utility of the Therapeutic Therapy Treatment of Lung Cancer in a University Hospital of Spain. Value in Health. 2018;21 (Supplement 3):S46.
157. Roth JA, Nguyen T, Goulart BHL. The potential cost-effectiveness of first-line immunotherapy + chemotherapy for advanced non-squamous non-small cell lung cancer (NSCLC). Journal of Clinical Oncology Conference. 2018;36(15 Supplement 1).
158. Tan WL, Huang M, Chandwani S, Hsu T, Tan SC, Tan D. Cost-Effectiveness of Pembrolizumab as 1st Line Treatment for Metastatic NSCLC Patients with High PD-L1 Expression in Singapore. Journal of Thoracic Oncology. 2018;13 (10 Supplement):S630.
159. Tfayli A, Elias F, Farhat F, Slim R, Hallal Z, Maatouk L, et al. Cost Utility Analysis of First-Line Paclitaxel with Carboplatin and Bevacizumab Followed by Maintenance Bevacizumab Versus Pemetrexed with Carboplatin Followed by Maintenance Pemetrexed in Patients with Advanced Non-Squamous Non-Small-Cell Lung Cancer in Lebanon. Value in Health. 2018;21 (Supplement 3):S47.
160. Chouaid C, editor Cost-effectiveness of pembrolizumab (Keytruda) plus platinum-pemetrexed for first-line treatment of metastatic non-squamous non-small cell lung cancer in France ISPOR; 2019; Copenhagen, Denmark.
161. Harding T, editor Cost-effectiveness analysis of pembrolizumab in combination with carboplatin and paclitaxel for previously untreated patients with metastatic squamous non-small cell lung cancer in England. ISPOR; 2019; Europe.
162. Harding T, editor Cost-effectiveness analysis of pembrolizumab in combination with platinum chemotherapy and pemetrexed for previously untreated patients with metastatic non-squamous non-small cell lung cancer in England. ISPOR; 2019; Europe.
163. Hu X, editor A cost-effectiveness analysis of pembrolizumab in chemotherapy-naive patients with non-small-cell lung cancer regardless of PD-L1 level. ISPOR Europe; 2018; Barcelona, Spain.
164. Chouaid C, Le Caer H, Corre R, Crequit J, Jullian H, Falchero L, et al. Cost effectiveness of erlotinib in first line treatment of advanced non small cell lung cancer (NSCLC) in vulnerable elderly patients: An economical analysis of a prospective phase 2 study (GFPC 0505). Value in Health. 2011;14(7):A448.

165. The National Institute for Health and Care Excellence (NICE). TA600. Pembrolizumab with carboplatin and paclitaxel or nab-paclitaxel for untreated squamous non-small-cell lung cancer [online] Available at: https://www.nice.org.uk/guidance/ta600/documents/committee-papers [Last accessed: 23/12/2019]. NICE; 2018 October 2018.
166. The National Institute for Health and Care Excellence (NICE). TA584. Atezolizumab in combination with bevacizumab, paclitaxel and carboplatin for the first-line treatment of adult patients with metastatic non-squamous NSCLC [online] Available at: https://www.nice.org.uk/guidance/ta584/documents/committee-papers [Last accessed: 23/12/2019].
167. The National Institute for Health and Care Excellence (NICE). TA557. Pembrolizumab with pemetrexed and platinum chemotherapy for untreated metastatic non-squamous non-small-cell lung cancer [online] Available at: https://www.nice.org.uk/guidance/ta557/documents/committee-papers [Last accessed: 23/12/2019].
168. National Institute for Health and Care Excellence. Pembrolizumab for untreated PD-L1-positive metastatic non-small-cell lung cancer [TA531] 2018 [Date Accessed 18th February 2020]. Available from: https://www.nice.org.uk/guidance/ta531.
169. The National Institute for Health and Care Excellence (NICE). TA411 Necitumumab for untreated advanced or metastatic squamous non-small-cell lung cancer, Spetember 2016 [online]. Available at: https://www.nice.org.uk/guidance/ta411 [Last accessed 14/05/2018].
170. The National Institute for Health and Care Excellence (NICE). TA190 Pemetrexed for the maintenance treatment of non-small-cell lung cancer [online]. Available at: https://www.nice.org.uk/guidance/ta190 [Last accessed 04/04/2018].
171. The National Institute for Health and Care Excellence (NICE). TA181 Pemetrexed for the first-line treatment of non-small-cell lung cancer [online]. Available at: https://www.nice.org.uk/guidance/ta181 [Last accessed 04/04/2018].
172. Woods B SE, Palmer S, Latimer N, Soares M. . NICE DSU Technical Support Document 19: TSD 19: Partitioned Survival Analysis as a decision modelling tool. . 2017.
173. National Institute for health and Care Excellence. Technology appraisal guidance [TA531] Pembrolizumab for untreated PD-L1-positive metastatic non-small-cell lung cancer 2018 [Date Accessed 2019 29th January]. Available from: https://www.nice.org.uk/guidance/ta531.
174. National institute for health and Care Excellence. Pembrolizumab for treating PD-L1-positive non-small-cell lung cancer after chemotherapy [TA428] 2017 [Date Accessed 30th January 2019]. Available from: https://www.nice.org.uk/guidance/ta428.
175. National Institute for health and Care Excellence. Nivolumab for previously treated non-squamous non-small-cell lung cancer [TA484] 2017 [Date Accessed 30th January 2019]. Available from: https://www.nice.org.uk/guidance/ta484.
176. National Institute for Health and Care Excellence. Atezolizumab for treating locally advanced or metastatic non-small-cell lung cancer after chemotherapy [TA520] 2018 [Date Accessed 3rd September 2020]. Available from: https://www.nice.org.uk/guidance/ta520.
177. National Institute for Health and Care Excellence. Atezolizumab for treating locally advanced or metastatic urothelial carcinoma after platinum-containing chemotherapy [TA525] 2018 [Date Accessed 30th January 2019]. Available from: https://www.nice.org.uk/guidance/ta525.
178. National institute for health and Care Excellence. Guide to the processes of technology appraisal 2018 [Date Accessed 30th January 2019]. Available from: https://www.nice.org.uk/process/pmg19/chapter/acknowledgements.
179. National Institute for Health and Care Excellence. Atezolizumab in combination for treating metastatic non-squamous non-small-cell lung cancer [TA584] 2019 [Date Accessed 25th June 2020]. Available from: https://www.nice.org.uk/guidance/ta584.
180. National Institute for Health and Care Excellence. Pembrolizumab with pemetrexed and platinum chemotherapy for untreated, metastatic, non-squamous non-small-cell lung

cancer [TA557] 2019 [Date Accessed 1st September 2020]. Available from: https://www.nice.org.uk/guidance/ta557.
181. National Institute for Health and Care Excellence. Pembrolizumab with carboplatin and paclitaxel for untreated metastatic squamous non-small-cell lung cancer [TA600] 2019 [Date Accessed 1st September 2020]. Available from: https://www.nice.org.uk/guidance/ta600.
182. Electronic Medicines Consortium. KEYTRUDA 25 mg/mL concentrate for solution for infusion 2020 [Date Accessed 1st September 2020]. Available from: https://www.medicines.org.uk/emc/product/2498/smpc#gref.
183. Spigel DR, McLeod M, Hussein MA, Waterhouse DM, Einhorn L, Horn L, et al. Randomized results of fixed-duration (1-yr) vs continuous nivolumab in patients (pts) with advanced non-small cell lung cancer (NSCLC). Annals of Oncology. 2017;28:v461.
184. Herbst RS, Garon EB, Kim DW, Cho BC, Perez-Gracia JL, Han JY, et al. Long-Term Outcomes and Retreatment Among Patients With Previously Treated, Programmed Death-Ligand 1–Positive, Advanced Non–Small-Cell Lung Cancer in the KEYNOTE-010 Study. Journal of clinical oncology : official journal of the American Society of Clinical Oncology. 2020;38(14):1580-90.
185. Remon J, Menis J, Aspeslagh S, Besse B. Treatment duration of checkpoint inhibitors for NSCLC. The Lancet Respiratory Medicine. 2019;7(10):835-7.
186. Latimer NR. Survival Analysis For Economic Evaluations Alongside Clinical Trials - Extrapolation with Patient-Level Data. London: unless otherwise stated; 2013 Mar.
187. Pocock SJ, Clayton TC, Altman DG. Survival plots of time-to-event outcomes in clinical trials: good practice and pitfalls. Lancet (London, England). 2002;359(9318):1686-9.
188. Data on file (Polito). 1st Line Treatment Patterns and Outcomes in aNSCLC Patients with PD-L1 Expression of ≥50% - outcomes of pembrolizumab monotherapy 2020.
189. Garon EB, Hellmann MD, Rizvi NA, Carcereny E, Leighl NB, Ahn M-J, et al. Five-Year Overall Survival for Patients With Advanced Non–Small-Cell Lung Cancer Treated With Pembrolizumab: Results From the Phase I KEYNOTE-001 Study. Journal of Clinical Oncology. 2019;37(28):2518-27.
190. Nafees B, Stafford M, Gavriel S, Bhalla S, Watkins J. Health state utilities for non small cell lung cancer. Health Qual Life Outcomes. 2008;6:84.
191. Chouaid C, Agulnik J, Goker E, Herder GJM, Lester JF, Vansteenkiste J, et al. Health-related quality of life and utility in patients with advanced non-small-cell lung cancer: A prospective cross-sectional patient survey in a real-world setting. Journal of Thoracic Oncology. 2013;8(8):997-1003.
192. National institute for Health and Care Excellence. Atezolizumab in combination for treating advanced non-squamous non-small-cell lung cancer [ID1210] - in development 2019 [Date Accessed 26th March 2019]. Available from: https://www.nice.org.uk/guidance/indevelopment/gid-ta10340.
193. National Institute for Health and Care Excellence. Atezolizumab for treating locally advanced or metastatic non-small-cell lung cancer after chemotherapy [TA520] 2018 [Date Accessed 30th January 2019]. Available from: https://www.nice.org.uk/guidance/ta520.
194. National Institute for Health and Care Excellence. Pembrolizumab with pemetrexed and platinum chemotherapy for untreated, metastatic, non-squamous non-small-cell lung cancer (TA557) 2019 [Date Accessed 29th March 2019]. Available from: https://www.nice.org.uk/guidance/ta557.
195. Chang C, Park S, Choi YR, Tan SC, Kang SH, Back HJ, et al. Measurement of utilities by time to death related to advanced non-small cell lung cancer in South Korea. Value in Health. 2016;19 (7):A744.
196. Huang M, Pellissier J, Kong F. A trial-based euroqol EQ-5D health utility analysis in patients with previously untreated metastatic NSCLC. Value in Health. 2017;20 (5):A115.
197. Khan I, Morris S, Pashayan N, Matata B, Bashir Z, Maguirre J. Comparing the mapping between EQ-5D-5L, EQ-5D-3L and the EORTC-QLQ-C30 in non-small cell lung cancer patients. Health Qual Life Outcomes. 2016;14:60.

198. Langer CJ, Anderson E, Jotte R, Goldman J, Haggstrom D, Modiano M, et al. Quality of life (QoL) in elderly NSCLC patients (pts) treated with nabpaclitaxel/ carboplatin (nab-P/C) in the ABOUND.701 trial. Annals of Oncology. 2017;28 (Supplement 5):v488-v9.
199. McTaggart-Cowan H, King MT, Chan K, Costa D, Hoch J, Norman R, et al. Estimating the Canadian utility weights for the cancer specific preference-based instrument, QLU-C10D. Quality of Life Research. 2017;26 (1 Supplement 1):49.
200. Meregaglia M, Borsoi L, Cairns J, Tarricone R. Mapping health-related quality of life scores from FACT-G, FAACT, and FACIT-F onto preference-based EQ-5D-5L utilities in non-small cell lung cancer cachexia. Eur J Health Econ. 2017:1-13.
201. Nafees B, Lloyd AJ, Dewilde S, Rajan N, Lorenzo M. Health state utilities in non-small cell lung cancer: An international study. Asia-Pacific journal of clinical oncology. 2017;13(5):e195-e203.
202. Rauma V, Andersson S, Rasanen J, Sintonen H, Salo J, Ilonen I. Thoracotomy and VATS-surgery in local non-small cell lung cancer: Differences in long-term health related quality of life. Journal of Thoracic Oncology. 2017;12 (1 Supplement 1):S752-S3.
203. Smith AB, Cocks K, Parry D, Taylor M. A Differential Item Functioning Analysis of the EQ-5D in Cancer. Value in Health. 2016;19(8):1063-7.
204. Taylor-Stokes G, Wood R, Lees M, Chirita O. Impact of brain metastases on the humanistic burden incurred by patients with advanced non-small cell lung cancer (A-nsclc). Journal of Thoracic Oncology. 2017;12 (11 Supplement 2):S2073.
205. Taylor-Stokes G, Wood R, Lees M, Malcolm B, Chirita O. The humanistic burden of advanced non-small cell lung cancer on patients and their caregivers. Journal of Clinical Oncology Conference. 2017;35(5 Supplement 1).
206. Taylor-Stokes G, Wood R, Malcolm B, Lees M, Chirita O. The humanistic burden of advanced non-small cell lung cancer patients in Europe - A real world survey. Journal of Thoracic Oncology. 2017;12 (1 Supplement 1):S685.
207. Tsiplova K, Pullenayegum E, Cooke T, Xie F. EQ-5D-derived health utilities and minimally important differences for chronic health conditions: 2011 Commonwealth Fund Survey of Sicker Adults in Canada. Quality of Life Research. 2016;25(12):3009-16.
208. Wood R, Taylor-Stokes G, Lees M, Chirita O. Impact of tobacco smoking on the humanistic and financial burden of advanced non-small cell lung cancer (A-NSCLC). Journal of Thoracic Oncology. 2017;12 (11 Supplement 2):S1773.
209. Chevalier J, Le Lay K, De Pouvourville G. Health state utility values in advanced non-small cell lung cancer patients. Value in Health. 2013;16(7):A419.
210. Chouaid C, Bischoff H, Vergnenegre A, Heigener D, Taylor- Stokes G, Roughley A, et al. Real life outcomes and health-related quality of life (HRQOL) in 1st line non-squamous non-small cell lung cancer (NSCLC): A european pilot study analysing bevacizumab-based versus non-bevacizumab-based treatments. Journal of Thoracic Oncology. 2011a;6(6):S1284-S5.
211. Galetta D, Cinieri S, Pisconti S, Gebbia V, Morabito A, Borsellino N, et al. Cisplatin/pemetrexed followed by maintenance pemetrexed versus carboplatin/paclitaxel/bevacizumab followed by maintenance bevacizumab in advanced nonsquamous lung cancer: The GOIM (Gruppo Oncologico Italia Meridionale) ERACLE phase III randomized trial. Clinical lung cancer. 2015;16(4):262-73.
212. Grutters JP, Joore MA, Wiegman EM, Langendijk JA, de Ruysscher D, Hochstenbag M, et al. Health-related quality of life in patients surviving non-small cell lung cancer. Thorax. 2010;65(10):903-7.
213. Iyer S, Taylor-Stokes G, Roughley A. Symptom burden and quality of life in advanced non-small cell lung cancer patients in France and Germany. Lung Cancer. 2013;81(2):288-93.
214. Lee LJ, Chung CW, Chang YY, Lee YC, Yang CH, Liou SH, et al. Comparison of the quality of life between patients with non-small-cell lung cancer and healthy controls. Qual Life Res. 2011;20(3):415-23.
215. Nafees B, Stafford M, Gavriel S, Bhalla S, Watkins J. Health state utilities for non small cell lung cancer. Health and Quality of Life Outcomes. 2008;6.

216. Roughley A, Damonte E, Taylor-Stokes G, Rider A, Munk VC. Impact of Brain Metastases on Quality of Life and Estimated Life Expectancy in Patients with Advanced Non-Small Cell Lung Cancer. Value Health. 2014;17(7):A650.
217. Schuette W, Tesch H, Buttner H, Krause T, Soldatenkova V, Stoffregen C. Second-line treatment of stage III/IV non-small-cell lung cancer (NSCLC) with pemetrexed in routine clinical practice: evaluation of performance status and health-related quality of life. BMC Cancer. 2012;12:14.
218. Tongpak P, Thongprasert S, Permsuwan U. Utility of advanced non-small cell lung cancer patients in Thailand: Preliminary study. Value in Health. 2012;15(7):A657.
219. Trippoli S, Vaiani M, Lucioni C, Messori A. Quality of life and utility in patients with non-small cell lung cancer. Quality-of-life Study Group of the Master 2 Project in Pharmacoeconomics. Pharmacoeconomics. 2001;19(8):855-63.
220. Huang M. Q-TWiST Analysis to Assess Benefit–Risk of Pembrolizumab in Patients with PD-L1–Positive Advanced or Metastatic Non-small Cell Lung Cancer. PharmacoEconomics. 2019:105-16.
221. Kim EJ, Ock M, Kim KP, Jung NH, Lee HJ, Kim SH, et al. Disease severity-based evaluation of utility weights for lung cancer-related health states in Korea. BMC Cancer. 2018;18(1):1081.
222. Kunikane H, Yokota I, Katakami N, Takeda K, Takayama K, Sawa T, et al. Prospective analysis of the association between skeletal-related events and quality of life in patients with advanced lung cancer (CSP-HOR13). Oncol Lett. 2019;17(1):1320-6.
223. O'Kane GM, Su J, Tse BC, Tam V, Tse T, Lu L, et al. The Impact of Brain Metastases and Associated Neurocognitive Aspects on Health Utility Scores in EGFR Mutated and ALK Rearranged NSCLC: A Real World Evidence Analysis. Oncologist. 2019;24(7):e501-e9.
224. Reck M, Schenker M, Lee KH, Provencio M, Nishio M, Lesniewski-Kmak K, et al. Nivolumab plus ipilimumab versus chemotherapy as first-line treatment in advanced non-small-cell lung cancer with high tumour mutational burden: patient-reported outcomes results from the randomised, open-label, phase III CheckMate 227 trial. Eur J Cancer. 2019;116:137-47.
225. Shen Y, Wu B, Wang X, Zhu J. Health state utilities in patients with advanced non-small-cell lung cancer in China. J Comp Eff Res. 2018;7(5):443-52.
226. Wood R, Taylor-Stokes G, Smith F, Chaib C. The humanistic burden of advanced non-small cell lung cancer (NSCLC) in Europe: a real-world survey linking patient clinical factors to patient and caregiver burden. Qual Life Res. 2019;28(7):1849-61.
227. Huang M, Chandwani S, Insinga R, Burke T, Pellissier J, Pickard AS. Health State Utilities in Metastatic NSCLC A Study of Multiple Immuno-Oncology Trials. Value in Health. 2018;21 (Supplement 3):S72-S3.
228. Witlox W, Ramaekers B, Groen H, Dingemans AM, Praag J, Belderbos J, et al. Health-related quality of life (QoL) after prophylactic cranial irradiation (PCI) vs no PCI for stage III NSCLC patients: Results from the NVALT-11/DLCRG-02 study. Journal of Thoracic Oncology. 2018;13 (4 Supplement 1):S60.
229. Swan JS, Lennes IT, Stump NN, Temel JS, Wang D, Keller L, et al. A Patient-Centered Utility Index for Non-Small Cell Lung Cancer in the United States. MDM Policy Pract. 2018;3(2):2381468318801565.
230. Huang M, Pellissier J, Liao J. A trial-based euroqol EQ-5D health utility analysis in patients with previously treated advanced NSCLC. Value in Health. 2016;19 (7):A744.
231. O'Kane G, Labbe C, Su S, Tse B, Tam V, Tse T, et al. The impact of brain metastases and their treatment on health utility scores in molecular subsets of lung cancer patients. Journal of Thoracic Oncology. 2017;12 (1 Supplement 1):S937.
232. British National Formulary. British National Formulary 2020 [Date Accessed 1st September 2020]. Available from: http://www.medicinescomplete.com/#/browse/bnf.
233. National Institute for Health and Care Excellence. NICE Pathways: Treating non-small-cell lung cancer 2020 [Date Accessed 1st September 2020]. Available from:

https://pathways.nice.org.uk/pathways/lung-cancer#path=view%3A/pathways/lung-cancer/treating-non-small-cell-lung-cancer.xml&content=view-index.
234. NHS. 2018/19 National Cost Collection data 2020 [Date Accessed 1st September 2020]. Available from: https://www.england.nhs.uk/national-cost-collection/.
235. Curtis L, Burns A. Unit Costs of Health and Social Care 2019 2019 [Date Accessed 1st September 2020]. Available from: https://www.pssru.ac.uk/project-pages/unit-costs/unit-costs-2019/.
236. National Institute for Health and Care Excellence. Lung cancer: diagnosis and management (CG121). 2011.
237. Taylor D, Carter S. Marie Curie Cancer Care; Understanding the cost of end of life care in different settings. School of Pharmacy, University of London,. 2004.
238. Curtis L, Burns A. PSSRU: Unit Costs of Health and Social Care 2017. 2017.
239. Reck M, Rodriguez-Abreu D, Robinson AG, Hui R, Csoszi T, Fulop A, et al. Updated Analysis of KEYNOTE-024: Pembrolizumab Versus Platinum-Based Chemotherapy for Advanced Non-Small-Cell Lung Cancer With PD-L1 Tumor Proportion Score of 50% or Greater. Journal of clinical oncology : official journal of the American Society of Clinical Oncology. 2019;37(7):537-46.
240. National Institute for Health and Care Excellence. Atezolizumab with nab-paclitaxel for untreated PD-L1-positive, locally advanced or metastatic, triple-negative breast cancer [TA639] 2020 [Date Accessed 2nd September 2020]. Available from: https://www.nice.org.uk/guidance/ta639.
241. Pacheco JM, Gao D, Camidge DR. Extended follow-up on KEYNOTE-024 suggests significant survival benefit for pembrolizumab in patients with PD-L1 ≥50%, but unanswered questions remain. Ann Transl Med. 2019;7(Suppl 3):S127-S.
242. Mok TSK, Wu YL, Kudaba I, Kowalski DM, Cho BC, Turna HZ, et al. Final analysis of the phase III KEYNOTE-042 study: Pembrolizumab (Pembro) versus platinum-based chemotherapy (Chemo) as first-line therapy for patients (Pts) with PD-L1-positive locally advanced/metastatic NSCLC. Annals of Oncology. 2019;30(Suppl 2):ii38.
243. National Institute for Health and Care Excellence. Atezolizumab for untreated PD-L1-positive locally advanced or metastatic urothelial cancer when cisplatin is unsuitable [TA492] 2018 [Date Accessed 1st September 2020]. Available from: https://www.nice.org.uk/guidance/ta492.
244. National Institute for Health and Care Excellence. Atezolizumab with carboplatin and etoposide for untreated extensive-stage small-cell lung cancer [TA638] 2020 [Date Accessed 2nd September 2020]. Available from: https://www.nice.org.uk/guidance/ta638.

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single technology appraisal

Atezolizumab monotherapy for untreated advanced non-small-cell lung cancer [ID1678]

Clarification questions

October 2020

File name	Version	Contains confidential information	Date
Final_ID1678 Atezolizumab ERG clarification questions v1 [ACIC]	v1	Yes	16/10/2020

Notes for company

Highlighting in the template

Square brackets and grey highlighting are used in this template to indicate text that should be replaced with your own text or deleted. These are set up as form fields, so to replace the prompt text in [grey highlighting] with your own text, click anywhere within the highlighted text and type. Your text will overwrite the highlighted section.

To delete grey highlighted text, click anywhere within the text and press DELETE.

Section A: Clarification on effectiveness data

Methods used to assess the main clinical effectiveness evidence

A1. Document B, Section B.2.5 and Appendix D.1.1.3. Please clarify how many reviewers carried out the risk of bias assessment and whether they worked independently.

RESPONSE: Two reviewers independently assessed the risk of bias for each included study using the Cochrane Risk of Bias tool. Any disagreements were resolved through discussion or by consulting a third reviewer. The risk of bias assessment for all the trials included in the systematic literature review can be found in section D1.3, Table 39 of the appendices (p250).

Main clinical effectiveness evidence (IMpower110)

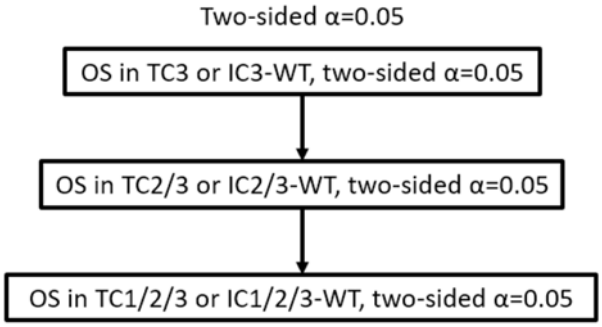
A2. Document B, Section B.2.4.2, page 34. Please provide a rationale for the interim efficacy analysis for the primary OS endpoint. The ITT population is described as TC1/2/3 or IC 1/2/3, however the submission focuses specifically on the TC3/IC3 sub-population.

RESPONSE: The IMpower110 study was designed to prospectively evaluate the efficacy and safety of atezolizumab monotherapy versus a platinum-based chemotherapy as first line (1L) treatment in programmed death-ligand 1 (PD-L1) positive metastatic NSCLC patients, as defined by the VENTANA PD-L1 SP142 Assay (SP142 assay). For study protocol versions 1-4 of IMpower110, patients were screened with the SP142 assay and deemed eligible for the study if their tumour PD-L1 result was TC3 or IC3 (tumour cell [TC] >= 50% or tumour-infiltrating immune cell [IC] >=10%). Version 5 and onwards of the protocol, patients were eligible for enrolment if their PD-L1 result was TC1/2/3 or IC1/2/3 (TC >=1% or IC >=1%).

Protocol changes were implemented during the course of the IMpower110 trial that reflected external clinical data. At the initiation of the IMpower110 study (first patient randomised July 2015), limited information was available regarding immune checkpoint inhibitors in the 1L setting for metastatic NSCLC, including the association of treatment effect with PD-L1 status. Based on the available information at that time, only patients with high PD-L1 expression (TC3 or IC3) were enrolled, as this population was anticipated to derive the most benefit from atezolizumab, and the comparator arm was an active standard of care chemotherapy regimen. Numerous emerging studies in 2L+ NSCLC, indicated that anti-PD-1/PD-L1 monotherapy provided clinical benefit at lower levels of PD-L1 expression (1-3) and as a result the IMpower110 protocol was updated to version 5 to enrol patients with any PD-L1 expression (TC1/2/3 or IC1/2/3). Subsequent to this modification, several 1L NSCLC anti-PD-1/PD-L1 monotherapy studies unblinded and indicated that the majority of clinical benefit was restricted to patients with the highest PD-L1 levels (4-6). Due to these emerging data, and the observed prevalence of TC3 or IC3 in IMpower110, which would lead to a fully powered study of OS evaluation in the TC3 or IC3-WT (wild type) subpopulation, the protocol (version 9) was updated so that the TC3 or IC3-WT subpopulation was tested first in the primary analysis testing hierarchy. To control for the overall type I error rate at a two-sided significance level of 0.05, the primary endpoint of overall survival was tested hierarchically as shown in

Figure 1: TC3 or IC3-WT subpopulation, then TC2/3 or IC2/3 subpopulation, and then TC1/2/3 or IC1/2/3 population.

Figure 1 Type I Error Control Plan



IC=tumour-infiltrating immune cell; OS=overall survival; TC=tumour cell; WT=wild-type (i.e., excluding patients with a sensitising epidermal growth factor receptor [EGFR] mutation or anaplastic lymphoma kinase [ALK] translocation).

The primary analysis endpoint was met as the prespecified interim analysis alpha boundary was crossed for OS in TC3 or IC3-WT subpopulation with a statistically significant and clinically meaningful OS benefit in the atezolizumab treatment arm. The results for OS in TC2/3 or IC2/3-WT subpopulation did not cross the prespecified alpha boundary. In accordance with the testing hierarchy, OS in TC1/2/3 or IC1/2/3-WT population was not formally tested. Therefore, the submission focuses specifically on the TC3 or IC3-WT subpopulation.

In response to your PFS question at the clarification meeting on Thursday 8th October; In protocol version 6, OS became the single primary efficacy endpoint, and PFS became a secondary endpoint. As a result, PFS could not be formally tested until the primary endpoint of OS for all prespecified PD-L1 subgroups was positive. The change to a primary endpoint of OS was made on the basis of accumulating data from the OAK and BIRCH studies in 2L+ NSCLC, which confirmed the robustness of OS as an endpoint for assessing efficacy of atezolizumab monotherapy. In addition, OS is a universally established endpoint and most objective measure of clinical benefit for patients with advanced lung cancer.

Indirect and mixed treatment comparisons

A3. PRIORITY. Document B, sections B.2.9.3 Please provide digitised data for the KEYNOTE-024 and KEYNOTE-042 Kaplan-Meier survival plots used in the submission for the relevant sub-populations.

RESPONSE: Please find attached the HR and digitised survival data from the NMA using both the IA 2018 and FA 2020 data-cut for IMpower110 (nsclc_xxx.csv).

A4. Document B, section B.2.9. Please provide the time to event data for OS and PFS for IMpower110, if possible with associated covariates.

RESPONSE: Please find attached the individual patient (ipd_fp_itwt_xxx.csv) survival data for the IA (10 SEP 2018) and FA (4 FEB 2020).

A5. Document B, section B.2.9. Please provide a side-by-side table of all characteristics for the relevant TC3/IC3 (and equivalent) sub-population from IMpower110, KEYNOTE-024 and KEYNOTE-042.

RESPONSE: Please see **Table** 1, Patient Demographics and Baseline Characteristics across IMpower110, KEYNOTE-042 and -024.

Table 1: Patient Demographics and across IMpower110, Baseline Characteristics KEYNOTE-042 and -024 (4, 7, 8)

	IMPOWER 110		KEYNOTE-042		KEYNOTE-024	
	Atezolizumab (N=107)	**Chemotherapy (N=98)**	**Pembrolizumab (N=299)**	**Chemotherapy (N=300)**	**Pembrolizumab (N=154)**	**Chemotherapy (N=151)**
Median age (range)	63 (33-79)	66 (33-87)	63.0 (56.0–68.0)	64.0 (57.0–69.0)	64.5 (33-90)	66.0 (38-85)
Male Sex — no. (%)	79 (73.8)	64 (65.3)	205 (69)	210 (70)	92 (59.7)	95 (62.9)
Race — no. (%)						
White	87 (81.3)	82 (83.7)	-	-	-	-
Asian	20 (18.7)	15 (15.3)	-	-	-	-
Black	0	0	-	-	-	-
unknown	0	1 (1.0)	-	-	-	-
ECOG performance-status Score — no. (%)						
0	35 (32.7)	38 (38.8	96 (32%)	91 (30)	54 (35.1)	53 (35.1)
1	72 (67.3	60 (61.2)	203 (68)	209 (70)	99 (64.3)	98 (64.9)
Smoking Status — no. (%)						
Never	9 (8.4)	15 (15.3)	64 (21)	67 (22)	5 (3.2)	19 (12.6)

Current	20 (18.7)	29 (29.6)	57 (19)	59 (20)	34 (22.1)	31 (20.5)
Former	78 (72.9)	54 (55.1)	178 (60)	174 (58)	115 (74.7)	101 (66.9)
Histologic type at diagnosis — no. (%)						
Non-squamous	80 (74.8)	75 (76.5)	192 (64)	186 (62)	125 (812)	124 (82.1)
Squamous	27 (25.2)	23 (23.5)	107 (36)	114 (38)	29 (18.8)	27 (17.9)
Disease status— no. (%)						
Locally advanced			27 (9)	35 (12)		
Metastatic			272 (91)	265 (88)		
Brain metastases			19 (6)	15 (5)	18 (11.7)	10 (6.6)
Previous treatment for non-metastatic disease— no. (%)						
Radiotherapy			40 (13)	39 (13)		
Neoadjuvant therapy			1 (<1)	5 (2)	3 (1.9)	1 (0.7)
Adjuvant therapy			8 (3)	4 (1)	6 (3.9)	3 (2.0)
Region of enrolment *— no. (%)						
Asia Pacific /East Asia	20 (18.7) *Asia Pacific	14 (14.3) *Asia Pacific	92 (31) *East Asia	94 (31) *East Asia	21 (13.6) *East Asia	19 (12.6) *East Asia
Europe	76 (71.0)	77 (78.6)	71 (24)	66 (22)	133 (86.4)	132 (87.4)

South America/Latin America	6 (5.6)	5 (5.1)	53 (18)	63 (21))	*not EAST ASIA	*not EAST ASIA
North America	5 (4.7)	2 (2.0)				
Other			83 (28)	77 26)		

* IMpower110 collected region enrolment data from Asia specific and South America, whereas KEYNOTE-024 and -042 collected from East Asia and Latin America

A6. Document B, Section B.2.9.7, Figure 19, page 65. Considering that the grey area is largely above 1, please provide the company's interpretation of the effectiveness of atezolizumab relative to pembrolizumab (OS data) over the reported follow-up period.

RESPONSE: The median duration of survival for the TC3 or IC-3 WT subpopulation between the two data cuts remained the same for atezolizumab: [redacted]. With extended follow up, chemotherapy's median duration of survival changed from : [redacted]. The effect of subsequent lines of cancer immunotherapies became increasingly observable. For this reason, Roche provided the FDA and NICE with the rank preserving structural failure time (RPSFT) adjusted analyses, that can be found in Appendix L. The RPSFT adjustment resulted in a [redacted].

The difference in follow up between the IMpower110 and the KEYNOTE studies means that without an appropriate adjustment, the NMA results are biased against atezolizumab. The effect of this can be seen in the "grey area" mentioned, particularly when comparing the NMA results based on the two data cuts, as shown below.

Figure 2 and Figure 3 below shows that, when using the 2018 data cut, the grey area is equally distributed around 1 when compared to pembrolizumab and largely below 1 when compared to chemotherapy. The 2020 data cut reverts this picture due to the increase in median duration of survival for chemotherapy, as described above.

Finally, it has to be noted that the grey area is largely above one for the extrapolated section of the FP model, where no evidence is available due to the trials follow up.

In TA447/TA531 it is also highlighted that *"...the survival benefit associated with pembrolizumab compared to SOC is diluted due to crossover in the SOC arm (either to pembrolizumab or alternative immunotherapy), conventional survival analysis will underestimate the survival benefit associated with pembrolizumab. Therefore, the OS observed in the SOC arm was adjusted, using alternative crossover adjustment methods, to reflect the actual benefit of patients receiving SOC in the absence of crossover." (9, 10)* As such, our CUA base case can be deemed overly conservative.

Figure 2: OS hazard ratios of atezolizumab relative to pembrolizumab between 1 and 60 months, for the random effects FP model, order 1, P1=0 (Weibull) 2018 data cut

Figure 3: OS hazard ratios of atezolizumab relative to pembrolizumab between 1 and 60 months, for the random effects FP model, order 1, P1=0 (Weibull) 2020 data cut

In summary we believe that these analyses, when read in the context of the data used to generate them, highlight that there is no conclusive evidence that one product is superior to the other for this indication and validates mainstream clinical opinion on the matter.

A7. Document B, Section B.2.9.7, Table 19 page 66. Please provide the number of participants for each arm of the study at each time for the OS data reported in the table.

RESPONSE:

Table 2: OS; HR and numbers at risk

OS; HR of comparators relative to ATZ (95% CrI); HR < 1 favours ATZ							
Time (months)	PEMB	Number at risk					
		IMp110_ATZ	IMp110_Chemo	KN024_Chemo	KN024_PEMB	KN042_Chemo	KN042_PEMB
3	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
6	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
12	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
18	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
24	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
36	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
48	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
60	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Second column: The first number indicates the median posterior estimate, while the numbers in brackets indicate the 95% posterior credible interval.

A8. Document B, Section B.2.9.7, Figure 21, page 67. Please clarify on which data cut is the forest plot based on.

RESPONSE: Figure 21: PFS hazard ratio based on hazard ratio data for pembrolizumab relative to atezolizumab, using the random effects model on page 67 in Section.2.9.7 of Document B is based on the FA 2020 data cut. The PFS HR from the ITC does not suffer from confounding from subsequent therapies. This confounding is thought to have an important impact on the OS HR, given the difference in follow up times between the IMpower110 and the KEYNOTE studies.

A9. Document B, Section B.2.9.7, Table 20, page 68. Please provide sample sizes.

RESPONSE:

Table 3: PFS; HR and numbers at risk

PFS; HR of comparators relative to ATZ (95% CrI); HR < 1 favours ATZ							
Time (months)	PEMB	Number at risk					
		IMp110_ ATZ	IMp110_ Chemo	KN024_ Chemo	KN024_ PEMB	KN042_ Chemo	KN042_ PEMB
3	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
6	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
12	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
18	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
24	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
36	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
48	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

60	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

A10. Document B, Section B.4, References. Please provide reference no. 60 (Data on File 2018 NMA, 2020), which does not seem to be among the references submitted.

RESPONSE: Apologies if this was not previously included. Please find the full NMA report for the IA data-cut attached. The full NMA report for the 2020 FA is not available at the moment. All the information available regarding the 2020 FA NMA is also sent here as an attachment, in the format of a NICE template.

PD-L1 Assays

A11. Document B, Section B.2.3.3, Table 5 summarises the different PD-L1 assays**.** Please can the company provide a fuller discussion of the importance of the different PD-L1 assays used in the relevant RCTs for atezolizumab and pembrolizumab, focusing on:

(1) alignment of definitions - with the respect to the different assays used to define the patient populations in the KEYNOTE and IMpower110 trials.

RESPONSE: The scoring algorithm of the SP142 immunohistochemistry (IHC) assay measures PD-L1 expression on tumour cells (TC) and tumour-infiltrating immune cells (IC). Other PD-L1 IHC diagnostic assays using different antibody clones (e.g. DAKO 22C3 and 28-8, and VENTANA PD-L1 (SP263) assay) were developed in parallel to SP142 by other pharmaceutical companies. These alternative assays exclusively score PD-L1 expression on TCs (and not ICs) in NSCLC. Each assay and their associated cutoffs have been analytically validated, clinically validated in phase III trials, and are indicated as an aid in identifying patients for treatment with one or more specific molecules in the anti-PD-1/PD-L1 class (4, 8, 11).

NSCLC definitions for 22C3, SP142, and SP263 used in the KEYNOTE studies and IMpower110 can be found in **Table 4**.

Table 4: SP142, 22C3 and SP263 assay Scoring Definitions (12-14)

SP142				**22C3**		**SP263**	
PD-L1 IHC TC Scoring		**PD-L1 IHC IC Scoring**		**Tumour Promoter Score**		**Assay Scoring Algorithm**	
TC Score	**Percent of PD-L1 Expressing TC**	**IC Score***	**Percent of PD-L1 Expressing IC**	**PD-L1 Expression status**	**PD-L1 Expression Levels**	**PD-L1 Interpretation**	**Staining Description**
TC2	≥5% and <50%	IC2	≥5% and <10%	High PDL-1 Expression	TPS ≥ 50%	≥ 50%	≥ 50% of tumour cells with membrane positivity for PD-L1 at any intensity above background staining as noted on the corresponding negative control.
TC1	≥1% and <5%	IC1	≥1% and <5%	PDL-1 expression	TPS ≥ 1%	≥ 1%	≥ 1% of tumour cells with membrane positivity for PD-L1 at any intensity above background staining as noted on the corresponding negative control.
TC0	<1%	IC0	<1%	No PD-L1	<1%	< 1%	< 1% of tumour cells with membrane positivity for PD-L1 at any intensity above background staining as noted on the corresponding negative control.
Taken from the SP142 package insert: Determination of PD-L1 status is indication-specific, and evaluation is based on either the proportion of tumour area occupied by PD-L1 expressing tumour-infiltrating immune cells (% IC) of any intensity or the percentage of PD-L1 expressing tumour cells (% TC) of any intensity. SP142 definitions for key cutoffs:				Taken from the 22C3 package insert: PD-L1 protein expression is determined by using Tumour Proportion Score (TPS), which is the percentage of viable tumour cells showing partial or complete membrane staining at any intensity. The specimen should be considered to have PD-L1 expression if TPS ≥1% and high PD-L1 expression if TPS ≥50%.		Taken from the SP263 EU CE-Mark package insert: Tumour cells with membrane positivity for PD-L1 at any intensity above background staining as noted on the corresponding negative control.	

TC1/2/3 or IC1/2/3 = TC>=1% or IC>=1% TC2/3 or IC2/3 = TC>=5% or IC>=5% TC3 or IC3 = TC>=50% or IC>=10%		
Note: * Tumour-infiltrating immune cells include macrophages, granulocytes, dendritic cells, and lymphocytes. Abbreviations: IC=tumor-infiltrating immune cell; IHC=immunohistochemistry; PD-L1=programmed death-ligand 1; TC=tumor cell.		

The NSCLC patients enrolled in the Keynote and IMpower110 studies were as follows:

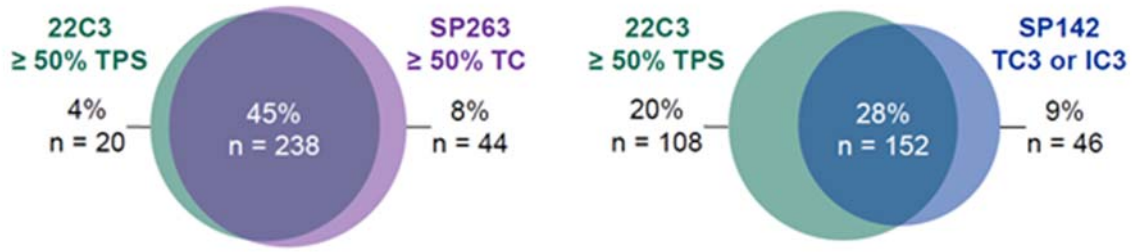
- **KEYNOTE-024** enrolled patients using the 22C3 assay that expressed TPS >=50% (8)
- **KEYNOTE-042** enrolled patients using the 22C3 assay that expressed TPS >=1% (4)
- **IMpower110** enrolled patients using the SP142 assay at the TC1 or IC1 cutoff (TC or IC >=1%). Samples from the patients were then tested using the SP263 assay (secondary endpoint) and then the 22C3 assay (exploratory endpoint) (7)

Numerous studies have been performed to compare the analytical features of each PD-L1 assay in an effort to potentially harmonise the PD-L1 testing landscape in NSCLC (15, 16). The key findings from these studies showed that the DAKO 22C3 assay, DAKO 28-8 assay, and SP263 assay showed highly comparable TC staining, but the SP142 assay was comparably less sensitive for both TC and IC staining. It should be noted that reduced sensitivity does not necessarily mean that the SP142 assay is an outlier, has performance problems, or is less predictive than the other assays. It only indicates that the assay may not detect patients with the lowest PD-L1 expression levels (from a staining intensity perspective).

(2) Whether those in the TC3-IC3 population of IMpower110 who do not meet the criteria of TPS ≥50% based on the 22C3 assay (n=46/198), would currently be eligible for pembrolizumab monotherapy in England; why Figure 26 (Appendix G) shows only 198 in the SP142 TC3-IC3 population (N 152+46).

RESPONSE:

Figure 4: Overlap between PD-L1-high subgroups in IMpower110 (17)



IC: immune cell; TC: tumour cell; TPS: tumour proportion score

To understand the eligibility of patients for pembrolizumab treatment in England it is important to note that the NHS England Blueteq form requires '*PD-L1 testing with an approved and validated tes*t', which means a centre is dependent on the test used in the pathology laboratory, and that could be any of the three available tests, 22C3, SP263 or SP142. The eligibility of a patient to receive an immunotherapy such as pembrolizumab will therefore be dependent on the result of the test used. Insights gathered from clinical experts across the country (Data on File) show that a patient is typically only tested with one assay and that the 22C3 assay is most prevalently used (21 centres), followed by SP263 (5 centres) and then SP142 (1 centre). Interestingly, when this question was asked to clinicians the majority struggled to remember which assay was used to test PD-L1 and when probed as to why, they said the actual assay was of low importance, and what really mattered was the test result and whether the patient demonstrated a high, low or negative PD-L1 expression and could therefore be treated with an immunotherapy in the first line.

Whilst there is limited data looking at the direct comparisons of the clinical predictive value across assays, there was an exploratory analysis completed in our second line

NSCLC atezolizumab monotherapy study OAK (which enrolled an all comer population) that looked to evaluate PD-L1 expression using the SP142 and 22C3 assays (18). Results showed that atezolizumab improves survival of patients in this setting irrespective of which assay was used and despite there being a level of variability between them.

When we discussed this with three clinical experts, they acknowledged the variability between available assays and the limitations with SP142, but all agreed there is largely overlapping concordance across these assays and that any of them could be used to test for PD-L1 expression ahead of immunotherapy treatment. They added that if assay restrictions were to be imposed it would make reflex testing much more challenging. Useful amounts of lung cancer tissue for testing is very difficult to obtain and therefore what is collected is very precious. If an additional sample would have to be tested with another assay this would not only potentially delay treatment, it would also use up the limited sample which is saved for additional molecular testing (i.e. NGS). This in turn could lead to the request of a repeat biopsy, which is not conducive to anyone. There is already a 2-week minimum wait for patients between diagnosis and seeing an oncologist, and therefore the aim is to treat first-line metastatic NSCLC patients as quickly as possible. With a 2-3 week wait for EGFR/ALK results you wouldn't want to increase that time any further in order to perform a retest for PD-L1.

In response to part two of the question, *'Why Figure 26 (Appendix G) shows only 198 in the SP142 TC3-IC3 population (N 152+46)?*', this overlap analysis of 22C3 and SP142 populations, patients must have both a 22C3 and SP142 result. Since a 22C3 result was not available for all IMpower110 enrolled patients (for example, due to limited tissue availability), the 198 SP142 TC3 or IC3 patients (n=152+46) represent the number of patients in the 22C3 evaluable population, which also had a SP142 TC3 or IC3 result. As a result, for this specific overlap analysis there are only 198 TC3 or IC3 patients, whereas in the full ITT-WT population (independent of 22C3 status) there are a total of 205 TC3 or IC3 patients.

(3) relevance of the RCT results to PD-L1 testing as currently carried out in the NHS

RESPONSE: Considering the extensive use of 22C3 and SP263 testing in NSCLC in clinical practice, PD-L1 subgroups defined by these assays were evaluated as pre-specified exploratory and secondary efficacy endpoints in IMpower110, respectively. Similar OS and PFS benefit favouring atezolizumab over chemotherapy was observed in patients with high PD-L1 expression across all three IHC assays (SP142, 22C3, SP263), despite different assay analytic sensitivities and scoring algorithms (Document B of the submission, Section B2.6.7, figure 14 [OS] and Section G1.3, Figure 27 [PFS]). However, there are limitations associated with these analyses and caution should be applied in interpreting the results. IMpower110 selected patients who were PD-L1 positive (TC1/2/3 or IC1/2/3) by the SP142 assay, and therefore additional analyses of subgroups defined by 22C3 and SP263 represent a double-selected patient population.

We also validated the IMpower110 OS and PFS results across the three assays with 3 clinical experts and they all agreed to the relevance of these data to clinical practice as currently carried out in the NHS. They also highlighted the importance of the 2-year OS landmark analysis as stronger descriptive of benefit when deciding how clinically similar biomarker assays are. Table 5 below shows the 2 year OS rates across IMpower110, KEYNOTE-024 and KEYNOTE-042 in the NSCLC with PD-L1 high expression. Whilst caution should be made when you make comparisons between studies one could infer regardless of the biomarker assay used to test PD-L1 (22C3 for KN-024 and KN-042 and SP142 for IMpower110) the 2-year landmark OS results are very similar across the three studies.

Table 5: Median follow up and landmark OS

Study	Median FU	2 YEAR OS rate
IMpower110 (CCOD Sep 2018) (7)	15.7 months	45% (TC3 or IC3) vs 25% (Chemotherapy)
IMpower110 (CCOD Feb 2020) (unpublished)	[redacted]	[redacted]
KEYNOTE-024 (CCOD Jul 2017) (19)	25.2 months	52% (TPS ≥50%) vs 35% (chemotherapy)
KEYNOTE-042 (CCOD Sept 2018) (20)	14.0 months	45% (TPS ≥50%) vs 30% (Chemotherapy)

(4) whether the company considered conducting the NMA using the 22C3 TPS ≥50% population from IMpower110, to improve comparability with the KEYNOTE trials.

RESPONSE: Conducting the NMA using the 22C3 TPS ≥50% population from IMpower110 was indeed considered, however it was concluded that it would not increase comparability with the KEYNOTE trials. The reason for this is IMpower110 selected patients who tested PD-L1 positive (TC1/2/3 or IC1/2/3) by the SP142 assay, and therefore additional analyses of subgroups defined by 22C3 and SP263 represent a double-selected patient population.

Section B: Clarification on cost-effectiveness data

Clinical efficacy inputs

B1. <u>PRIORITY.</u> Document B, Section B.3.3.2, Figure 28. The figure compares OS curves for atezolizumab and pembrolizumab, with the following explanation: "*As previously mentioned, the comparator curves were constructed using the atezolizumab curve as a reference, applying the time dependent relative treatment effects from the ITC*." From the base case settings in the model, it appears that the NMA random effects hazard ratios (HRs) are being applied, assuming constant proportional hazards, rather than the time dependent HRs from the fractional polynomial NMA. Please confirm which data were used for the relative treatment effects and provide a rationale.

RESPONSE: Apologies for the error. It should read "..applying NMA random effects HRs assuming constant proportional hazard." Indeed, at first, it was considered to use the HRs from the fractional polynomial NMA. The FP NMA results are available in the model and the resulting extrapolations are shown below.

We observed that the fitting of the curves is not ideal for both PFS and OS when the fractional polynomial model is used. This causes implausible results for this comparison. It should be noted that when using the 2018 IA data cut, OS extrapolations based on the FP NMA results are less affected. This could suggest that the difference in the data maturity might have an impact on the NMA results, which cause implausible extrapolations, as can be seen in the curves below. Thus, the HR RE model is preferred over NMA FP in this case.

Figure 5: PFS - HR RE

Figure 6: PFS - FP RE

Figure 7: OS - HR RE

Figure 8: OS - FP RE

B2. PRIORITY. **Document B, Section B.2.9.3.** The individual patient survival times were reconstructed from the Kaplan-Meier data from the KEYNOTE studies. Please provide a naïve comparison of the reconstructed KM plots of PFS and OS for pembrolizumab, and any parametric curves you fitted independently to this data, with the corresponding PFS and OS curves for atezolizumab.

RESPONSE: Plots of the reconstructed KM data are shown below in Figure 9 and Figure 10, and provided as a separate file with higher resolution.

We have not fitted parametric curves independently to the KEYNOTE studies and can only provide the comparison through the NMA results. These are shown in Figure 11 and

Figure 12 below and are provided as high-resolution images separately.

Figure 9: KM OS curves

Figure 10: KM PFS curves

Figure 11 OS: extrapolation models

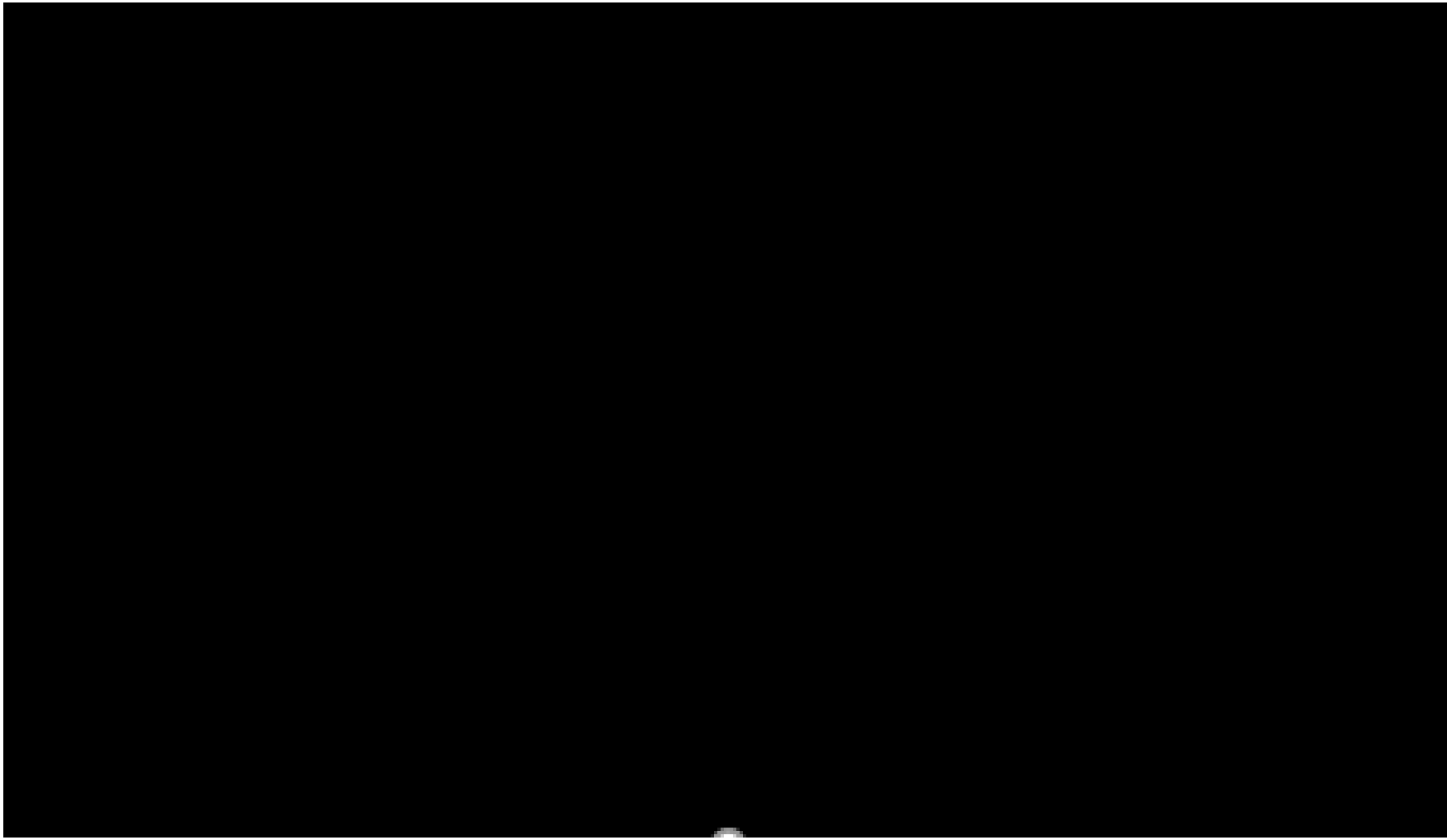


Figure 12: PFS extrapolation models

B3. Document B, Section B.2.2, BIRCH phase II study. Given that the BIRCH study includes patients matching the license and has longer follow-up than IMpower110, please present the latest PFS and OS analyses. Please explain how these compare to your extrapolated OS and PFS curves for atezolizumab.

RESPONSE: The BIRCH study has a follow up of 34.3 months, while the IMpower110 follow up is 31.3 months. This longer-term follow up was presented at WCLC in 2017 (21).

Figure 13 shows the OS KM curve for the TC3/IC3 subpopulation, with a median OS of 26.9 months and a 24 landmark OS of 52%. These values are higher than both the IMpower110 study and the economic model. This can be interpreted as additional and supporting evidence of both the economic model being based on conservative and probably over pessimistic assumptions, given the lack of adjustment for subsequent therapies, as well as reinforcing the clinical equivalence between atezolizumab and pembrolizumab in this indication. Particularly when comparing OS landmark data points, we can see how the values for atezolizumab and pembrolizumab across trials are in a similar range, confirming not only that the products are comparable, but also that the populations included in the trials are similar, although different assays were used at recruitment.

Figure 13: BIRCH study: OS Kaplan-Meier

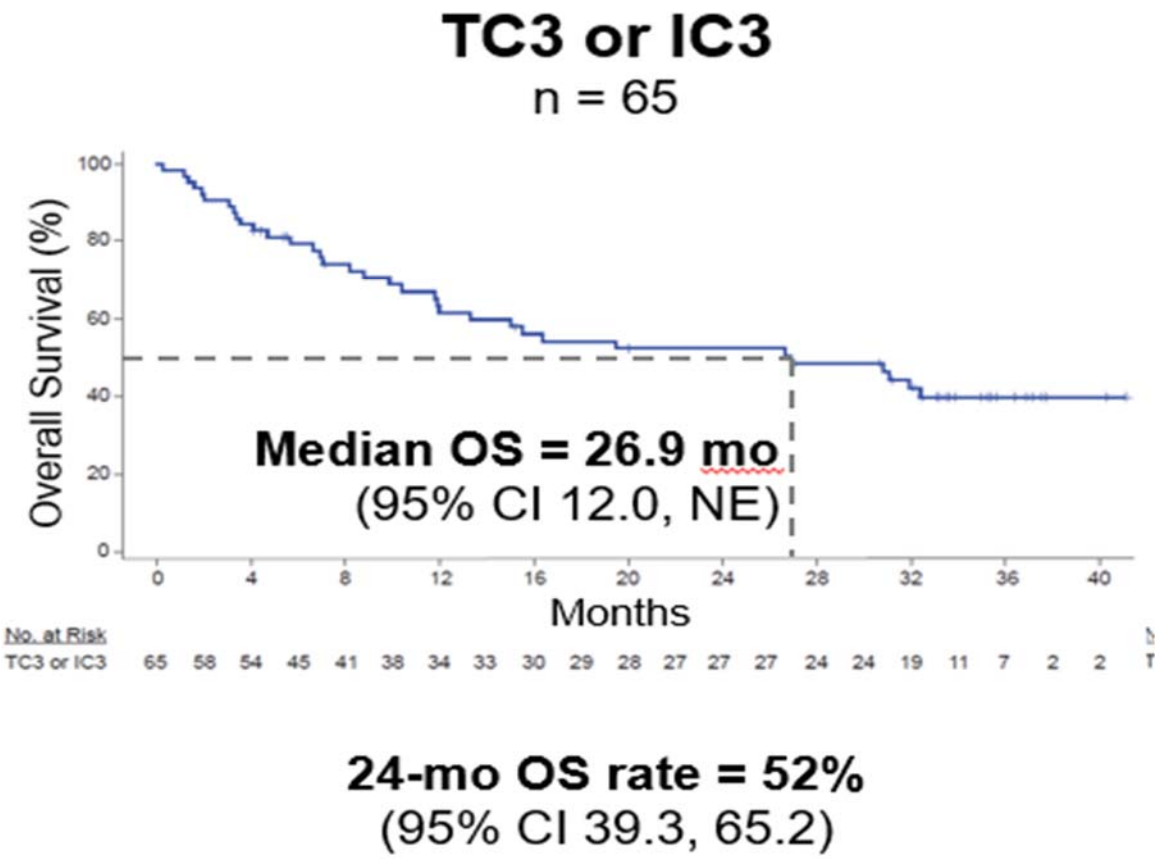


Table 6: Comparison of median and landmark OS across trials

	Model	**IMpower 110 (FA)**	**BIRCH study**	Pembro from TA531
Median OS (months)	[redacted]	[redacted]	26.9months	30months
24-month OS	[redacted]	[redacted]	52%	51.5%

From Figure 14 below, the OS KM seems to be almost overlapping up to approximately 20 months, after which the KM from BIRCH is above the Impower110 KM, particularly approximately between 20-35 months. It is interesting to observe that a similar patter can be seen in Figure 9 for the KEYNOTE-024 pembrolizumab arm, with the difference of a shorter follow up for the KEYNOTE study.

Figure 14: OS parametric extrapolations including BIRCH studies KM plot

From Figure 15 we see little or no difference for PFS until over 30 months, the point where the number of observations is enough to be interpreted.

Figure 15: PFS parametric extrapolations including BIRCH studies KM plot

Table 7: Comparison of median and landmark PFS across trials

	Model	IMpower 110 (FA)	BIRCH (n=65)
Median PFS (months)	[redacted]	[redacted]	7.3 months (4.9-13.6)
24-month PFS	[redacted]	[redacted]	28.8% (17.2-40.5)
30-month PFS	[redacted]	[redacted]	22.3% (11.2-33.4)

B4. Document B, Section B.2.7, exploratory analyses using the 2020 data. Please provide a summary table analogous to Table 8 (pages 37-38 of Document B) for the primary efficacy analysis.

RESPONSE:

Table 8: IMpower110: Overview of Efficacy (CCOD: 04 February 2020)

Clinical Cut-off: 04 February 2020		
Parameter	**Chemotherapy**	**Atezolizumab**
Primary Endpoint: Overall Survival		
TC3 or IC3-WT Population	n=98	n=107
Patients with event (%)	[redacted]	[redacted]
Median duration of survival (95% CI) (months)	[redacted]	[redacted]
Stratified HR (95% CI) p-value (Stratified log-rank)	[redacted]	
Secondary Endpoints		
Progression-Free Survival		
TC3 or IC3-WT Population	[redacted]	[redacted]
Patients with event (%)	[redacted]	[redacted]
Median duration of survival (95% CI) (months)	[redacted]	[redacted]
Stratified HR (95% CI) p-value (log-rank)	[redacted]	
Objective Response Rate		
TC3 or IC3-WT Population	n=98	n=107
ORR (%) (95% CI)	28.6% (19.90, 38.58)	40.2% (30.82, 50.11)
Duration of Response		
Other Key Efficacy Objectives (in ITT)		
TC3 or IC3-WT Population	n=28	n=43
Median DOR (95% CI)	[redacted]	[redacted]

CI=confidence interval; DOR=duration of response; NE=Not estimable; PFS=progression-free survival; WT=wild-type

Summaries of Time-to-Event (median, percentiles) were Kaplan-Meier estimates. 95% CI for median was computed using the method of Brookmeyer and Crowley. Hazard ratios were estimated by Cox regression. Stratification factors for the TC3 or IC3-WT subpopulation were: sex (male vs. female) and ECOG (0 vs. 1). WT patients are populations excluding patients with a sensitising EGFR mutation or ALK translocation.

[a]. p-value is descriptive only

B5. Document B, Section B.3.2.1. It is stated that the patient population in the model matches the license; however, subsequent sections of the economic analysis refer to data being taken from the IMpower110 study. Please clarify if all the IMpower110 data referred to as inputs to the cost-effectiveness model are for the 205 patients matching the license and for the 4/2/20 data cut.

RESPONSE: Yes, all the IMpower110 data referred to as inputs to the cost-effectiveness model are for the 205 patients matching the license and for the 4/2/20 data cut. This can also be seen in the cost effectiveness model in the 'settings' tab cells F51 and F52 and from the data shared in response to question A4.

The statement should read: "the patient population in the model [redacted]

B6. Document B, TA531. Please clarify which parametric functions were used to model OS and PFS for pembrolizumab in TA531 and how they compare to your extrapolations for pembrolizumab in the economic model. Please provide a comparison where data are available between the TA531 extrapolations of PFS and OS and those in your model.

RESPONSE: Almost all the relevant information in TA531 is marked as confidential and we were able to gather only very limited insights:

1. In TA531 a 2-phase piecewise model using KM+exponential with 1. a two stage crossover adjustment and 2. no crossover adjustment, were presented. The importance of crossover adjustment was recognised in the appraisal and the lack of adjustment for subsequent IO therapy for the chemotherapy arm in our submission can be seen as overly conservative.

2. *"At 24 months, OS rates were 51.5% for the pembrolizumab arm"* (pg.27 of the company submission (10)): Our model estimates 53% of patients to be alive at 2 years on pembrolizumab.

3. *"Median OS was 30 months for pembrolizumab"* (pg.27 of the company submission (10)). From our model median OS is [redacted] for pembrolizumab.

We note that the above Appraisal was based on the KEYNOTE-024 study and suggest to look at these data in the context of the response given to question A6, A7, A9 and B2.

B7. Document B, Section B.3.3.2.1. It is stated: *"It is worth noticing how unadjusted Flatiron data for pembrolizumab show at 36 months an OS of [redacted]."* Please confirm that [redacted] should read [redacted] and that the Flatiron data reflect patients with untreated metastatic disease and PD-L1 of 50% or more. In addition, please explain why the Flatiron data are relevant to England.

RESPONSE: Yes, [redacted] should read [redacted] and these Flatiron data reflect patients with untreated metastatic disease and PD-L1 of 50% or more. The demographics and the unadjusted KM can be found in the confidential reference slide deck "Polito 2020" slide 8 and 9. Also, from the pembrolizumab and chemotherapy KM presented in the slide deck the impact on the HR of not adjusting for subsequent lines of therapies can be observed, as discussed in response to question A6 regarding the IMpower110 trial.

Flatiron data have been used and accepted in previous atezolizumab NICE appraisals to inform long term OS extrapolation. While these are USA data, they are the best available data, closest to the population being appraised here.

We amend the CIC marking for the figures in this question to AIC. This will be submitted together with a new confidentiality checklist.

B8. Document B, Section B.3.3.5. Please confirm that the data in the first column of Table 39 (TTD Generalised Gamma) are the same as those used for the atezolizumab curve in Figure 35.

RESPONSE: Yes, this seems correct to us. In addition, in Table 39 the numbers have been rounded to the nearest whole number, compared to Table 37.

B9. Company model, "Model inputs", cell F124. The pembrolizumab duration of effect for PFS is maintained indefinitely, while the duration of effect for OS is assumed to wane from 5 years. Please explain the reason for maintaining the PFS effect but not the OS effect.

RESPONSE: OS benefit is capped in line with previous pembrolizumab's appraisals (10). Pembrolizumab's evidence base underpinning the recommendation was designed with a two year treatment stopping rule and the Committees agreed on OS waning from 5 years. Atezolizumab's evidence base on the contrary does not support stopping treatment at an arbitrary time point.

To our knowledge, capping the effect of PFS has not been considered in other immunotherapy appraisals to date. Maintaining the PFS benefit indefinitely for pembrolizumab is a conservative assumption, the impact of which is relatively small. It can be labelled as conservative not only based on the impact on the ICER, but also based on a clinical assumption that PFS benefit is persistent regardless of when and if treatment is stopped. Most patients will have progressed by the time the treatment effect wanes. In fact, it is only at and after 78 months when we can observe a 1% difference in patients still progression free on pembrolizumab (from 8% to 7% comparing no PFS cap to PFS cap, at 60 months).

We have included a scenario analysis exploring the impact of this assumption in Table 13, in response to question B16, at the end of the document.

Utilities

B10. Document B, Section B.3.4.1. It is stated that EQ-5D data were available for 193 patients. Please explain how this relates to the 572 patients recruited; for example, were only the TC3/IC3 sub-population used for informing the utility inputs?

If the EQ-5D values presented in the submission are the values from the TC3-IC3 sub-population only, please provide a comparison with the values (by progression status) provided by non-TC3-IC3 patients.

RESPONSE: Only the TC3 or IC3-WT subpopulation was considered for the estimation of utility, as this is the target population of the submission. In general, there were small differences in the utilities for the two TC3 or IC3 subgroups and the 95% confidence intervals overlapped, both in the pre-progression and post-progression states.

In the whole ITT WT population, 475 had a baseline utility value. The following table summarises the baseline utility for the whole ITT WT population and by TC3 or IC3 subgroup. Given the ITT WT population has a higher number of observations and similar baseline utility values, we have run a scenario analysis using these values instead of the TC3/IC3 specific ones. This can be found in Table 13, in response to question B16 below. In summary, pembrolizumab's ICER increases by £75,867, to £636,699

Table 9: Baseline utility values

	TC3 or IC3	TC1/2/3 or IC1/2/3 excluding TC3 or IC3	ITT WT
N	[redacted]	[redacted]	[redacted]
Min.	[redacted]	[redacted]	[redacted]
1st Qu.	[redacted]	[redacted]	[redacted]
Median	[redacted]	[redacted]	[redacted]
Mean	[redacted]	[redacted]	[redacted]
3rd Qu.	[redacted]	[redacted]	[redacted]
Max.	[redacted]	[redacted]	[redacted]

A subset of 425 patients with available baseline utility and at least a post-baseline utility measurement. The number of patients and observations available by progression status and TC3 or IC3 subgroup is presented in the table below for the 4th February 2020 data-cut:

Table 10: Number of patients and observations

Treatment arm	Number of patients	Number of observations
Pre-progression	[redacted]	[redacted]
TC3 or IC3	[redacted]	[redacted]
TC1/2/3 or IC1/2/3 excluding TC3 or IC3	[redacted]	[redacted]
Post-progression	[redacted]	[redacted]
TC3 or IC3	[redacted]	[redacted]
TC1/2/3 or IC1/2/3 excluding TC3 or IC3	[redacted]	[redacted]

The utility values for pre and post progression were estimated separately for each TC3 or IC3 subgroup and are presented in Table 11.

Table 11: Utility values

Label	Estimate	SE	Lower limit 95% CI	Upper limit 95% CI
Pre progression				
TC3 or IC3	[redacted]	[redacted]	[redacted]	[redacted]
TC1/2/3 or IC1/2/3 excluding TC3 or IC3	[redacted]	[redacted]	[redacted]	[redacted]
ITT WT	[redacted]	[redacted]	[redacted]	[redacted]
Post progression				
TC3 or IC3	[redacted]	[redacted]	[redacted]	[redacted]
TC1/2/3 or IC1/2/3 excluding TC3 or IC3	[redacted]	[redacted]	[redacted]	[redacted]
ITT WT	[redacted]	[redacted]	[redacted]	[redacted]

Costs

B11. Company model, "Atezo Mono" and "Active comparator" worksheets. It may be inappropriate to apply the half-cycle correction for TTD, because it is the proportion of patients on treatment at the start of each 3-week treatment cycle, who receive atezolizumab or pembrolizumab. Please provide a scenario that omits the half-cycle correction for drug and administration costs in the progression-free state.

RESPONSE: A scenario that omits the half-cycle correction for drug and administration costs in the progression-free state can be found below in response to question B16. The functionality to select this has been built into the model ('Model input sheet' row 83). Pembrolizumab's ICER increases by £5,896, to £566,728.

B12. Company model, "Atezo Mono", column CA and "Active comparator" Column DU. The subsequent therapy cost calculations appear to assume that everyone receives chemotherapy following discontinuation of atezolizumab or pembrolizumab, with no adjustment for pre-progression mortality or mortality as a PFS event. Please provide scenarios that:

a) adjust for deaths prior to progression or treatment discontinuation
b) assumes that less than 100% of patients who progress receive subsequent chemotherapy.

RESPONSE:

a) Time to treatment discontinuation (TTD) data is based on the observations from the IMPower110 trial, accounting for death.

b) We have built a functionality in the model to select the percentage of patients that receive subsequent chemotherapy ('Model input' sheet, row 32). We have also consulted three practicing oncologists who commented that between 50%-70% of patients on first line IO monotherapy would receive subsequent treatment. One of the clinicians pointed out how this percentage might be even lower now due to the COVID situation and the risk derived from patients' fitness. We have run a scenario analysis assuming 50% of patients who progress receive subsequent chemotherapy, which is

included in Table 13, in response to question B16 below to show the impact of this assumption. Pembrolizumab's ICER decreases by £3,474, to 557,358.

Model results and output

B13. Document B, Section B.3.8.1, Figure 41. The presented share of PSA iterations favouring each treatment in the presented CEACs do not sum to one. The same issue is present in the model "Results Charts". This seems to arise from a bug in the "Simulation" worksheet (columns CW to DF/DG), where iterations favouring each strategy are summed over 1000 but divided by a simulation number of 2000. Please amend this error in the model and provide updated CEACs.

RESPONSE: Apologies this has been corrected. Plots are below:

Figure 16: Cost-Effectiveness Plane - (PAS price)

Figure 17: Incremental Cost-Effectiveness Plane (PAS price)

Figure 18: Cost-Effectiveness Acceptability Curves - (PAS price)

Figure 19: Cost-Effectiveness Acceptability Curves - (List price)

B14. Company model. Please clarify where the switch for re-running the PSA is in the model.

RESPONSE: On the tab list at the top of the Excel, the switch can be found in the 'CE Model' tab.

B15. Document B, Section B.3.7.2, Table 63. The cost comparison analysis, which assumes equal efficacy, shows the mean cost of progression to be slightly different for atezolizumab and pembrolizumab. Please clarify why this is the case.

RESPONSE: Difference in the cost of progression in the cost comparison analysis

Subsequent treatment is calculated based on time to treatment discontinuation (TTD). TTD of atezolizumab is set to Gen Gamma, pembrolizumab's TTD until progression. If we set pembrolizumab's TTD to 'actual treatment duration' in the 'model input sheet' and so set pembrolizumab's and atezolizumab's treatment duration equal, the difference is reduced slightly from £573 to £283.

The remaining small difference is driven by the stopping rule applied for pembrolizumab in the model. If we remove the stopping rule for pembrolizumab from the 'model input sheet' the mean cost of progression becomes exactly the same for both products.

B16. <u>PRIORITY.</u> Document B, Section B.3.7.1 Please provide a table with results of the net monetary benefit (NMB) approach at a willingness to pay (WTP) threshold of £20,000 and a WTP threshold of £30,000. We acknowledge that NMB at a WTP threshold of £30,000 is currently available in the appendices. The company may also provide results of net health benefit (NHB) analyses at both a WTP threshold of £20,000 and £30,000, if they choose to do so.

RESPONSE: As requested, please find below the updated tables.

Table 12: Base case results of <u>pembrolizumab versus atezolizumab</u> * (PAS price)

	Total costs (£)	Total LY	Total QALYs	Incr. costs (£)	Incr. LY	Incr. QALYs	ICER* (£/QALY)	NMB* WTP £30,000	NMB* WTP £20,000	NHB* WTP £30,000	NHB* WTP £20,000
Pembro	[redacted]	[redacted]	[redacted]	47,059	0.14	0.08	560,832*	-44,542*	-45,381*	-1.5 *	-2.3*
Atezo	[redacted]	[redacted]	[redacted]								

*pembro versus atezo: high ICER indicates atezo is worth funding; ICER, incremental cost-effectiveness ratio;

NMB, net monetary benefit, NMB is calculated as: *(incremental gain in QALYs x threshold) – incremental cost*. A positive incremental NMB indicats that the intervention is cost-effective compared with the alternative at the given willingness-to-pay threshold.;

NHB, net health benefit calculated as: *incremental gain in QALYs – (incremental cost / opportunity cost threshold)*. A positive NHB implies that overall population health would be increased as a result of the new intervention LYs, life years; QALYs, quality-adjusted life years;

Negative NMB and negative NHB mean atezo is worth funding

Table 13: Scenario analyses results pembrolizumab vs. atezolizumab* (PAS price)

Parameter	Value	Atezo Mono			Pembro mono			Pembro Mono vs. Atezo Mono						
		Life Years	QALYS	Costs	Life Years	QALYS	Costs	Inc. QALYs	Inc. Costs	ICER*	NMB* WTP £30K	NMB* WTP £20K	NHB* WTP £30K	NHB* WTP £20K
Base case		[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	0.08	47,059	560,832*	-44,542*	-45,381*	-1.5*	-2.3*
Distribution OS	Exponential	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	0.10	48,475	476,303*	-45,422*	-46,439*	-1.5*	-2.3*
	Log-normal	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	0.12	47,481	401,488*	-43,933*	-45,116*	-1.5*	-2.3*
	Gen Gamma	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	0.09	47,186	536,154*	-44,546*	-45,426*	-1.5*	-2.3*
	Log-logistic	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	0.12	47,445	405,563*	-43,935*	-45,105*	-1.5*	-2.3*
	Gompertz	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	0.29	48,869	170,602*	-40,276*	-43,140*	-1.3*	-2.2*
	KM with Exponential tail	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	0.10	48,235	461,996*	-45,103*	-46,147*	-1.5*	-2.3*
	KM with Weibull tail	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	0.08	47,010	565,197*	-44,514*	-45,346*	-1.5*	-2.3*
	KM with Log-normal tail	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	0.12	47,386	392,050*	-43,760*	-44,969*	-1.5*	-2.2*
	KM with Gamma tail	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	0.09	47,090	538,405*	-44,466*	-45,340*	-1.5*	-2.3*
	KM with Log-logistic tail	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	0.12	47,358	402,037*	-43,824*	-45,002*	-1.5*	-2.3*
	KM with Gompertz tail	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	0.29	48,746	170,678*	-40,178*	-43,034*	-1.3*	-2.2*
Distribution PFS	Exponential	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	0.09	59,018	645,357*	-56,275*	-57,189*	-1.9*	-2.9*
	Weibull	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	0.09	51,166	576,877*	-48,505*	-49,392*	-1.6*	-2.5*
	Log-normal	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	0.08	47,451	561,842*	-44,917*	-45,762*	-1.5*	-2.3*
	Log-logistic	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	0.08	46,549	552,459*	-44,022*	-44,864*	-1.5*	-2.2*

	Gompertz	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	0.08	46,559	563,118*	-44,079*	-44,906*	-1.5*	-2.2*
	KM with Exponential tail	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	0.09	45,394	507,668*	-42,711*	-43,606*	-1.4*	-2.2*
	KM with Weibull tail	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	0.09	45,574	523,873*	-42,964*	-43,834*	-1.4*	-2.2*
	KM with Log-normal tail	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	0.08	45,866	552,201*	-43,374*	-44,205*	-1.4*	-2.2*
	KM with Gamma tail	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	0.08	45,883	553,930*	-43,398*	-44,226*	-1.4*	-2.2*
	KM with Log-logistic tail	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	0.08	45,885	554,118*	-43,401*	-44,229*	-1.4*	-2.2*
	KM with Gompertz tail	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	0.08	45,925	558,277*	-43,457*	-44,280*	-1.4*	-2.2*
Distribution TTD	Exponential	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	0.08	55,120	656,895*	-52,603*	-53,442*	-1.8*	-2.7*
	Weibull	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	0.08	46,041	548,696*	-43,524*	-44,363*	-1.5*	-2.2*
	Log-normal	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	0.08	35,726	425,770*	-33,209*	-34,048*	-1.1*	-1.7*
	Log-logistic	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	0.08	35,866	427,431*	-33,348*	-34,188*	-1.1*	-1.7*
	Gompertz	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	0.08	37,358	445,211*	-34,840*	-35,679*	-1.2*	-1.8*
	KM with Exponential tail	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	0.08	57,250	682,279*	-54,733*	-55,572*	-1.8*	-2.8*
	KM with Weibull tail	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	0.08	46,510	554,282*	-43,992*	-44,832*	-1.5*	-2.2*
	KM with Log-normal tail	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	0.08	37,683	449,090*	-35,166*	-36,005*	-1.2*	-1.8*
	KM with Gamma tail	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	0.08	47,536	566,506*	-45,018*	-45,857*	-1.5*	-2.3*
	KM with Log-logistic tail	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	0.08	38,132	454,439*	-35,615*	-36,454*	-1.2*	-1.8*

	KM with Gompertz tail	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	0.08	36,104	430,267*	-33,586*	-34,425*	-1.1*	-1.7*
Pembro treatment duration assumption	Set it equal to atezo actual treatment duration up to two years, when pemro is discontinued	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	0.08	51,873	618,203*	-49,356*	-50,195*	-1.6*	-2.5*
Utility method	IMpower110 (On/Off treatment)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	0.03	47,059	1,433,902*	-46,075*	-46,403*	-1.5*	-2.3*
	IMpower110 (Proximity to death)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	0.11	47,059	441,166*	-43,859*	-44,926*	-1.5*	-2.2*
	Chouaid et al. 2013	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	0.08	47,059	591,720*	-44,674*	-45,469*	-1.5*	-2.3*
	Nafees et al. 2008	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	0.00	47,059	22,209,162*	-46,996*	-47,017*	-1.6*	-2.4*
	KEYNOTE-024	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	0.05	47,059	864,808*	-45,427*	-45,971*	-1.5*	-2.3*
Time horizon	5 years	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	0.12	55,315	453,856*	-51,658*	-52,877*	-1.7*	-2.6*
	10 years	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	0.14	49,792	363,872*	-45,687*	-47,055*	-1.5*	-2.4*
	15 years	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	0.10	47,830	456,515*	-44,687*	-45,735*	-1.5*	-2.3*
NMA	FE model	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	0.06	37,862	677,054*	-40,811*	-41,442*	-1.4*	-2.1*
Administration schedule	Q6W vs. Q4W atezo	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	0.08	48,555	578,658*	-46,038*	-46,877*	-1.5*	-2.3*
Capping of treatment benefit	Atezo OS treatment effect capped at 96 months	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	0.14	47,464	345,711*	-43,345*	-44,718*	-1.4*	-2.2*

	Atezo OS treatment effect capped at 60 months	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	0.2	48,022	234,870*	-41,888*	-43,933*	-1.4*	-2.2*
# Pembro PFS cap	Pembro PFS and OS cap at 60 months	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	0.08	47,403	597,908*	-45,025*	-45,818*	-1.5*	-2.3*
# half cycle correction	No half-cycle correction for drug and administration costs in the progression-free state	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	0.08	47,554	566,728*	-45,037*	-45,876*	-1.5*	-2.3*
# % of patients receiving subsequent therapy	50% of patients receive subsequent therapy	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	0.08	46,768	557,358*	-44,251*	-45,090*	-1.5*	-2.3*
# Utilities	Utility values for the whole ITT WT population	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	0.07	47,059	636,699*	-44,842*	-45,581*	-1.5*	-2.3*
# half cycle correction, % of patients receiving subsequent therapy and utilities	All three changes as suggested by the ERG and described in the previous three scenarios	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	0.07	47,263	639,448*	-45,045*	-45,784*	-1.5*	-2.3*

*pembro versus atezo: high ICER indicates atezo is worth funding; ICER, incremental cost-effectiveness ratio; LYs, life years; QALYs, quality-adjusted life years; KM, Kaplan Meier; NMA, network meta-analysis; HR, hazard ratio; FE, fixed effects; #, new scenario analyses provided

NMB, net monetary benefit, NMB is calculated as: *(incremental gain in QALYs x threshold) – incremental cost*. A positive incremental NMB indicats that the intervention is cost-effective compared with the alternative at the given willingness-to-pay threshold.;

NHB, net health benefit calculated as: *incremental gain in QALYs – (incremental cost / opportunity cost threshold).* A positive NHB implies that overall population health would be increased as a result of the new intervention

Negative NMB and negative NHB mean atezo is worth funding

References

1. Rittmeyer A, Barlesi F, Waterkamp D, Park K, Ciardiello F, von Pawel J, et al. Atezolizumab versus docetaxel in patients with previously treated non-small-cell lung cancer (OAK): a phase 3, open-label, multicentre randomised controlled trial. Lancet (London, England). 2017;389(10066):255-65.

2. Herbst RS, Baas P, Kim DW, Felip E, Perez-Gracia JL, Han JY, et al. Pembrolizumab versus docetaxel for previously treated, PD-L1-positive, advanced non-small-cell lung cancer (KEYNOTE-010): a randomised controlled trial. Lancet (London, England). 2016;387(10027):1540-50.

3. Borghaei H, Paz-Ares L, Horn L, Spigel DR, Steins M, Ready NE, et al. Nivolumab versus Docetaxel in Advanced Nonsquamous Non–Small-Cell Lung Cancer. New England Journal of Medicine. 2015;373(17):1627-39.

4. 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.

5. Rizvi NA, Cho BC, Reinmuth N, Lee KH, Luft A, Ahn M-J, et al. Durvalumab With or Without Tremelimumab vs Standard Chemotherapy in First-line Treatment of Metastatic Non-Small Cell Lung Cancer: The MYSTIC Phase 3 Randomized Clinical Trial. JAMA oncology. 2020;6(5):661-74.

6. Carbone DP, Reck M, Paz-Ares L, Creelan B, Horn L, Steins M, et al. First-Line Nivolumab in Stage IV or Recurrent Non–Small-Cell Lung Cancer. New England Journal of Medicine. 2017;376(25):2415-26.

7. Herbst RS, Giaccone G, de Marinis F, Reinmuth N, Vergnenegre A, Barrios CH, et al. Atezolizumab for First-Line Treatment of PD-L1–Selected Patients with NSCLC. New England Journal of Medicine. 2020;383(14):1328-39.

8. Reck M, Rodríguez-Abreu D, Robinson A, Hui R, Cs?szi T, Fülöp A, et al. Pembrolizumab versus Chemotherapy for PD-L1-Positive Non-Small-Cell Lung Cancer. New England journal of medicine. 2016;375(19):1823-33.

9. National Institute for Health and Care Excellence. Pembrolizumab for untreated PD-L1 positive metastatic non-small-cell lung cancer (CDF Review of TA447) [ID1349] 2018 [Available from: https://www.nice.org.uk/guidance/ta531/documents/committee-papers.

10. National Institute for Health and Care Excellence. Pembrolizumab for untreated PD-L1-positive metastatic non-small-cell lung cancer [TA531] 2018 [Date Accessed 18th February 2020]. Available from: https://www.nice.org.uk/guidance/ta531.

11. Antonia SJ, Villegas A, Daniel D, Vicente D, Murakami S, Hui R, et al. Durvalumab after Chemoradiotherapy in Stage III Non-Small-Cell Lung Cancer. N Engl J Med. 2017;377(20):1919-29.

12. Vennapusa B, Baker B, Kowanetz M, Boone J, Menzl I, Bruey J-M, et al. Development of a PD-L1 Complementary Diagnostic Immunohistochemistry Assay (SP142) for Atezolizumab. Appl Immunohistochem Mol Morphol. 2019;27(2):92-100.

13. Food and Drug Administration. VENTANA PD-L1 (SP142) Assay 2016 [Date Accessed 16th October 2020]. Available from: https://www.accessdata.fda.gov/cdrh_docs/pdf16/p160002c.pdf.

14. Food and Drug Administration. VENTANA PD-L1 (SP263) Assay 2017 [Date Accessed 16th October 2020]. Available from: https://www.accessdata.fda.gov/cdrh_docs/pdf16/P160046C.pdf.

15. Hirsch FR, McElhinny A, Stanforth D, Ranger-Moore J, Jansson M, Kulangara K, et al. PD-L1 immunohistochemistry assays for lung cancer: results from phase 1 of the blueprint PD-L1 IHC assay comparison project. 2017;12(2):208-22.

16. Tsao MS, Kerr KM, Kockx M, Beasley MB, Borczuk AC, Botling J, et al. PD-L1 Immunohistochemistry Comparability Study in Real-Life Clinical Samples: Results of Blueprint Phase 2 Project. Journal of thoracic oncology : official publication of the International Association for the Study of Lung Cancer. 2018;13(9):1302-11.

17. Herbst RS, de Marinis F, Giaccone G, Reinmuth N, Vergnenegre A, Barrios CH, et al. LBA1 Clinical efficacy of atezolizumab (atezo) in biomarker subgroups by SP142, SP263 and 22C3 PD-L1 immunohistochemistry (IHC) assays and by blood tumour mutational burden (bTMB): Results from the IMpower110 study. Annals of Oncology. 2019;30(Supplement_11).

18. S. Gadgeel, M. Kowanetz, W. Zou, F.R. Hirsch, K.M. Kerr, D.R. Gandara, et al. Clinical efficacy of atezolizumab (atezo) in PD-l1 subgroups defined by SP142 and 22C3 ihc assays in 2l+ NSCLC: Results from the randomized OAK study 2017 [Date Accessed 31st March 2020]. Available from: https://oncologypro.esmo.org/meeting-resources/esmo-2017-congress/Clinical-Efficacy-of-Atezolizumab-Atezo-in-PD-L1-Subgroups-Defined-by-SP142-and-22C3-IHC-Assays-in-2L-NSCLC-Results-From-the-Randomized-OAK-Study.

19. Reck M, Rodriguez-Abreu D, Robinson AG, Hui R, Csoszi T, Fulop A, et al. Updated Analysis of KEYNOTE-024: Pembrolizumab Versus Platinum-Based Chemotherapy for Advanced Non-Small-Cell Lung Cancer With PD-L1 Tumor

Proportion Score of 50% or Greater. Journal of clinical oncology : official journal of the American Society of Clinical Oncology. 2019;37(7):537-46.

20. Mok TSK, Wu YL, Kudaba I, Kowalski DM, Cho BC, Turna HZ, et al. Final analysis of the phase III KEYNOTE-042 study: Pembrolizumab (Pembro) versus platinum-based chemotherapy (Chemo) as first-line therapy for patients (Pts) with PD-L1-positive locally advanced/metastatic NSCLC. Annals of Oncology. 2019;30(Suppl 2):ii38.

21. Carcereny E, Felip E, Reck M, Patel J, Heist R, Balmanoukian A, et al. OA 17.02 Updated Efficacy Results From the BIRCH Study: First-Line Atezolizumab Therapy in PD-L1–Selected Patients With Advanced NSCLC. Journal of Thoracic Oncology. 2017;12(11):S1791-S2.

Atezolizumab monotherapy for untreated advanced non-small-cell lung cancer [ID1678]

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Rider on responsibility for report

The view 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.

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Contribution of authors

Clare Robertson summarised and critiqued the company's definition of the decision problem and the clinical effectiveness evidence reported within the company submission. Lorna Aucott critiqued the statistical methods and analyses presented in the company submission and checked all the numerical results related to the review of the clinical effectiveness evidence. Graham Scotland with assistance from Andrew Walker critiqued the cost-effectiveness evidence submitted by the company, checked their economic model, and conducted further sensitivity analyses. Paul Manson critiqued the methods used for identifying relevant studies and checked the search strategies presented in the company submission. Gillian Price provided clinical advice during the appraisal. Miriam Brazzelli coordinated all aspects of the appraisal and acted as lead for the clinical effectiveness side of the appraisal. Graham Scotland acted as lead for the cost-effectiveness side of the appraisal. All authors contributed to the writing of this report and approved its final version.

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List of main abbreviations

NSCLC	Non-small-cell lung cancer
EGFR	Epidermal growth factor receptor
ALK	Anaplastic lymphoma kinase
CS	Company submission
TPS	Tumour proportion score
HRQoL	Health-related quality of life
EMA	European Medicines Agency
OS	Overall survival
CCOD	Clinical cut-off date
TC	Tumour cells
PFS-INV	Investigator-assessed progression free survival
DOR	Duration of response
ORR	Objective response rate
PRO	Patient-reported outcome
EORTC-QLQ	European Organisation for the Research and Treatment of Cancer Quality of Life Questionnaire
IHC	Immunohistochemistry
ERG	Evidence Review Group
PFS	Progression free survival
IC	Immune cells
ICER	Incremental cost-effectiveness ratio
INV	Investigator-assessed
CI	Confidence interval
Atezo	Atezolizumab
ECOG	Eastern Cooperative Oncology Group
TRAE	Treatment-related adverse event
AESI	Adverse event of special interest

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 main aspects of the company submission and ERG's key issues

The company submission (CS) focuses on atezolizumab monotherapy as a first line treatment for patients with untreated advanced non-small-cell lung cancer (NSCLC). In a deviation from the NICE scope, the CS focuses on pembrolizumab monotherapy as the sole comparator treatment.

The key clinical effectiveness evidence is provided by one Phase III, multicentre, open-label randomised controlled trial (RCT), the IMpower110 trial. The IMpower110 trial compared atezolizumab with chemotherapy (cisplatin or carboplatin and pemetrexed, or gemcitabine) in PD-L1–selected (≥1% of tumour cells [TC] or immune cells [IC] covering ≥1% of the tumour area [TC1/2/3 or IC1/2/3]), chemotherapy-naive patients with Stage IV non-squamous or squamous NSCLC without EGFR mutations or ALK translocations. [redacted] The CS, therefore, considers data for 107 patients randomised to atezolizumab and 98 patients randomised to chemotherapy. The company reports data for the IMpower110 primary and exploratory analyses (clinical cut-off dates of September 2018 and February 2020, respectively). The primary endpoint of IMpower110 was overall survival (OS). Secondary endpoints included progression-free survival (PFS), objective response rate (ORR), duration of response (DOR).

In the absence of a direct head-to-head comparison with atezolizumab and pembrolizumab, the company conducted a network meta-analysis (NMA) of three RCTs: IMpower110, KEYNOTE-042 and KEYNOTE-024. The two KEYNOTE trials compared pembrolizumab monotherapy versus chemotherapy in 599 and 305 NSCLC patients, respectively. Different methods were used to determine PD-L1 expression across the three trials. PD-L1 expression in KEYNOTE-024 and KEYNOTE-042 was determined on TCs using the 22C3 immunohistochemistry (IHC) assay, whereas PD-L1 expression in IMpower110 was determined on TCs and ICs using the SP142 assay. KEYNOTE-024 only recruited patients whose tumours had the highest level of PD-L1 expression (TPS ≥50%), whereas IMpower110 and KEYNOTE-042 both recruited patients whose tumours had any PD-L1 expression. The company's NMA used a fractional polynomial approach (FP-NMA) for OS and PFS.

Table 1 presents a summary of the key issues identified by the ERG.

Table 1. Summary of the key issues

Issue number	Summary of issue	Report sections
Issue 1	Narrower population than that specified in the NICE final scope and choice of comparator	Sections 1.3 and 2.2.2
Issue 2	Atezolizumab effect over time	Sections 2.4 and 2.4.1
Issue 3	Assays comparability	Sections 2.3 and 2.4
Issue 4	Relative duration of treatment effects for the technology and its comparator	Section 3.2.6 and 5.3
Issue 5	Time on treatment with pembrolizumab relative to its PFS curve	Section 3.2.6
Issue 6	The validity of certain resource use frequencies in the progressive disease state of the model	Section 3.2.8

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. In the current appraisal, a network meta-analysis found no evidence to support a meaningful difference in efficacy between the technology (atezolizumab monotherapy) and it comparator (pembrolizumab monotherapy). Therefore,

the company presented a cost comparison case which assumed equal efficacy alongside a cost-effectiveness case that applied the best estimates of relative treatment effects from the NMA. For the cost-effectiveness case, hazard ratios for pemrolizumab versus atezolizumab were applied to the selected OS and PFS curves for atezolizumab in the context of a partitioned survival model.

Overall, the technology is modelled to affect QALYs by:

- affecting overall survival and progression free survival relative to pembrolizumab monotherapy.
- Increasing the assumed duration of treatment effect compared to pembrolizumab

Overall, the technology is modelled to affect costs by:

- Having different acquisition costs compared to its comparator.
- Increasing the treatment duration relative to its comparator
- Changing the timing of progression to subsequent therapy and the progressive disease state

The modelling assumptions that have the greatest effect on the ICER are:

- The relative treatment effects, in the form of hazard ratios for OS and PFS, for pembrolizumab (the comparator) versus atezolizumab (the technology)
- The assumed duration of the treatment effect on overall survival for the technology and the comparator relative to the common comparator in the NMA (platinum-based chemotherapy) - this being longer for the technology in the company's base case
- The assumption that time on treatment with pembrolizumab equates with PFS up until the two-year stopping rule applies.

1.3 The decision problem: summary of the ERG's key issues

The ERG's key issue related to the decision problem is detailed in Table X below.

Table 2. Issue 1. Narrower population than that specified in the NICE final scope and choice of comparator

Report section	Sections 1.3 and 2.2.2
Description of issue and why the ERG has identified it as important	[redacted], the CS focuses on the IC3 (infiltrating immune cell PD-L1 expression >10%) or TC3 (tumour cell PD-L1 expression ≥50%) subpopulation; but do not report a clear breakdown of the number of patients who met IC3 and TC3 criteria. Since the NICE recommendation for pembrolizumab in untreated PD-L1 positive metastatic NSCLC is conditional on a tumour proportion score of at least 50% (TA531), the ERG is currently unclear whether pembrolizumab is the relevant comparator for the IMpower110 IC3 patients. However, in IMpower110 the number of patients in this category is likely to be small. The company also provide an exploratory analysis to assess the relative treatment effect in IMpower110 for high PD-L1 expression groups defined by different assays, including TPS ≥ 50% as defined by the 22C3 assay (used to determine PD-L1 expression in the KEYNOTE trials included in the NMA). This analysis showed a very similar magnitude of benefit for atezolizumab in both groups.
What alternative approach has the ERG suggested?	Proportions of both the TC3 and IC3 subpopulations should have been given to identify the scale of the issue.
What is the expected effect on the cost-effectiveness estimates?	This uncertainty leads to further uncertainty in the NMA that the company conducted, which feeds through to uncertainty surrounding the economic case.
What additional evidence or analyses might help to resolve this key issue?	As indicated in Table 4, Issue 3 below, a sensitivity analysis using the 22C3 TPS ≥ 50% subgroup (or TC3 subgroup) of IMpower110 in the NMA, could have helped to reduce uncertainty regarding the comparative efficacy of the two treatments in those who are eligible for pembrolizumab monotherapy according to the wording of the NICE recommendation in TA531 ('with at least a 50% tumour proportion score').

1.4 The clinical effectiveness evidence: summary of the ERG's key issues

The ERG's key issues that relate to the clinical effectiveness evidence are detailed below in Tables 3 and 4.

Table 3. Issue 2 Atezolizumab effect over time

Report section	Sections 2.4 and 2.4.1
Description of issue and why the ERG has identified it as important	The company report log cumulative hazard plots for the trials included in their indirect comparison, which suggest that the assumption of proportional hazards may not have been met. The company tried to adopt a Fractional Polynomial (FP) approach to accommodate the possible changing relative hazards over time; but in relation to the atezolizumab pembrolizumab comparison, the direction of the effect increasingly appears to favour pembrolizumab over time. However, the comparison is complicated by different durations of follow up in the respective trials, dwindling sample sizes with increasing follow up, varying degrees of cross-over in the comparator arms of the different trials, and possibly varying degrees of immunotherapy re-challenge in the treatment arms of the trials. The above issues make it very difficult to determine if or how the relative efficacy of pembrolizumab and atezolizumab changes over time. See also issue 6 in relation to this point.
What alternative approach has the ERG suggested?	The ERG do not have a suggested alternative approach; but note that it is possible that the comparability between atezolizumab and pembrolizumab may not hold with time.
What is the expected effect on the cost-effectiveness estimates?	The company chose to use the standard random effects NMA HRs for cost-effectiveness. The ERG agree that this produces the most plausible outputs but have some remaining concern about potential for longer-term difference in effect.
What additional evidence or analyses might help to resolve this key issue?	The ERG is of the opinion that without additional and more homogeneous data between the two treatments, this uncertainty cannot be solved.

Table 4. Issue 3. Assays comparability

Report section	Sections 2.2.2 and 2.3
Description of issue and why the ERG has identified it as important	IMpower110 used assay SP142 to select IC3 (infiltrating immune cell PD-L1 expression >10%) or TC3 (tumour cell PD-L1 expression ≥50%) patients while the KEYNOTE trials used assay 22C3 to select patients with tumour proportion score ≥50%. The 22C3 assay is the most commonly used assay in UK clinical practice according to clinicians consulted by the company. The concern is how this translates into the NMA estimates, which should be developed on comparable populations across studies. IMpower110 also conducted a subgroup analysis using the 22C3 assay. While the atezolizumab/chemotherapy HRs were similar across assays, there is still a concern that the sample populations might not be fully matched. This issue relates to Issue 1 described above.
What alternative approach has the ERG suggested?	Acknowledging the double selection issue for IMpower110, selection of participants to inform the NMA could have been based on similar criteria (preferably the 22C3 assay given it is the more commonly used) or, if not possible, the proportions of both the TC3 and IC3 patients should have been given.
What is the expected effect on the cost-effectiveness estimates?	Any bias driven by lack of comparability between the IMpower110 and KEYNOTE trials populations will correspondingly lead to bias in the cost-effectiveness model.
What additional evidence or analyses might help to resolve this key issue?	IMpower110 also provides information on PD-L1 expression assed using the 22C3 assay and, therefore, a sensitivity analysis might be possible. To quantify similarity, it would be useful to identify the proportions of the TC3 and IC3 patients, separately.

1.5 The cost-effectiveness evidence: summary of the ERG's key issues

In addition to the uncertainty surround the hazard ratios from the NMA applied in the economic model, the ERG has three main issues with the company's cost-effectiveness case, as detailed in Tables 5, 6 and 7 below.

Table 5. Issue 4: the relative duration of treatment effects for the technology and its comparator

Report section	Sections 3.2.6 and 5.3
Description of issue and why the ERG has identified it as important	The company base case applies a treatment stopping rule for pembrolizumab at two years, in line with its NICE recommendation in TA521. Correspondingly they assume that this leads to loss of efficacy relative to chemotherapy from five years onward. For atezolizumab, no stopping rule is applied in line with its clinical evidence base, and therefore no loss of efficacy is assumed over the time horizon of the model. This capping of the treatment effect duration for pembolizumab is uncertain and not based on observed data, as is the added benefit of continued treatment with atezolizumab beyond two years. The capping of the pembrolizumab treatment effect, is an important determinant of the expected QALY difference between the two medicines in the cost-effectiveness model, and so the point estimate of the ICER is sensitive to changes in this assumption.
What alternative approach has the ERG suggested?	The ERG is not able to propose an alternative assumption with confidence since there are no long-term follow-up data (beyond five years) available for either medicine in this indication. Scenario analyses were performed to assess the impact of the assumption.
What is the expected effect on the cost-effectiveness estimates?	Assuming the treatment effect for permrolizumab is maintained further into the future, increases the expected QALY gain versus atezolizumab, and reduces its ICER. The ICERs in the report are not appropriate for decision making because they do not include a confidential PAS price for pembrolizumab. To give an indication of impact, increasing the treatment effect duration for pembrolizumab from 5 years to 8 years increases the deterministic point estimate of the QALY gain from 0.08 to 0.197 versus atezolizumab. However, the QALY difference remains uncertain given the uncertainty around the hazard ratios driving the difference in effects.
What additional evidence or analyses might help to resolve this key issue?	It is not an easy point to resolve given lack of longer term data available, but a more considered discussion of the assumption in light of all the available evidence and expert opinion may help to better inform the validity of the assumption.

Table 6. Issue 5: the time on treatment with pembrolizumab relative to its PFS curve

Report section	Section 3.2.6 (Treatment duration)
Description of issue and why the ERG has identified it as important	As no data were available for time on treatment with pembrolizumab, the company assumed this would follow progression free survival up to the stop rule at 2 years. However, data from the consort diagrams of the relevant KEYNOTE trials show that some patients stop treatment prior to progression and prior to two years (either due to toxicity or choice). Thus the company's assumption may overestimate treatment costs for pembrolizumab.
What alternative approach has the ERG suggested?	The ERG identified a study that provides Kaplan Meier time on treatment data for the relevant subgroups of KEYNOTE-042 which can be compared with the PFS Kaplan Meier data from the same data cut. This does suggest that time on treatment fall below PFS over the first year of follow-up, but then crosses it and runs above or very close to it in the second year. To assess the impact, the ERG has used the relative difference between the PFS and time on treatment curves from KEYNOTE-042, to adjust time on treatment in the model relative to selected PFS curve.
What is the expected effect on the cost-effectiveness estimates?	The change has a modest impact on pembrolizumab drug costs and the incremental cost of pembrolizumab compared to atezolizumab, reducing its ICER: from £560,832 per QALY gained in the company base case to £527,006 (including atezolizumab PAS, with pembrolizumab at list price).
What additional evidence or analyses might help to resolve this key issue?	Exploration of more formal methods of comparing available pembrolizumab PFS and time on treatment data, such as curve fitting to reconstructed patient level data, could better inform the relationship between the two outcomes and provide a more precise approach for the model.

Table 7. Issue 6: The validity of certain resource use frequencies in the progressive disease state of the model

Report section	Section 3.2.8 (Health care resource use)
Description of issue and why the ERG has identified it as important	The company referenced sources for GP home visits and occupational therapist visits in the progressive disease state of the model, which the ERG has been unable to trace. In addition, the ERGs clinical advisor felt that these seemed very high at 26.06 per year for application throughout time spent time in the PD state. These costs have an impact on the ICER resulting from differences in PFS between the alternatives. Those in the pembrolizumab arm spend a greater duration of time in this state of the model in the company base case.
What alternative approach has the ERG suggested?	Although the ERG has not identified an alternative source for these parameters, it prefers to reduce the frequencies based on clinical advice received.
What is the expected effect on the cost-effectiveness estimates?	Reducing the frequency of these visits by 50% has a modest impact on the incremental cost for pembrolizumab versus atezolizumab and reduces its ICER accordingly.
What additional evidence or analyses might help to resolve this key issue?	The ERG acknowledges the uncertainty around its alternative approach for these parameters, and would welcome some more clinical validation of the company's resource use frequencies as set out in Table 53 of the company submission, document B.

1.6 Summary of ERG's preferred assumptions and resulting ICER

In addition to the issues raised, the ERG identified several other minor issues that it prefers to revise. The ERGs preferred assumptions are the same as the company's except for the following:

1. No half-cycle correction for time on treatment (for both drugs), to ensure all patients receive treatment in the first cycle of the model.
2. Adjustment of pembrolizumab PFS curve to ensure it always remains below OS. This was to correct a minor issue of the PFS curve crossing the OS curve in the tail of the distribution in the company's base case (see section 4.3).
3. Pembrolizumab time to subsequent chemotherapy based on extrapolated PFS rather than applied immediately to all who discontinue at the two-year stopping point (section 4.1).
4. Pembrolizumab time on treatment adjusted relative to PFS using data from KEYNOTE-042 (as a proposed solution to issue 5 above).

5. Assuming 50% receive subsequent therapy rather than 100%, in line with the company's clinical expert opinion that they received at the clarification stage.
6. Assuming a 50% reduction in GP home visits and therapist visits in the progressive disease health state of the model, given the ERGs inability to identify the companies applied frequencies in the stated sources and the ERGs clinical expert advice.

The impact of each individual change is documented in Table 8. These results are not appropriate for decision making as they do not include the PAS price available for pembrolizumab. A confidential appendix with the appropriate PAS price for pembrolizumab will be provided for the committee.

Table 8 Summary of the ERGs preferred assumptions and ICER (PAS price for atezolizumab, list price for pembrolizumab)

Scenario	Incremental cost (atezo versus pembro)	Incremental QALYs (atezo versus pembro)	ICER (change from company base case)
Company base case	-47,059	-0.084	560,832
1. No half cycle correction for time on treatment	-47,554	-0.084	566,728
2. Pembro PFS adjusted to always remain below OS in the tail of the distribution	-47,066	-0.084	561,530
3. Pembrolizumab time to subsequent chemotherapy based on extrapolated PFS	-46,770	-0.084	557,388
4. Pembrolizumab time on treatment adjusted relative to PFS using data from KEYNOTE-042	-44,221	-0.084	527,006
5. Assume 50% receive subsequent therapy rather than 100%	-46,768	-0.084	557,358
6. Assume 50% reduction in GP home visits and therapist visits in the progressive disease health state	-46,171	-0.084	550,242
ERG base (all combined changes)	-43,715	-0.084	521,544
ERG base (probabilistic)*	-43,080	-0.14	309,723

*Caveat: PSA does not include distributions on the relative hazards used to adjust the pembrolizumab time on treatment curve relative to its PFS curve in change number 4.

Rather than factor in changes to the assumptions about treatment effect durations in the ERG base case, several additional scenarios were conducted to explore the impact of this using the ERG base case as the reference point. These are presented in section 5.3 of the report.

As indicated, the company also provided a cost-comparison analysis which assumes equal efficacy between treatment arms. The committee may find this appropriate for decision making should they believe there is sufficient evidence to assume equal efficacy between the alternatives in the relevant population.

1 INTRODUCTION AND BACKGROUND

1.1 Introduction

The relevant health condition for this submission is untreated advanced non-small-cell lung cancer. The company's description of the prevalence, symptoms and complications of non-small-cell lung cancer (NSCLC) generally accurate and in line with the decision problem. The relevant intervention for this submission is atezolizumab monotherapy as a first line treatment.

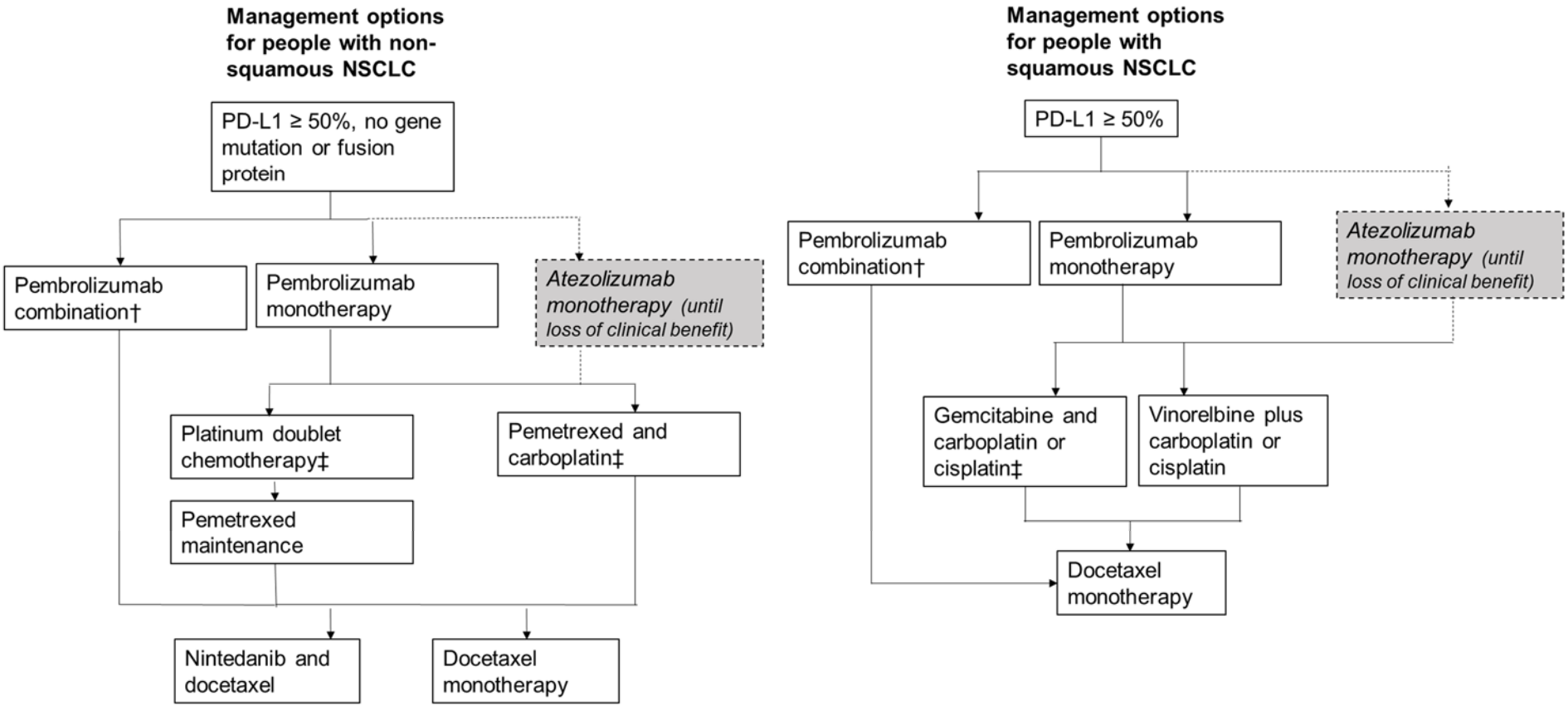
1.2 Background

Lung cancer is the UK's third most common cancer with a yearly incidence of approximately 47,200 cases.[1] NSCLC is the predominant subtype of lung cancer, accounting for 88% of all lung cancer cases in the UK in 2018.[2] NSCLC can be further divided into two major histologic types: non-squamous, representing over half of all NSCLC, and squamous, which accounts for approximately 25-30% of NSCLC cases.[3] In 2016, 70% of patients diagnosed with lung cancer in the UK had stage III or IV disease.[4] More than half of NSCLC patients are diagnosed with distant disease, which contributes to poor survival prognosis, along with advanced stage of disease at time of initial diagnosis, poor performance status and history of unintentional weight loss.[5] The 5-year survival of all treated and untreated lung cancer patients with stage IV disease is 3%, and 5-year survival rates for patients with distant metastatic NSCLC is only 6%.[6, 7] Advanced stage NSCLC has a negative impact on health-related quality of life (HRQoL). Disease-related symptoms include pain, fatigue, dyspnea, and cough, which can increase in frequency and intensity during disease progression.[8-12]

Molecular testing for epidermal growth factor receptor (EGFR) mutations, anaplastic lymphoma kinase (ALK) rearrangements, ROS1, or PD-L1 (programmed death-ligand 1) expression is recommended for all patients with NSCLC to inform treatment options. Determination of PD-L1 tumour expression is used to judge suitability for checkpoint inhibitor therapy and several immunohistochemistry (IHC) assays are routinely used in UK practice to identify patients who would benefit from therapy, including 22C3 (Dako), SP142 (Ventana) and SP263 (Ventana).[13, 14] In a global observation study of 2368 patients, assessed using the 22C3 test, 22% of patients had high PD-L1 expression (tumour proportion score [TPS] $\geq$50%), 52% had TPS $\geq$1%, and 48% had TPS<1%.[15] Atezolizumab, is a humanized IgG monoclonal antibody, which attaches itself to the PD-L1 protein on cancer cells, and reduces its effects by increasing the ability of the immune system to attack cancer cells and slow disease progression.[16]

The company describes the management of metastatic squamous and non-squamous NSCLC, whose tumours have PD-L1 expression ≥50%, and who do not have EGFR mutant or ALK positive NSCLC in section B.1.3.2 of the CS, and presents the current clinical care pathway based on the current NICE guideline NNG122 in Figure 1, Document B. This pathway is reproduced by the ERG as Figure 1.[17]

Figure 1. First-line treatment algorithm for adult patients with metastatic non-squamous and squamous NSCLC whose tumours have a PD-L1 expression ≥50% and who do not have EGFR mutant or ALK-positive NSCLC (including atezolizumab positioning)[17]



† Available via the Cancer Drugs Fund

‡ This combination/some of these combinations of drugs do not have a UK marketing authorisation for this indication

The grey box indicates the proposed positioning of atezolizumab

1.3 Critique of company's definition of decision problem

A summary of the company's decision problem in relation to the NICE final scope is presented in Table 9. A critique of how the company's economic modelling adheres to the NICE reference case is provided in Chapter 3.

Table 9 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 non-squamous or squamous untreated metastatic non-small cell lung cancer (NSCLC) with PD-L1 positive tumour expression and without epidermal growth factor receptor (EGFR)- or anaplastic lymphoma kinase (ALK)-positive mutations.	Adult patients with [redacted].	Population in accordance with anticipated licence and trial population, i.e. metastatic NSCLC patients with high PD-L1 expression.	The CS addresses a narrower population than that specified in the NICE final scope and focuses on adult patients with [redacted]. The company state that the population addressed in the CS is in accordance with the anticipated licence for atezolizumab. The ERG clinical expert is of the opinion that patients with high PD-L1 status with a high immune background are a select group that are most likely to respond well to the study drug.
Intervention	Atezolizumab	Per final scope.	N/A	The intervention described in the CS matches that described in the NICE final scope. Atezolizumab is administered intravenously at a recommended dose of: 840 mg every two weeks, or 1200 mg every three weeks, or 1680 mg every four weeks. The initial dose should be administered over 60 minutes but, if the first infusion is well-tolerated, subsequent infusions may be delivered over 30 minutes. Treatment is recommended until loss of clinical benefit or the patient experiences unmanageable toxicity.[13] Atezolizumab is currently approved by the European Medicines Agency

				(EMA) for several indications, and an application to extend the licence [redacted] was submitted to the EMA in November 2019. The company expect marketing authorisation for this indication in [redacted]. The company provide details of atezolizumab in section B.1.2 and Appendix C of the CS.
Comparator	For people whose tumours express PD-L1 with at least a 50% tumour proportion score: • Pembrolizumab For people with non-squamous NSCLC whose tumours express PD-L1 with a tumour proportion score below 50%: • Atezolizumab plus bevacizumab, carboplatin and paclitaxel • Chemotherapy (docetaxel, gemcitabine, paclitaxel or vinorelbine) in combination with a platinum drug (carboplatin or cisplatin) o with or without pemetrexed maintenance treatment For people with adenocarcinoma or large-cell carcinoma whose tumours express PD-L1 with a tumour proportion score below 50%: • Pemetrexed in combination with a	Pembrolizumab	Per final scope, pembrolizumab is the appropriate comparator with respect to the patient population, i.e. metastatic NSCLC patients with high PD-L1 expression.	The CS addresses a narrower selection of comparators than that specified in the NICE final scope. The company collected insights on prescribing patterns from 24 lung cancer consultants from NHS hospitals in England and Scotland. These data are presented in Table 3, Document B of the CS. The data indicate that pembrolizumab monotherapy is the dominant first-line standard of care, followed by pembrolizumab in combination with chemotherapy (through the Cancer Drug Fund), and with only a small number of patients being prescribed chemotherapy alone. The ERG clinical expert agrees with the company's description of the current UK clinical management options and prescribing patterns. The ERG note that for IMpower110, the company does not report a clear breakdown of the number of patients who met the IC3 definition (infiltrating immune cell PD-L1 expression $\geq$10%) and those who met the TC3 definition (tumour cell PD-L1 expression $\geq$50%) in the main CS (Documents A, B and Appendices). Since the NICE recommendation for pembrolizumab in untreated PD-L1 positive metastatic NSCLC is

	platinum drug (carboplatin or cisplatin) o with (following cisplatin-containing regimens only) or without pemetrexed maintenance treatment For people with squamous NSCLC whose tumours express PD-L1 with a tumour proportion score below 50%: Chemotherapy (gemcitabine or vinorelbine) in combination with a platinum drug (carboplatin or cisplatin)			conditional on a tumour proportion score of at least 50% (TA531), the ERG is currently unclear whether pembrolizumab is the relevant comparator for IC3 patients. However, the number of patients in IMpower110 in this category is likely to be small. The company also provide an exploratory analysis to assess the relative treatment effect in IMpower110 for high PD-L1 expression groups defined by different assays, including TPS ≥ 50% as defined by the 22C3 assay (used to determine PD-L1 expression in the KEYNOTE trials included in the NMA). This analysis showed a very similar magnitude of benefit for atezolizumab in both groups.
Outcomes	The outcome measures to be considered include: • overall survival • progression-free survival • response rate • adverse effects of treatment health-related quality of life	Per final scope.	The outcome measures to be considered include: • overall survival • progression-free survival • response rate • adverse effects of treatment health-related quality of life	The outcomes in the CS matches the outcomes described in the final scope. The company reports primary overall survival (OS) analysis with a clinical cut-off date (CCOD) of 10th September 2018 from the IMpower110 trial, which is the key source of evidence submitted by the company. The company also reports an exploratory OS analysis with the CCOD of 4th February 2020. The exploratory analysis is of long-term follow-up data [redacted].
Subgroups	If evidence allows, subgroup analysis by: • Level of PD-L1 expression Squamous and non-squamous status	No subgroups considered.	The population under consideration for this appraisal is already limited to the highest level of PD-L1 expression and cannot be subgrouped further. The IMpower110	The ERG clinical expert has indicated that, while squamous and non-squamous patients are treated differently for some treatment options, these patients are not treated differently for immunotherapy. The ERG, therefore, has no concerns with the company decision to not carry out subgroup analysis by squamous and non-squamous patient status.

			study included patients with both squamous and non-squamous histology. However, the trial was not statistically powered to assess efficacy in either subgroup. Consequently, subgroup analysis by histology is not appropriate.	
Special considerations including issues related to equity or equality	N/A	N/A	N/A	The ERG agrees with the company that there are no anticipated equality issues related to atezolizumab

2 CLINICAL EFFECTIVENESS

2.1 Critique of the methods of review(s)

Full details of the methods used to identify and select the clinical evidence relevant to this appraisal are reported in Appendix D of the CS. The ERG appraisal of the company's systematic review methods is summarised in Table 10 below.

Table 10. ERG appraisal of the systematic review methods presented in the CS

Review process ERG	ERG response	Comments
Were appropriate searches (e.g., search terms, search dates) performed to identify all relevant clinical and safety studies?	Yes	The CS provides full details of the searches used to identify the studies for the clinical effectiveness review. The search strategies include relevant controlled vocabulary and text terms with appropriate use of Boolean operators and are fully reproducible. Details provided in Appendix D.1 of the CS.
Were appropriate bibliographic databases/sources searched?	Yes	Sources included Embase, Medline, and CENTRAL for primary research, CDSR and HTA organisations for evidence syntheses, and relevant conference proceedings. Details provided in Appendix D.1.1.1 of the CS.
Were eligibility criteria consistent with the decision problem outlined in the NICE final scope?	Yes	See Table 1, Appendix D.1.1 of the CS.
Was study selection conducted by two or more reviewers independently?	Yes	See Appendix D.1.1.3 of the CS.
Was data extraction conducted by two or more reviewers independently?	Yes	See Appendix D.1.15 of the CS
Were appropriate criteria used to assess the risk of bias of identified studies?	Yes	See Table 39, Appendix D.1.3 of the CS.
Was risk of bias assessment conducted by two or more reviewers independently?	Yes	Two reviewers independently assessed the risk of bias for each included study using the Cochrane Risk of Bias tool. Any disagreements were

		resolved through discussion or by consulting a third reviewer
Was identified evidence synthesised using appropriate methods?	Yes	NMA: See Section B.2.9.2 to B.2.9.4 , Appendix D.1.4 Appendix D.1.5 for methods and B.2.9.5 to B.2.9.7, D.1.5 for results. Heterogeneity was assessed in B.2.9.8 and D.1.6 Assumptions also investigated.

The ERG conducted a quality assessment of the methods used by the company for the systematic review of clinical evidence using the Centre for Review and Dissemination (CRD) criteria. The results are presented in Table 11.

Table 11. Quality assessment of the company's systematic review of clinical effectiveness evidence

CRD quality item	Yes/No/Unclear
1. Are any inclusion/exclusion criteria reported relating to the primary studies, which address the review question?	Yes
2. Is there evidence of a substantial effort to search for all of the relevant research?	Yes
3. Is the validity of included studies adequately assessed?	Yes
4. Are sufficient details of the individual studies presented?	Yes
5. Are the primary studies summarised appropriately?	Yes

2.1.1 Critique of evidence synthesis methods

Based on a systematic literature review, the company identified 12 relevant studies. The key evidence for the efficacy and safety of atezolizumab first-line monotherapy in advanced NSCLC is provided by one Phase III, multicentre, open-label randomised controlled trial, the IMpower110 trial.[18] In the absence of a direct head-to-head

comparison with atezolizumab and pembrolizumab, the company performed a series of indirect comparisons based on a connected network of the 12 RCTs.

2.2 Critique of trials of the technology of interest, the company's analysis and interpretation (and any standard meta-analyses of these)

2.2.1 Included studies

Details of the key clinical effectiveness evidence are provided in Table 4, Document B, of the CS and are reproduced by the ERG as Table 12.

Table 12. Key clinical effectiveness evidence

Study	IMpower110
Study design	Randomised, Phase III, global, multicentre, open-label study
Population	PD-L1–selected (≥1% of TC or IC covering ≥1% of the tumour area [TC1/2/3 or IC1/2/3]*), chemotherapy-naive patients with Stage IV non-squamous or squamous NSCLC without EGFR mutations or ALK translocations
Intervention	Atezolizumab
Comparator(s)	Cisplatin or carboplatin and pemetrexed (non-squamous) or gemcitabine (squamous)
Application for marketing authorisation	Yes
Used in the economic model	Yes
Rationale for use/non-use in the model	The IMpower110 trial comprises the relevant population, intervention, comparators and outcomes

IC: immune cells; NSCLC: non-small cell lung cancer; TC: tumour cells

The IMpower110 trial compared atezolizumab with cisplatin or carboplatin and pemetrexed, or gemcitabine in PD-L1–selected (≥1% of TC or IC covering ≥1% of the tumour area [TC1/2/3 or IC1/2/3]), chemotherapy-naive patients with Stage IV non-squamous or squamous NSCLC without EGFR mutations or ALK translocations. Patients with non-squamous disease were randomized 1:1 to receive either atezolizumab alone or pemetrexed in combination with cisplatin or carboplatin. Patients with squamous disease were randomized 1:1 to receive either atezolizumab alone or gemcitabine in combination with cisplatin or carboplatin. The intended

number of treatment cycles of chemotherapy (four or six cycles) was specified by the investigator prior to study randomization. Crossover from chemotherapy to atezolizumab was not allowed. Atezolizumab treatment continued as long as patients were experiencing clinical benefit, as assessed by the investigator, or until unacceptable toxicity or death.

[redacted] The CS, therefore, considers data for 107 patients randomised to atezolizumab and 98 patients randomised to chemotherapy in IMpower110. The groups were well balanced for participant baseline characteristics, including participant demographics, ECOG performance status, HRQoL, and squamous/non-squamous status. Slightly more participants were aged under 65 years in the atezolizumab arm and the number of participants who had a previous history of tobacco use was higher in the atezolizumab arm compared with the chemotherapy arm (78/107 [72.9%] versus 54/98 [55.1%]); however, when combined with current smoking status, the ERG believe this difference is unlikely to influence the trial results (91.6% of participants had current or previous tobacco use in the atezolizumab compared with 84.7% in the chemotherapy arm). Participants in both arms were mainly white, male, with a history of tobacco use and had a baseline ECOG performance status of 1. The ERG clinical expert's opinion is that trial participants are representative of patients seen in UK practice.

The company presents details of the participant demographics and baseline characteristics in Table 6, Document B, of the CS. The ERG provide details of the demographic and baseline characteristics of patients enrolled in IMpower110, along with those of patients enrolled in the KEYNOTE-042 and KEYNOTE-024 trials, in Table 17 of this report.

The primary endpoint of IMpower110 was OS. An interim analysis was planned for the TC3 or IC3 subpopulation when approximately 96 OS events and an event-patient ratio of 45% had occurred. If the OS interim analysis was not statistically significant, the final analysis would be conducted when approximately 135 OS events had occurred in the subpopulation, and if this analysis was statistically significant, OS would be tested at planned interim and final analyses in the TC2/3 or IC2/3 and TC1/2/3 or IC1/2/3 subpopulations. The final investigator-assessed progression-free survival (PFS-INV) is presented without formal statistical testing as the company

state that secondary endpoint of PFS can only be tested formally when the primary endpoint is positive in all three PD-L1 subgroups. At clarification, the company indicated that this strict regime was put in place to control for type 1 errors at 5% level in response to several protocol participant eligibility change over the course of recruitment. Further, PFS was dropped to be a secondary outcome and tested only once OS was completed. The ERG are not entirely convinced of this approach.

The methodological quality of the IMpower110 trial was judged by the company to be at low risk of bias for all domains with the exception of blinding of outcome assessors, which was judged to be unclear (section section B.2.5 of the CS). The ERG checked the quality assessment against the study protocol (provided as an appendix to the Herbst et al 2020 New England Journal of Medicine article) and agree with the company's assessment of the methodological quality of the IMpower110 trial.[19]

2.2.2 Primary and secondary efficacy endpoints in IMpower110

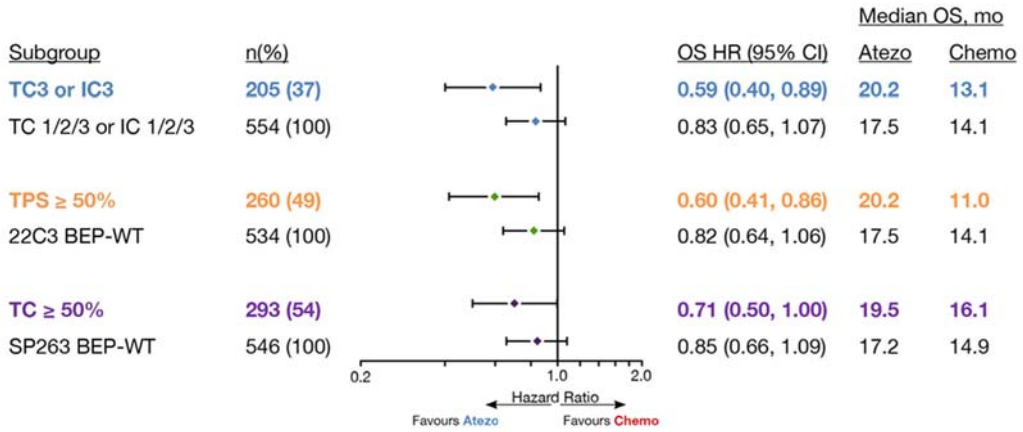
An overview of the efficacy results for the TC3 or IC3 subpopulation is presented in Table 13 below (reproduced from Table 8, Section B.2.6.1 of the CS).

Primary efficacy endpoint: overall survival

The median duration of survival follow-up was 15.7 months, with [redacted] and [redacted] death events occurring in the atezolizumab and chemotherapy arms, respectively at the time of the clinical cutoff date of 10th September 2018. Treatment with atezolizumab was associated with a 41% reduction in the risk of death compared with chemotherapy. The Kaplan-Meier estimated median OS was 7.1 months longer in the atezolizumab arm compared with the chemotherapy arm (20.2 months versus 13.1 months, respectively; stratified HR: 0.59 [95% CI, 0.40, 0.89]; p=0.0106).

The company presents OS by key subgroups within the IMpower110 TC3/IC3 subpopulation in section B.2.6.7 and Appendix G of the CS. OS favoured atezolizumab compared with chemotherapy across almost all subgroups, including patients with high PD-L1 expression across all PD-L1-IHC assays. The company present OS by the different IHC assays in Figure 14 of the CS, and this is reproduced by the ERG as Figure 2 below. The company state that improvement in OS in the atezolizumab arm compared with the chemotherapy arm is demonstrated across the IHC assays.

Figure 2: OS by high PD-L1 expression subgroups (defined by the SP142, SP263, and 22C3 assays)[20]



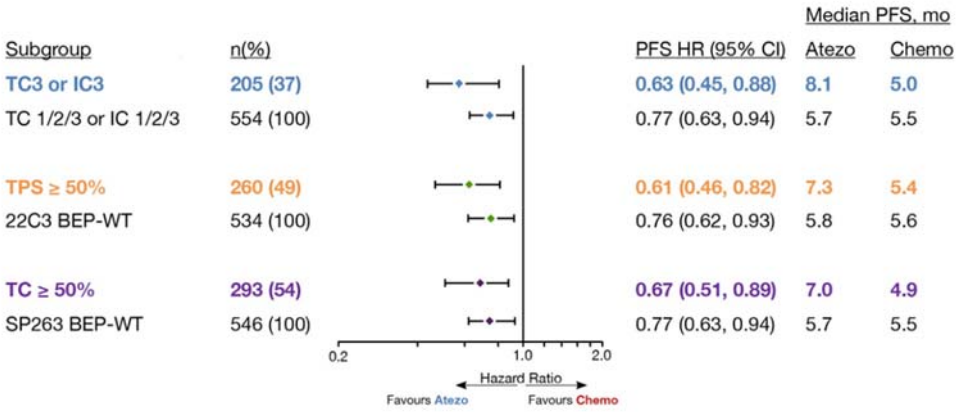
BEP: biomarker-evaluable population; CI: confidence interval; HR: hazard ratio; IC: immune cells; OS: overall survival; TC: tumour cells; TPS: tumour proportion score
Colour code: blue = SP142, orange = 22C3, purple = SP263
Note:

- TC1/2/3 or IC1/2/3 population represents the SP142-enrolled IMpower110 population without EGFR or ALK genetic alterations
- TC3 or IC3 = TC ≥ 50% or IC ≥ 10% PD-L1
- Stratified HRs for SP142 and unstratified HRs for 22C3 and SP263

Secondary endpoints: progression-free survival, objective response rate, duration of response

The company state that PFS-INV could not be formally tested as OS had not reached statistical significance in the TC2/3 or IC2/3 subpopulation at the time of the clinical cutoff date of 10th September 2018. The company state that the p-values for PFS reported in the CS should be treated as descriptive only. At September 2018 the median PFS was 3.1 months longer in the atezolizumab arm than in the chemotherapy arm (5.0 months versus 8.1 months, respectively; stratified HR 0.63 [95% CI: 0.45, 0.88]). The company present their analysis of PFS in the PD-L1 subpopulations by the different IHC assays in Figure 27 of the CS appendices, and this is reproduced by the ERG as Figure 3 below.

Figure 3 PFS in PD-L1 subpopulations by different IHC assays[20]



Stratified HRs for SP142 TC3 or IC3-WT; unstratified HRs for all other subgroups.

Atezo: atezolizumab; BEP: biomarker-evaluable population; chemo: chemotherapy; HR: hazard ratio; PFS: progression-free survival; TC: tumour cell; WT: wild type

By considering the hazard ratios alone, the different assay give very similar results. However, the comparator groups in each of the trials may differ depending on the assay used, thereby not fully comparing like with like. While assuming that these different methods of assessing PD-L1 are comparable the company do acknowledge this limitation by suggesting that 'Sensitivity analyses may be possible with PD-L1 expression reassessed using 22C3 assay in IMpower110'. The ERG is of the opinion that such sensitivity analyses would have been beneficial. A break down further of the IC3 group would also be relevant.

Investigator-assessed confirmed ORR was higher in the atezolizumab arm compared with the chemotherapy arm (38.3% [95% CI: 29.08, 48.22] versus 28.6% [95% CI: 19.90, 38.58]), as measured by RECIST version 1.1 criteria.

[redacted]. The median duration of response was not reached in the atezolizumab arm while the chemotherapy arm was 6.7 months at the time of the analysis.

Table 13. Overview of efficacy in the TC3 or IC3 subpopulation of IMpower110[21]

Parameter	Atezolizumab	Chemotherapy
Primary Endpoint: Overall Survival		
TC3 or IC3 subpopulation	n = 107	n = 98
Patients with event (%)	[redacted]	[redacted]
Median duration of survival (95% CI) (months)		
Median OS, months	20.2	13.1
Stratified Hazard Ratio (95% CI)	0.59 (0.40, 0.89)	
p-value (Stratified log-rank)	0.0106	
Secondary Endpoints		
Progression-Free Survival		
TC3 or IC3 subpopulation	n =107	n = 98
Patients with event (%)	[redacted]	[redacted]
Median duration of PFS-INV (95% CI) (months)	8.1 (6.8, 11.0)	5.0 (4.2, 5.7)
Stratified Hazard Ratio (95% CI)	0.63 (0.45, 0.88)	
p-value (Stratified log-rank)	0.007[a]	
Objective Response Rate		
TC3 or IC3 subpopulation	n =107	n = 98
ORR (%)	38.3%	28.6%
(95% CI)	(29.08, 48.22)	(19.90, 38.58)
Duration of Response		
TC3 or IC3 subpopulation	n = 41	n = 28
Median DOR	NE	6.7
(95% CI)	(11.8, NE)	(5.5, 17.3)

CI: confidence interval; DOR: duration of response; NE: Not estimable; PFS: progression-free survival; WT: wild-type

Summaries of Time-to-Event (median, percentiles) were Kaplan-Meier estimates. 95% CI for median was computed using the method of Brookmeyer and Crowley. Hazard ratios were estimated by Cox regression. Stratification factors for the TC3 or IC3-WT population were: sex (male vs. female) and ECOG (0 vs. 1).

[a] p-value is descriptive only

Subsequent anti-cancer therapy

The company reports details of subsequent anti-cancer therapies in section B.2.6.3, Table 9 of the CS. A higher percentage of patients in the chemotherapy arm than in the atezolizumab arm received more than one anti-cancer therapy (46.9% versus 24.3%) and subsequent immunotherapy (29.6% versus 1.9%.). The majority of patients in the atezolizumab arm received subsequent chemotherapy.

IMpower110 TC3 or IC3 subpopulation exploratory analysis

The company present in in section B.2.7 of the CS the results of an exploratory analysis of the TC3 and IC3 subpopulations at the same time as the final analysis of OS for the TC2/3 or IC2/3, and TC1/2/3 or IC1/2/3 subpopulations (cutoff date 4th February 2020). Results of this exploratory analysis show [redacted]

The company present OS by the different IHC assays in Table 13, Document B, of the CS, which is partially reproduced by the ERG as Table 14 below. The company note that [redacted] in the atezolizumab arm compared with the chemotherapy arm was observed using the IHC assays. *The ERG have the same reservations explained earlier in the text about the comparability of the different assays.*

Table 14. OS by high PD-L1 expression subgroups as defined by the SP142, SP263, and 22C3 Assays (CCOD: 04 February 2020)[22]

Subgroups	n	HR	Atezolizumab Median OS, months	Chemotherapy Median OS, months
TC3 or IC3 (SP142)	205	[redacted]	[redacted]	[redacted]
TPS ≥50% (22C3)	260	[redacted]	[redacted]	[redacted]

Adverse reactions

The company presents the results of the IMpower110 primary and exploratory safety analyses (cutoff date 4th February 2020) in section B.2.10 of the CS, and the ERG

presents a summary of these results in Table 15 below. The safety analysis was performed on all treated patients (not just on the TC3 and IC3 subpopulations), including patients who received any amount of atezolizumab (n=286) and patients who received chemotherapy only (n=263). The median treatment duration was 5.3 months in the atezolizumab arm. In the chemotherapy arm, median treatment duration was 2.1 months for cisplatin, 2.3 months for carboplatin, 2.6 months for gemcitabine and 3.5 months for pemetrexed.[21] Fewer atezolizumab patients experienced treatment-related adverse events (TRAEs) than chemotherapy patients (60.5% versus 85.2%, respectively), with most patients experiencing Grade 3-4 TRAEs (12.9% versus 44.1% in the atezolizumab and chemotherapy arms, respectively), the most common of which were anaemia, nausea, neutropenia and thrombocytopenia (all with chemotherapy). These increased slightly in both arms for the longer available data cut, [redacted] of atezolizumab patients compared with [redacted] of chemotherapy patients. Numbers of patients experiencing serious TRAEs was lower in the atezolizumab arm compared with the chemotherapy arm (8.4% versus 15.6%, respectively in the primary analysis) and hardly changed ([redacted] versus [redacted], respectively) in the exploratory analysis. One patient (0.4%) died in the chemotherapy arm (due to pancytopenia) and no patients died in the atezolizumab arm.

A higher proportion of patients who received atezolizumab experienced adverse events of special interest events (AESIs) compared with patients who received chemotherapy (40.2% versus 16.7%, respectively). The most common AESIs (≥5%) included hepatitis (diagnosis and lab abnormality), rash, and hypothyroidism. In particular, [redacted] There were [redacted] Grade 5 AESIs, the [redacted] AESIs were Grade 1-2 and [redacted]. Immune-mediated AEs occurred more frequently among patients receiving atezolizumab than those receiving chemotherapy (40.2% versus 16.7%, respectively). Most common immune-mediated AEs (≥5% in either arm) were hepatitis and hepatic laboratory abnormalities, rash and hypothyroidism. As expected, immune-mediated AEs requiring systemic corticosteroid treatment were higher among patients treated with atezolizumab, compared with those treated with chemotherapy ([redacted] versus [redacted] respectively).

Table 15. Summary of the IMpower110 safety profile (primary and exploratory analyses)

	Primary analysis (cutoff date 10th September 2018)		Exploratory analysis (cutoff date 4th February 2020)	
	Atezolizumab n=286	**Chemotherapy n=263**	**Atezolizumab (n=286)**	**Chemotherapy (n=263)**
Any-cause AE, n (%)	258 (90.2)	249 (94.7)	[redacted]	[redacted]
Related AE (%)	173 (60.5)	224 (85.2)	[redacted]	[redacted]
Grade 3-4 AE, n (%)	91 (31.8)	141 (53.6)	[redacted]	[redacted]
Treatment-related Grade 3-4 AE	37 (12.9)	116 (44.1)	[redacted]	[redacted]
Serious AE, n (%)	81 (28.3)	75 (28.5)	[redacted]	[redacted]
Treatment-related serious AE	24 (8.4)	41 (15.6)	[redacted]	[redacted]
Grade 5 AE, n (%)	11 (3.8)	11 (4.2)	[redacted]	[redacted]
Treatment-related Grade 5 AE	0	1 (0.4)	[redacted]	[redacted]
AE leading to any treatment withdrawal, n (%)	18 (6.3)	43 (16.3)	[redacted]	[redacted]
Immune-mediated AE, n (%)	115 (40.2)	44 (16.7)	NR	NR
Grade 3-4 immune-mediated AE	19 (6.6)	4 (1.5)	NR	NR
Immune-mediated AE requiring use of corticosteroids, n (%)	[redacted]	[redacted]	NR	NR
Adverse events of special interest (AESIs)				
All Grade AESIs, n (%)	[redacted]	[redacted]	[redacted]	[redacted]

Grade 3-4 AESIs, n (%)	[redacted]	[redacted]	[redacted]	[redacted]
All Grade AESIs requiring use of corticosteroids, n (%)	[redacted]	[redacted]	[redacted]	[redacted]

*One more Grade 5 AE (pulmonary oedema) in the atezolizumab arm since the primary analysis
AE: adverse event; AESI: adverse event of special interest; Atezo: atezolizumab; CCOD: clinical cut-off date

Overall, the ERG agrees with the company that the safety profile of atezolizumab is similar between the primary analysis and the exploratory analysis and that no new safety signals were identified among patients enrolled in the IMpower110 trial.

Health-related quality of life

In section B.2.6.6 of the CS, the company presents details of the impact of lung cancer treatment and symptoms on HRQoL, as measured by the Symptoms in Lung Cancer (SILC), European Organisation for the Research and Treatment of Cancer quality of life questionnaire EORTC QLQ-C30 and EORTC QLQ-LC13 tools. The ERG notes the company's statement that interpretation of patient-reported outcome (PRO) data may be limited beyond week 57 due to the low number of patients remaining on treatment and, therefore, the low number of patients expected to complete PRO assessments. The ERG have no concerns regarding the methods used to collect PRO data or participant response rates. There were no clinically meaningful improvements in mean HRQoL in either treatment arm; however, from week 24 to week 57, the decline in mean HRQoL was smaller in the atezolizumab arm than in the chemotherapy arm. Time to deterioration of lung cancer-related symptoms [redacted] in both arms. More specifically, there were non-clinically significant changes from baseline in global health status for both arms until week 24 after which the chemotherapy arm had clinically significant decline. Physical functioning had albeit not clinically important early improved function to baseline in both arms with atezolizumab having some advantage until week 20 after which the two arms were similar but not clinically different to baseline. Coughing symptoms in both arms improved, being clinically meaningful by week 42 and 48 for chemotherapy and atezolizumab respectively, but returning to baseline levels thereafter. Chest pain and fatigue, were improved in the atezolizumab arm compared to their baseline and

with the chemotherapy arm although not with any clinical meaning; chest pain and fatigue both increased after week 42 and 30 respectively, in both arms. Baseline changes in dypsnoea were not clinically meaningful for either treatment arm.[23] The chemotherapy group had raised nausea and vomiting levels compared to baseline and the atezolizumab group through out particularly early on but these were not of clinical relevance.

2.2.3 Meta-analyses

As IMpower110 was the only RCT comparing atezolizumab versus chemotherapy in treatment-naïve, high PD-L1 expression, NSCLC patients, the company did not conduct a meta-analysis.

2.3 Critique of trials identified and included in the indirect comparison and/or multiple treatment comparison

In the absence of relevant direct head-to-head data, the company conducted a network meta-analysis (NMA) based on a connected network of 12 RCTs. Details of these trials are provided in Table 10, Appendix D of the CS.

In addition to the IMpower110 trial, the company included the following Roche trials in the indirect comparison: IMpower150, IMpower130, IMpower131, and IMpower132. The remaining trials in the network included: KEYNOTE-021, KEYNOTE-024, KEYNOTE-042, KEYNOTE-189, KEYNOTE-407, CHECKMATE-026, and CHECKMATE-227. The company present the characteristics of these trials in Table 13 of Appendix D. In order to align with the marketing authorisation, the company excluded the CHECKMATE-026 and CHECKMATE-227 trials, which assessed nivolumab versus chemotherapy, the pembrolizumab combination trials (KEYNOTE-021, KEYNOTE-189, KEYNOTE-047) and the atezolizumab combination trials (IMpower150, IMpower130, IMpower131, IMpower132) and focused on the atezolizumab monotherapy trial (IMpower110) and the two pembrolizumab monotherapy trials (KEYNOTE-024 and KEYNOTE-042). The patient target population was the PD-L1 >50% or TC3/ICT3 population with mixed histology (non-squamous or squamous). The ERG agree with the company's choice.

Details of the study design and baseline characteristics of the IMpower110 and KEYNOTE-042 and KEYNOTE-024 trials are provided in Tables 16 and 17.

The ERG is satisfied that, despite some differences, the participants' baseline characteristics are similar across the three trials in terms of age, ECOG status and disease stage. All three trials included participants with both squamous and non-squamous NSCLC and focused on patients with an absence of EGFR mutations or ALK translocations. Chemotherapy treatments varied between trials (see Table 16).

The ERG agree with the company that the definitions of OS and PFS are comparable between the trials. The methods used to assess PFS are, however, variable as the IMpower110 used progression based on investigator assessment (PFS-INV), whereas the KEYNOTE trials used blinded independent central review (PFS-IRC). The company have assumed PFS-INV and PFS-IRC are comparable for the purposes of the indirect comparison. Similarly, ORR as assessed by investigators in IMpower110 is considered comparable to ORR as assessed by an independent review committee in the other trials. The company acknowledge the limitation of these assumptions in the CS. *The ERG agree with the company that the heterogeneous methods for assessing PFS and ORR may represent a potential risk of bias.*

Different methods were used to determine PD-L1 expression across the trials.

- PD-L1 expression in KEYNOTE-024 and KEYNOTE-042 was determined on TCs using the 22C3 assay, whereas PD-L1 expression in IMpower110 was determined on TCs and ICs using the SP142 assay.

- KEYNOTE-024 only recruited patients whose tumours had the highest level of PD-L1 expression (TPS ≥50%), whereas IMpower110 and KEYNOTE-042 both recruited patients whose tumours had any PD-L1 expression.

Full details of the range of methods are presented by the company in Table 14, Appendix D of the CS, and the different assay tests and classification criteria used to determine PD-L1 expression are presented by the ERG in Table 16 in this report. The company recognises that the SP142 assay used in the IMpower110 consistently shows fewer tumour cells stained compared with the 28-8, 22C3 and SP263 assays; however, the company state that the reduced sensitivity of the SP142 assay only indicates that the assay may not detect patients with the lowest PD-L1 expression and is not less predictive than the other assays. The company also state that insights gathered from clinical experts across the country show that a patient is typically only tested with one assay and that the 22C3 assay is most prevalently used in the UK

(21 centres), followed by SP263 (5 centres) and by SP142 (1 centre), and that while variability between available assays and the limitations with SP142 are recognised, there is largely overlapping concordance across these assays and that any of them could be used to test for PD-L1 expression ahead of immunotherapy treatment. The company also cite their NSCLC atezolizumab monotherapy study OAK, a phase 3, open-label, RCT in which patients with previously treated NSCLC received atezolizumab monotherapy (n=425) or docetaxel (n=425). PD-L1 expression was evaluated using the SP142 and 22C3 assays.[24] Results showed that atezolizumab improves survival of in the TC1/2/3 or IC1/2/3 subpopulation irrespective of which assay was used.

The company presents the NSCLC definitions for 22C3, SP142, and SP263 used in the KEYNOTE studies and IMpower110 in **Error! Reference source not found.** of their clarification response.

The company present their risk of bias assessment of the trials included in the indirect comparison in Table 39, Appendix D.1.3 of the CS. The ERG has no concerns about the methodological quality of the trials included in the NMA.

Table 16. Comparison of study designs of the IMpower110, KEYNOTE-042 and KEYNOTE-024 trials

Study	IMpower110	KEYNOTE-042	KEYNOTE-024
Study design	Randomised, Phase III, global, multicentre, open-label study	Randomised, Phase III, multicentre open-label study	Randomised, Phase III, multicentre open-label study
Population	PD-L1–selected (≥1% of TC or IC covering ≥1% of the tumour area [TC1/2/3 or IC1/2/3]*), chemotherapy-naive patients with Stage IV non-squamous or squamous NSCLC without EGFR mutations or ALK translocations	Treatment-naïve, stage IV NSCLC, PD-L1 tumour proportion score ≥1% NSCLC	Chemotherapy-naïve, stage IV NSCLC, PD-L1 tumour proportion score of ≥50%, without EGFR or ALK mutations
Intervention(s)	Atezolizumab	Pembrolizumab	Pembrolizumab
Comparator(s)	Cisplatin or carboplatin and pemetrexed (non-squamous) or gemcitabine (squamous)	Carboplatin and pemetrexed (then pemetrexed maintenance for non-squamous) Carboplatin and paclitaxel (then pemetrexed maintenance for non-squamous)	Carboplatin or cisplatin and pemetrexed (non-squamous only) or Carboplatin or cisplatin and gemcitabine or carboplatin and paclitaxel
Assay used to determine PD-L1 expression	SP142 (Ventana) Subgroup efficacy analyses with 22C3 pharmDx assay and SP263	22C3 pharmDx (Agilent)	22C3 pharmDx (Dako)

Details of PD-L1 expression classification	NR	Expression was categorised by tumour presentation score, which was defined as the percentage of tumour cells with membranous PD-L1 staining	NR

Table 17. Demographics and baseline characteristics of the trials included in the NMA (IMpower110, KEYNOTE-042, KEYNOTE-024)

	IMpower100 TC3 or IC3 subpopulation		KEYNOTE-042		KEYNOTE-024	
Characteristic	**Atezolizumab n=107**	**Chemotherapy n=98**	**Pembrolizumab N=299**	**Chemotherapy N=300**	**Pembrolizumab N=154**	**Chemotherapy N=151**
Age, years						
Median	63	65.5	63.0	64.0	64.5	66.0
Range	33-79	33-87	(56.0–68.0)	(57.0–69.0)	(33-90)	(38-85)
Age group, n (%)						
<65 years	59 (55.1)	43 (43.9)	-	-	-	-
65-74 years	33 (30.8)	47 (48.0)	-	-	-	-
75-84 years	15 (14.0)	7 (7.1)	-	-	-	-
≥85 years	0	1 (1.0)	-	-	-	-
Sex, n (%)						
Male	79 (73.8)	64 (65.3)	205 (69)	210 (70)	92 (59.7)	95 (62.9)
Race, n (%)						
White	87 (81.3)	82 (83.7)	-	-	-	-
Asian	20 (18.7)	15 (15.3)	-	-	-	-

Black or African American	0	0	-	-	-	-
Multiple	0	0	-	-	-	-
Unknown	0	1 (1.0)	-	-	-	-
ECOG performance status, n (%)						
0	35 (32.7)	38 (38.8)	96 (32)	91 (30)	54 (35.1)	53 (35.1)
1	72 (67.3)	60 (61.2)	203 (68)	209 (70)	99 (64.3)	98 (64.9)
Tobacco use history, n (%)						
Never	9 (8.4)	15 (15.3)	64 (21)	67 (22)	5 (3.2)	19 (12.6)
Current	20 (18.7)	29 (29.6)	57 (19)	59 (20)	34 (22.1)	31 (20.5)
Previous	78 (72.9)	54 (55.1)	178 (60)	174 (58)	115 (74.7)	101 (66.9)
Histology at diagnosis, n (%)						
Non-squamous	80 (74.8)	75 (76.5)	192 (64)	186 (62)	125 (812)	124 (82.1)
Squamous	27 (25.2)	23 (23.5)	107 (36)	114 (38)	29 (18.8)	27 (17.9)
Disease status— no. (%)						
Locally advanced			27 (9)	35 (12)		

Metastatic			272 (91)	265 (88)		
Brain metastases			19 (6)	15 (5)	18 (11.7)	10 (6.6)
Previous treatment for non-metastatic disease— no. (%)						
Radiotherapy			40 (13)	39 (13)		
Neoadjuvant therapy			1 (<1)	5 (2)	3 (1.9)	1 (0.7)
Adjuvant therapy			8 (3)	4 (1)	6 (3.9)	3 (2.0)
Region of enrolment *— no. (%)						
Asia Pacific /East Asia	20 (18.7) *Asia Pacific	14 (14.3) *Asia Pacific	92 (31) *East Asia	94 (31) *East Asia	21 (13.6) *East Asia	19 (12.6) *East Asia
Europe	76 (71.0)	77 (78.6)	71 (24)	66 (22)	133 (86.4) *not EAST ASIA	132 (87.4) *not EAST ASIA
South America/Latin America	6 (5.6)	5 (5.1)	53 (18)	63 (21))		
North America	5 (4.7)	2 (2.0)				
Other			83 (28)	77 26)		

*

IMpower110 collected region enrolment data from Asia specific and South America, whereas KEYNOTE-024 and KEYNOTE-042 collected from East Asia and Latin America

2.4 Critique of the indirect comparison and/or multiple treatment comparison

Analyses were conducted for OS, PFS, ORR and the safety outcomes (TRAE, TRAE Grade 3+, TRSAE and withdrawal due to AEs) as having direct comparison between atezolizumab versus chemotherapy and between pembrolizumab versus chemotherapy; thus providing indirect comparison for atezolizumab versus pembrolizumab.

The patient population considered was the PD-L1 ≥ 50% or TC3/IC3 population, with mixed (non-squamous or squamous) histology. It is worth recalling that PD-L1 expression in the KEYNOTE trials was determined on **TCs** using the 22C3 assay, whereas in IMpower110 was determined on **TCs and ICs** using the SP142 assay.

The company have assumed that the different methods of assessing PD-L1 are comparable for the purpose of conducting their analyses. The ERG note the difference between the numbers of patients identified as ≥50% TPS by 22C3 and by SP142 in Figure 14, page 52 Doc B and Figure 27, page 284 of the company's Appendices. *The ERG's clinical expert opinion is that using different assays will identify slightly different patient populations, which creates uncertainty around whether these patients are suitable for both pembrolizumab and atezolizumab. Also, laboratories would not have the capacity or funding to perform multiple assays, thus decisions maybe made upon assessment with the alterative assay.*

The company has also assumed equivalence between the chemotherapy arms and between nab-paclitaxel and paclitaxel treatments. *The ERG clinical expert agrees that the appropriate chemotherapy treatments have been administered for the corresponding pathologies and, therefore, the company are correct to assume equivalence between treatments.*

For OS and PFS, analyses were conducted on both reported hazard ratio (HR) data and on individual patient survival times (reconstructed from Kaplan-Meier [KM] data for the KEYNOTE trials). The company submitted these reconstructed data at clarification. The ERG found only minor discrepancies in the reconstructed HR estimates for the KEYNOTE-042 trial compared with the originally published estimates. For OS, the published HR was 0.69 (95%CI: 0.56, 0.85) whilst the reconstructed HR was 0.70 (95%CI: 0.58, 0.86); for PFS the published HR was 0.81(95%CI: 0.67, 0.99) whilst the reconstructed HR was 0.83 (95%CI: 0.69, 1.00)]. The ERG was unable to verify these.

The possible networks are describe in the CS Appendix D.1.13 for all mixed non-squamous and squamous groups (Figure 1), the non-squamous group only (Figure 2) and the

squamous group only (Figure 3). The company for the purpose of the current evidence submission and in order to align with the marketing authorisation and reimbursement from NICE, only included IMpower110, KEYNOTE-024 and KEYNOTE-042 as assessing interventions relevant to this appraisal. The ERG are in agreement with the company's decision.

In addition to the standard HRs, the company also adjust for the effect of anti-cancer immunotherapy, using the Reserved Rank Preserving Structural Failure Time (RPSFT) method on the exploratory analyses data (CCDO: 4 February 2020). These additional analyses are presented in Appendix L, **Error! Reference source not found.** and **Error! Reference source not found.** (KM plot). They were based on data available at the 4 February 2020 cut. The company also include discount analyses at 10%, 30% and 50%, but conclude that the RPSFT estimate of OS HR is smaller and more strongly favours atezolizumab across all additional analyses: The original exploratory result was ([redacted] whilst the RPSFT result was [redacted]. The ERG consider that the underlying assumptions for cross-over adjustment methods are hard to prove and that these analyses are only useful as sensitivity analyses.[25] It is likely that the 'truth' lies somewhere between them. However, because of the different follow up lengths between the KEYNOTE and the IMpower110 trials, the company maintain that this effect increases the confounding due to subsequent therapies for the atezolizumab arms*. The ERG is of the opinion that although this may be the case, without similar analyses conducted on the KEYNOTE trials this cannot be determined with certainty.*

The company claim to adopt NMA methods in line with DSU recommendations, using a Normal distribution and identity link on the log HR's and associated standard errors for OS and PFS and a Binomial distribution and logit link for ORR and the safety outcomes.[26]

In addition, the company used a fractional polynomial approach (FP-NMA) stating that their methods follow those of Jasen et al. for OS and PFS.[27] The FP approach allows for modeling the hazard function with multiple parameters as a function of time, permitting the HR to change over time in the presence of non-proportional hazards. This approach was chosen since the profiles were potentially not parallel in the two arms (see section B.2.9.9, Figures 24 and 26), a basic assumption for proportional hazard models. *The ERG accept the company's initial rationale for presenting the FP-NMA approach.*

All outcomes were evaluated using both fixed and random effects models. The company used informative priors for the between study variances for the random models as suggested by Turner et al., 2015.[28] Models were assessed using the DIC for the non-FP models eventually favouring the random effects models for all outcomes. *The ERG consider the company approach appropriate.*

Table 18 shows the characteristics of the NMA.

Table 18. Characteristics of the company's NMA

Trials	Treatments	Population	Outcomes	Analysis methods
IMpower 110 KEYNOTE-024 KEYNOTE-042	Atezolizumab monotherapy Pembrolizumab monotherapy Chemotherapy	PD-L1 ≥50% or TC3/IC3 with mixed histology (non-squamous or squamous).	OS PFS ORR Safety outcomes (any TRAE, TRAE Grade 3+, any TRSAE, withdrawal due to AEs)	OS and PFS = time to event data allowing for time-varying HRs through the use of fractional polynomial models. ORR and safety outcomes = NMA assuming a binomial distribution and a logit-link. For all outcomes both fixed and random effects models.

For the FP-NMA models (OS and PFS) the company assessed the 1st and 2nd order polynomials as well as the proportional hazard exponential models. The company decided the 2nd FP models gave unrealistic extrapolations. The powers explored for the 1st polynomial reflect the Exponential, Weibull and Gompertz distributions, each with advantages depending on the outcome. However, for consistency the company decided to

adopt the Weibull FP-NMA model for both OS and PFS. The ERG understand the rationale for this decision.

All the NMA models seemed to have been run using 3 chains, 5000 burn-in iterations followed by 30000 samples, thinned by a factor of 6 (the default is 1).

The ERG attempted to replicate the standard proportional hazard models comparing the interventions to chemotherapy for IMpower110 and KEYNOTE-024 and KEYNOTE-042 using the reconstructed data the company supplied. While the IMpower110 results were comparable with the CS, the replicated results did not mirror either the CS results or the published results for the KEYNOTE-024 and KEYNOTE-042 trials. The ERG also attempted to run the standard NMA and FP-NMA, using code provided in the CS and with reference to other code. However, persistent errors occurred with each and while point estimated for the NMA were similar, they had very wide credible intervals. Although the FP models after revision compiled with the company specification, HR results were not available. The company sent their R and JAGs codes just prior to the ERG report submission, but due to time constraints, the *ERG was not in the position to verify the results*. *Therefore, the company results currently can only be taken at face value.*

The NMA results for OS and PFS were conducted by the company on the estimates from both the final and the exploratory analyses although they favour the CCOD Feb 2020 for extrapolation for cost effectiveness. The ERG presume this is similar for ORR and AEs.

Heterogeneity between the pembrolizumab studies was assessed for the HRs of OS and PFS and for the OR of ORR (note: AEs were only assessed for pembrolizumab in the KEYNOTE-024 study). The only cause of concern is for PFS and this casts some doubts about the reliability of the NMA PFS results.

2.4.1 Results of the NMA

The indirect comparisons from both the standard and the FP-NMA for OS and PFS imply no significant differences between atezolizumab and pembrolizumab. Similarly, there is no evidence from the presented results for difference between atezolizumab and pembrolizumab for the other outcomes (ORR and safety outcomes).

Table 19 presents a summary of the results of the direct comparison between atezolizumab and chemotherapy. A summary of the results of the indirect comparison between atezolizumab and pembrolizumab is reported in Table 20 below.

Table 19. Direct comparison between atezolizumab and chemotherapy in the IMpower110

	Primary analysis (CCOD: 10th September 2018)	Exploratory analysis (CCOD: 4th February 2020)
OS	HR_{AC}=0.59 (0.40, 0.89)	HR_{AC}=0.76 (0.54, 1.09)
PFS	Descriptive only HR_{AC}=0.73 (0.45, 0.88)	HR_{AC}=0.59 (0.43, 0.81)
ORR	38.3% (29.08, 48.22) vs 28.6%(19.90, 38.58) OR_{AC}=[redacted] Doc B, page 42	40.2%(30.8, 50.1) vs 28.6%(19.9, 38.6)
DOR	Median not reached for atezolizumab Median time to DOR was 6.7 for chemotherapy	
AEs	**Fewer** TRAE, TRAE Grade 3+, TRSAE and AEs leading to withdrawal in the atezolizumab arm **More** Immune–mediated AEs **More** AESIs but mainly at Grade 1-2	**Fewer** TRAE, TRAE Grade 3+, TRSAE and AEs leading to withdrawal in the atezolizumab arm **More** Immune–mediated AEs **More** AESIs mainly at Grade 1-2 and AESIs requiring systemic corticosteriods

HR_{AC}: Direct comparison Hazard Rate between ATZ and Chemo
OR_{AC}: Direct comparison Odds ratio between ATZ and Chemo

Table 20. Summaries of indirect comparisons between atezolizumab (ATZ) and pembrolizumab (PEMB) for OS PFS ORR and AEs. Based on the results of the IMpower110, KEYNOTE-024 and KEYNOTE-042 trials

Primary analysis (CCOD: 10th September 2018)			
OS	NMA	[redacted]	n/s; point estimates favours ATZ
Exploratory analysis (CCOD: 4th February 2020)			
OS	NMA	[redacted]	n/s
	FP-NMA		
	3 months	[redacted]	n/s; point estimates favours ATZ.
	6 months	[redacted]	n/s
	12 months	[redacted]	n/s; point estimate favours PEMB
	2+ years	This trend towards favouring PEMB continues with time but with widening credible limits and small sample sizes indicating they may be less reliable. The company expresses a concern that IMpower has longer follow up and many participants would go onto other therapies washing out possible ATZ/chemotherapy comparison. [the ERG is of the opinion that this should be similar for both interventions since the model accounts for time].	
PFS	NMA	[redacted]	n/s; point estimate slightly favours ATZ.
	FP-NMA		
	3 months	[redacted]	n/s; but point estimate favours ATZ
	12 months	[redacted]	n/s
	2+ years	Point estimates favour PEMB but sample sizes small. Treatment cross-over is not a concern here	
ERG presume: Exploratory analysis (CCOD: 4th February 2020)			
OOR	NMA only	[redacted]	n/s
AE's	NMA only	[redacted]	IMpower110 and KEYNOTE-024
	TRAE	[redacted]	n/s but point estimate favours PEMB
	TRSAE	[redacted]	n/s but point estimate slightly favours ATZ
	TRAE>=3	[redacted]	n/s but point estimate favours ATZ
	AE withdrawal	[redacted]	Marginally n/s: point estimate favours ATZ

1. ATZ: atezolizumab; PEMB: pembrolizumab
2. HR_{AP}: Indirect comparison Hazard Rate between ATZ and PEMB
3. OR_{AP}: Indirect comparison Odds Ratio between ATZ and PEMB
4. n/s: statistically non-significant

The company's conclusions for all the models is that there is insufficient evidence of a difference between atezolizumab and pembrolizumab for OS, PFS, ORR and safety outcomes. Based on their presented figures and estimates, the ERG largely agree with the company's conclusions. However, i) there is some doubt about maintenance of the comparable effect over time based on the FP-NMA model, ii) the robustness of the PFS results may be questioned, iii) the 'withdrawal due to AEs' outcome shows borderline results in favour of atezolizumab (Figure 19, Appendix D.1.5), and iv) the differing assays in the different studies detailed earlier may be a cause of concern with respect to the homogenerity of the sample population between the trails. For this latter point, SP142 (as used in IMpower110) is not widely in use in practice (only one UK centre) and the ERG's clinical advice has suggested this is not as sensitive as 22C3, which is commonly used in clinical practice (and used in the KEYNOTE trials). A breakdown of the IC3 and TC3 groups by means of a sensitivity analysis would have been useful.

2.5 Additional work on clinical effectiveness undertaken by the ERG

Despite several attempts, the ERG was unable to replicate the FP-NMA or indeed the standard NMA for OS and PFS. Recently received code may make their finer details more transparent.

2.6 Conclusions of the clinical effectiveness section

The company's decision problem is appropriate for addressing the final scope issued by NICE in relation to this appraisal. Overall, the ERG consider the methods used to conduct the systematic review of clinical effectiveness evidence to be in line with current methodological standards.

Results of the IMpower110 trial indicate that atezolizumab has statistical benefit over chemotherapy for OS and PFS based on the data available at the September 2018 cut; but only clinical benefit for OS based on the data available at the February 2020 data cut.

While patients who received atezolizumab were more likely to experience adverse events of special interest than patients who received chemotherapy in the IMpower110 trial, no unexpected adverse events were identified. The ERG have no concerns about the safety profile of atezolizumab based on the results of the IMpower110 trial.

In the absence of direct clinical evidence, the company conducted a NMA to indirectly estimate OS, PFS, ORR and safety outcomes to compare atezolizumab and

pembrolizumab. Three trials contributed to the NMA: IMpower110 assessing atezolizumab versus chemotherapy and KEYNOTE-024 and KEYNOTE-042 assessing pembrolizumab versus chemotherapy.

The ERG currently cannot verify the results, but mostly accepts the company's interpretation of the NMA results indicating that overall atezolizumab monotherapy (using IMpowere110 data) is comparable to pembrolizumab monothereapy (using both the KEYNOTE-24 and KEYNOTE-042 data). This is indicated by the NMA HR's. However, the FP-NMA results possibly suggests that this may not be sustained with time. The company have various suggestions for this, which could be plausible but the ERG would prefer a more cautionary approach. In addition, the ERG is unclear about the homogeneity of the study populations between the trials because of the differing assays used.

COST EFFECTIVENESS

3.1 ERG comment on company's review of cost-effectiveness evidence

The company reviewed previous economic evaluations of medicines for first line locally advanced or metastatic NSCLC. The method was described in an appendix with the studies identified and an overview provided in Section B3.1 on page 82 of the submission. The search was undertaken in October 2019 and included published studies, main HTA agencies (including NCE), conference abstracts, and searching the cited studies in the published economic evaluations. The review identified 57 published papers, 7 HTAs and 30 conference abstracts. In Appendix H the company provided tables summarising the methods and results of these studies over 115 pages, before concluding on page 428, "Consideration of the caveats and limitations of previous studies will ensure the most appropriate methods are utilised in future analyses, and robust cost-effectiveness estimates are achieved in this indication." However, it is not clear from the Appendix or from Document B what these were and it is difficult to trace any specific link between the SLR and the design of the model.

It could be argued that the SLR gave the company confidence in their design, but there is a sense that this was a huge amount of effort with no very visible returns. The ERG suggests the SLR could have been more focused. For example, it could have been restricted to previous economic evaluations of PD-L1 inhibitors and the specific ways they have modelled PFS and OS. It could also have been restricted to the economic evaluations in NSCLC most closely matching the current decision problem, where one medicine with a certain mechanism of action (MoA) is 'standard of care' and the HTA considers a second medicine with a similar MoA. This could also have sought previous experience on more specific issues such as under what circumstances clinical evidence is sufficiently similar to be considered a basis for a cost comparison / cost-minimisation analysis. These could potentially have been a more productive focus of the effort and more useful in shaping the submission.

No existing economic evaluations of atezolizumab monotherapy for untreated patients with advanced NSCLC were identified. Of greatest relevance to the current decision problem, is the economic model used to inform NICE guidance on pembrolizumab monotherapy for untreated PD-L1-positive metastatic non-small-cell lung cancer (TA531).[29] The company provided a comparison of some of their own model's features against this previous model (Document B, Table 27). More in-depth comparisons were, however, limited by the redaction of key modelling details from the TA531.

3.2 Summary and critique of the company's submitted economic evaluation by the ERG

3.2.1 NICE reference case checklist

Table 21. NICE reference case checklist

Element of health technology assessment	Reference case	ERG comment on company's submission
Perspective on outcomes	All direct health effects, whether for patients or, when relevant, carers	Yes
Perspective on costs	NHS and PSS	Yes
Type of economic evaluation	Cost–utility analysis with fully incremental analysis	Yes
Time horizon	Long enough to reflect all important differences in costs or outcomes between the technologies being compared	Yes, 20 years is in line with previous appraisals for this indication.
Synthesis of evidence on health effects	Based on systematic review	Yes, NMA of relevant trials
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.	Yes, EQ-5D-3L measured directly from patients in IMpower110
Source of data for measurement of health-related quality of life	Reported directly by patients and/or carers	Yes, patients
Source of preference data for valuation of changes in health-related quality of life	Representative sample of the UK population	Yes, UK general population tariffs.
Equity considerations	An additional QALY has the same weight regardless of the other characteristics of the	Yes

	individuals receiving the health benefit	
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	Yes
Discounting	The same annual rate for both costs and health effects (currently 3.5%)	Yes
PSS, personal social services; QALYs, quality-adjusted life years; EQ-5D, standardised instrument for use as a measure of health outcome; NMA, network meta-analysis		

3.2.2 Model structure

This was presented in Document B, pages 85-86. The company submission presented a three-state partitioned survival model – using parametric curves fitted to PFS and OS data from IMpower110 for atezolizumab and hazard ratios for pembrolizumab versus atezolizumab derived from the NMA applied to these reference curves. The rationale for the structure was that it is:

- Simple and intuitive
- Allows multiple extrapolations
- Is in line with NICE DSU guidance to compare the data from Impower110 to other RCTs where IPD were not available

Time to treatment discontinuation data from IMpower110 was further used to determine treatment on treatment for atezolizumab, whilst time on treatment was assumed equal to PFS for pembrolizumab up to 2 years where a stopping rule was applied in line with its recommendation from TA531. No stopping rule was applied for atezolizumab, in line with its clinical evidence base in which treatment was allowed up until the loss of clinical benefit.

The company submission included a comparison of the design and inputs to the company model compared to those used for pembrolizumab in TA531 (Document B, pages 88-89, Table 27) and this shows the design of the two economics models to be similar.

The ERG agrees the company's model structure is acceptable. Due to limited availability of data, there is some inconsistency in the approach used to model time on treatment between the two alternatives. This could potentially overestimate time on treatment for pembrolizumab relative to its derived PFS curve.

3.2.3 Population

The modelled population is in line with the TC3 or IC3 subgroup of IMpwer110 trial, [redacted] outlined in company submission (Document B, Table 1):

"Adult patients with [redacted]."

The Final Scope proposed two sub-groups, different levels of PD-L1 and histology (squamous and non-squamous). The company submission pointed out that the [redacted], so further sub-groups within this biomarker are not presented. The company also argue analysis by histology sub-group is not appropriate because the RCT was not powered to detect differences.

The ERG acknowledges seeking sub-group analysis for PD-L1 levels above 50% is not appropriate. However, other sub-groups such as histology could have been presented, even if with caveats.

3.2.4 Interventions and comparators

The intervention, atezolizumab, is applied according to its marketing authorisation: 1200mg administered intravenously every three weeks until unmanageable toxicity or loss of clinical benefit as defined in section B3.2.2.3 of the company submission. It can be noted that the definition of 'clinical benefit' allows for some use of permbrolizumab following progression according to RECIST v1.1.

The comparator in the submission was pembrolizumab monotherapy applied according to its marketing authorisation: 200mg administered intravenously every three weeks. In line with the NICE recommendation from TA531 for pembrolizumab monotherapy, the treatment duration is limited to a maximum of two years of uninterrupted treatment.

[redacted]. *However, there may be a group of patients who meet the IC3 definition of IMpower110 (infiltrating immune cell PD-L1 expression ≥ 10%) who do not meet the TC3 definition (tumour cell PD-L1 expression ≥ 50%). Since the NICE recommendation for pembrolizumab in untreated PD-L1 positive metastatic NSCLC is conditional on a tumour proportion score of at least 50% (TA531), it is*

unclear whether pembrolizumab is the revenant comparator for IC3 only patients. However, the number of patients in IMpower110 in this category is likely to be small. The company also provided an exploratory analysis to assess the relative treatment effect in IMpower110 for high PD-L1 expression groups defined by different assays, including TPS ≥ 50% as defined by the 22C3 assay (used to determine PD-L1 expression in the KEYNOTE trials) [see also Chapter 2 about comparability of assays]. This showed a very similar magnitude of benefit in this subgroup (see Figure 14 and Table 13 of the company submission, Document B) compared to the TC3 or IC3 group defined by the SP142 assay.

3.2.5 Perspective, time horizon and discounting

The perspective and approach to discounting were in line with the NICE reference case. A time horizon of 20 years was chosen for the base case analysis. Whilst generally appropriate and consistent with TA531, it can be noted that in the company base case [redacted] and [redacted] remain alive at this time point in the atezolizumab and perbrolizumab arms of the model, respectively.

3.2.6 Treatment effectiveness and extrapolation

This was presented in Document B of the company submission, Section B.3.3.

IMpower110 data were used in the model for atezolizumab, from the analysis on 4th February 2020 (minimum follow-up 24 months, median 31 months). Data for pembrolizumab were generated by applying hazard ratios estimated in the indirect comparison.

Extrapolation in the model was by parametric functions fitted to observed Kaplan-Meier data. The parametric functions considered included the most commonly used forms: Weibull, log-normal, log-logistic, exponential, generalised gamma, Gompertz.

In the company base case parametric functions were fitted from Month 0, as in Figures 28 (OS), 31 (PFS) and 35 (TTD) of the company submission (Document B). An alternative method with extrapolations fitted only to the tails of the Kaplan-Meier plots was used in sensitivity analyses (see Table 66, Document B). The ERG notes that the choice of 20% was based on a methods paper published in the Lancet in 2002, although no specific justification for the relevance of that figure to this case was given.[30] However, the ERG notes that whether a given parametric function was fitted from month 0 or from where 20% were still at risk made almost no difference to the estimated QALY difference between treatments.

The choice of parametric function for the base case was based on three factors:

1. Statistical fit to the observed data using Akaike Information Criterion (AIC) and Bayesian Information Criterion (BIC).
2. Curves were (i) visually inspected and (ii) validated against relevant long-term data sources available to help identify the most plausible survival model.
3. Opinion was sought from three clinicians to validate the extrapolation approach taken and determine which of the extrapolations better represent UK clinical practice.

The ERG agrees these were the appropriate methods to use to make the selection.

Overall survival

Based on the AIC and BIC statistics (Document B, Table 28), visual inspection, and clinical plausibility of the extraploations, the alternative parametric functions were ranked. These rankings are provided in Table 30 of the company submission, document B (reproduced below as Table 22).

Table 22. Company rankings of OS distributions for atezolizumab based on AIC/BIC, visual fit and clinical plausibility (source: Table 30, Document B of the CS).

Parametric distribution	Atezo AIC (rank)	Atezo BIC (rank)	Visual fit to KM	Clinical plausibility	Ranking
Exponential	6	6	~	~	-
Weibull	2	2	✓	✓	1
Log-Logistic	1	1	✓	~	~
Log-Normal	3	3	~	×	-
Gen Gamma	5	5	✓	~	2
Gompertz	4	4	✓	×	-

The ERG has reservations about the importance of the rankings based on AIC and BIC. The difference in AIC/BIC figures for the five highest ranked curves were minimal, which could be taken as evidence that all these distributions offer plausible fits to the observed data. Visual fit was assessed subjectively. In Document B two of the six curve fits were presented; the other four were located in Appendix N, pages 562-563. The company's judgement was that the exponential and log-normal were the poorest fits (indicated by their failure to achieve a tick in Table 2 above).

The ERG agrees with the company that the exponential appears to have the poorest fit to the observed data, but find little to choose between the visuals fits of other curves.

The company report that the three UK clinicians they consulted reached a consensus that the Weibull best reflected their expectations, but no supporting evidence was provided for why they believed this. From Table 30 of the company submission, use of external data did not appear to play a role in curve selection.

The level of OS at each time point with each extrapolation was set out in Table 29 of the company submission (Document B) reproduced as Table 23 below.

Table 23. Percentage of patients alive with alternative parametric OS distributions for atezolizumab (source, Company submission, document B, Table 29)

Months	Exponential	Weibull	Gamma	Log-logistic	Log-Normal	Gompertz
6	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
12	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
24	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
36	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
48	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
60	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
72	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
84	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
90	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
120	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
126	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
132	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Having selected the Weibull as base case with generalised gamma as the second choice, the company submission then turned to external data as validation. Two sources were quoted, both giving longer-term data on pembrolizumab outcomes:

- 'Flatiron data', which the company clarified to be 'real world data' on use of pembrolizumab for the relevant indication in the USA. This showed pembrolizumab OS at 3 years of 32% (confidence interval from 27% to 38%). The company submission compares that to the Weibull estimates of [redacted] for atezolizumab and [redacted] for pembrolizumab but the only comment is that the atezolizumab estimate is within the confidence interval for pembrolizumab.
- Garon et al (described as real-world data in section B.3.3.2.1 of Document B) is a report of the 5-year results of KEYNOTE-001 clinical study.[31] In the context of a study of the use of pembrolizumab in a broader population with NSCLC, this included some patients with PD-L1 over 50% who were previously untreated and therefore appear to match the license for atezolizumab considered here. This showed 5-year OS with pembrolizumab was 29.6%.

It was not clear whether these two studies represented all the available evidence on longer-term OS as no literature review was reported. Neither data source is described in the company submission to allow a judgement on its reliability and relevance as a source of data to judge likely OS in NHS patients. For example, Flatiron was not described at all, although

the company provided some more details on it in response to the clarification letter, and note that it has been used in previous appraisals of atezolizumab to validate OS extraploations. Garon et al. is based on only 27 cases (from Figure 1, panel C of the original publication) which is a small sample size for judging OS.[31]

The company believe these data validate their choice of the Weibull, but there is a degree of uncertainty. As noted above, the Flatiron data show pembrolizumab has an OS of [redacted] after three years but the base case model in this submission predicts [redacted]. However, the five-year Garon data are consistent with the Weibull based five-year projections for permbrolizumab ([redacted]). Of relevance to the discussion of OS is the recent announcement that five year data from the KEYNOTE-024 trial have now been analysed.[32] Although no publication was available at time of writing, it has been announced that the five year OS rate was 31.9%, which is reasonably consistent with the pembrolizumab OS projections when applying the company's preferred hazard ratios to the generalised gamma or log-logistic curves for atezolizumab ([redacted] and [redacted] survival at five years).

The company submission reports the log normal and Gompertz were excluded as they were 'too optimistic' beyond 120 months, but no supporting evidence was provided. Both of these distributions do, however, appear to result in five-year OS projections for pembrolizumab above [redacted].

Overall, the company's justification for its base case parametric function seemed unconvincing to the ERG. Visual fit selection was based on judgements that were not explained. Key clinical opinion was summarised as favouring the Weibull with no other explanation. External supporting data, which should have been central to the judgement, seemed to be brought in after the selection had been made and divergences between projections and observed external data are not explored in any depth.

Nevertheless, the ERG believe that the Weibull offers a reasonable base case, and that the generalised gamma and log-logistic offer the most relevant alternatives for scenario analysis. In light of the recent five-year data announced for KEYNOTE-024, the ERGs clinical advisor was of the opinion that the change in OS between 36 months and 60 months predicted by the Weibull appeared quite steep, and tended towards favouring the generalised gamma curve.

Progression-free survival

The company's approach was presented in Document B, section B.3.3.3.

The same general approach was used as for the overall survival modelling i.e. fitting parametric functions to the Kaplan-Meier data (starting Month 0) from IMpower110, then applying a hazard ratio derived from the indirect comparison for permbrolizumab. The same criteria were used for selecting a parametric function for the base case.

On AIC and BIC, four curves appeared to offer a similarly good fit to the observed data: log-logistic, log-normal, generalised gamma, and Gompertz.

The ERG agrees that the exponential and Weibull do offer a poorer fit to the observed data than the other four distributions.

For visual fit, the company's judgement was that exponential and Weibull also performed poorly on this assessment, but the other functions provided a satisfactory fit (presented in Document B, Figures 31-33 and Appendices N.1.2, Figures 40 to 42).
The ERG agrees.

In terms of clinical plausibility, little information is presented in the company submission but the Gompertz was ruled out because clinicians found the predictions beyond 5 years implausible.

It would have been helpful to know why the clinicians thought the Gompertz predictions were implausible.

The company selected the generalised-gamma as this was consistent with the parametric fit for time on treatment (see below). However, it was emphasised that log-logistic and log-normal were very similar.

The ERG agrees with the rationale.

Relative treatment effects (pembrolizumab versus atezolizumab)
The ERG appraised the company's NMA in Section 2.4 of this report. The HRs were estimated by the company followed DSU guidance. The company noted proportional hazards (PH) may not hold and estimated HRs based on fractional polynomials. The ERG accepts this was an appropriate method, but the ERG describe problems in reproducing the company's results.

In the methods section for the economics model, the company said that OS and PFS estimates for pembrolizumab were generated by applying hazard ratios from the ITC, without specifying which ones were used (pages 91-92, Document B). It was not clear if this referred to HRs using random effects (assuming PH) or fractional polynomials (assuming PH did not apply) and the ERG asked for more detail in Clarification Question B1. The company responded to say they used the random effects HRs in the economics base case (Company's Response to CQs, page 22). They explained, "We observed that the fitting of the curves is not ideal for both PFS and OS when the fractional polynomial model is used. This causes implausible results for this comparison."

The ERG has been able to confirm this and does not believe FP HRs should be used in the model.

Capped treatment effect

The company submission did not include a specific section on this topic in Document B. However, it was assumed in the company base case that as pembrolizumab has a maximum duration of treatment of two years, then the treatment effect should be capped at five years. From this point the hazard of mortality in the pembrolizumab arm was set to the hazard for the chemotherapy arm of the NMA. For atezolizumab, which has no stopping rule, the company assumes no cap to the treatment effect in terms of OS in the base case. With the company base case curve selections, these assumptions cause the permbrolizumab OS curve to converge with and then drop below the atezolizumab OS curve from about 93 months.

In a sensitivity analysis, a treatment effect cap of eight years was applied for atezolizumab (Document B, page 94). The justification for this was that if the cap for atezolizumab was set at 5 years this would suggest no additional benefit for treatment beyond two years, which the company suggest is unreasonable. Eight years was selected as a longer time than five years. The company note that in this alternative scenario, the OS curves converge and overlap from about 90 months onwards, which the company interested as being consistent with clinicians' opinions that the two products were comparable in terms of efficacy.
The company describes the cap at eight years as the 'worst case scenario' for atezolizumab but also provides a sensitivity analysis with a cap at five years for atezolizumab (to match pembrolizumab).

The ERG notes that the difference between pembrolizumab and atezolizumab is 0.08 QALYs in the base case, 0.14 when the atezolizumab cap is at 8 years and 0.2 when the atezolizumab cap is at 5 years (all favouring pembrolizumab).

The ERG agrees that atezolizumab is likely to have a longer treatment duration than pembrolizumab, but relative benefits versus pembrolizumab beyond five years remain an area of uncertainty. The company argue that to use the same cap on treatment benefit would imply no additional benefit to treating for more than two years with atezolizumab, but the ERG point out that no evidence was presented in the company submission confirming a longer treatment effect duration with treatment extended beyond two years. Hence, it is possible that after two years of treatment the immunological effect of treatment has reached a maximum achievable. Therefore, the same duration of treatment effect as for pembrolizumab is also a possible, albeit pessimistic scenario.

Given how central the issue of treatment effect capping is to the estimate of QALY gains, a specific section in the company submission giving more detailed consideration to these issues would have been helpful.

For PFS, the company base case assumed no capping of the treatment effect for atezolizumab or pembrolizumab versus chemotherapy. The company submission included one diagram (Document B, Figure 34) showing the effect of capping the treatment effect at five years for both atezolizumab and pembrolizumab. No explanation or interpretation of this scenario was supplied. However, the model provided the functionality to test this, and the company did provide a scenario in response to the clarification letter, which capped the PFS treatment effect at five years for pembrolizumab.

Treatment duration

In the company's economic model, atezolizumab was modelled as it was used in the RCT (Document B, section B.3.2.2.3) defined as: "until unmanageable toxicity or loss of clinical benefit as defined by the following criteria:

- Evidence of clinical benefit as assessed by the investigator
- Absence of symptoms and signs (including worsening of laboratory values [e.g., new or worsening hypercalcemia]) indicating unequivocal progression of disease
- No decline in ECOG Performance Status that was attributed to disease progression

- Absence of tumour progression at critical anatomical sites (e.g., leptomeningeal disease) that could not be managed by protocol-allowed medical interventions
- Patients must have provided written consent to acknowledge deferring other treatment options in favour of continuing study treatment at the time of initial radiographic progression per RECIST v1.1"

Pembrolizumab was modelled to time of progression with an upper limit on the duration of treatment of two years. While this is not stated in the licensed use of pembrolizumab, an upper limit of 35 cycles was used in the RCT protocol for KEYNOTE-024 and NHS England stated this would be their criterion for funding pembrolizumab in this role. The Summary of Product Characteristics for pembrolizumab states that "Patients should be treated with KEYTRUDA until disease progression or unacceptable toxicity".[33] It also notes that "It is recommended to continue treatment for clinically stable patients with initial evidence of disease progression until disease progression is confirmed."

The company submission did not use an equivalent 'stop rule' for atezolizumab for three reasons:

1. To impose a stop rule on atezolizumab would not be consistent with the IMpower110 RCT evidence
2. There is a lack of rationale for a stop rule at two years
3. The company identified re-challenge as the biggest unmet medical need and believes that extending the IO availability to allow (re-challenge or) continued treatment would be a valuable option for some patients. However, the company was not aware on any available data about re-challenge (CS, section B.3.3.5)

They cited support by clinicians for their approach, given that re-challenge was not permitted.

As stated, time to treatment discontinuation data for atezolizumab were taken from the IMpower110 RCT (Document B, section B.3.3.4). The standard set of six parametric functions was considered to extrapolate this beyond the time period observed in the RCT. The selection was made on the basis of goodness-of-it and clinical plausibility; the company reports the three clinicians said a maximum of 10% of patients would still be on treatment after 5 years (page 103, Document B). The company judged the generalised-gamma to meet these criteria to the greatest extent, with the Weibull as the next best alternative.

The generally ERG agrees with the selections.

For pembrolizumab, the company reported that data on time to treatment discontinuation are not available. PFS data were used instead with an assumption of 'treat to progression' up to 2 years when the imposed 'stop rule' applies.

However, assuming treatment depends only on progression may underestimate discontinuation because stopping as a result of adverse events or patient preference is not included. This could make pembrolizumab seem more expensive than if the model had been based on actual time on treatment data.

In fact, the ERG notes that the following data are reported for pembrolizumab:
KEYNOTE 024[34]

- *In the supplementary appendix to Reck 2016, the CONSORT diagram showed that 80/154 patients had discontinued pembrolizumab at median follow-up of 11.2 months. Of the 80, 57 had stopped for reasons that would be captured in PFS but 23 had stopped for other reasons including 17 with adverse events.*
- *Reck 2016 also reported that at median follow-up of 11.2 months, the median duration of treatment was 7 months, while median PFS was 10.3 months.*
- *Reck 2019 reported median treatment duration with pembrolizumab in KEYNOTE 024 of 7.9 months at a median follow-up was 25.2 months.*

KEYNOTE 042[35]

- *In the consort diagram in the report of the RCT (Mok 2019 NEJM), of 298 patients with PD-L1 of 50% or more, 298 received pembrolizumab and 217 had discontinued. Of the 217, 149 discontinued for reasons that would be captured in PFS, but a further 68 stopped for other reasons including 61 with adverse events.*
- *Mok (2019 NEJM) also reports that after a median follow-up of 12.8 months, median PFS was 7.1 months for pembrolizumab while the median number of doses administered was 9 (equates to approximately 6.5 months).*

The ERG notes that considering the data above for the two pembrolizumab RCTs, a PFS-based definition of treatment discontinuation (as used in the company submission for atezolizumab) would likely underestimate the hazard of discontinuing pembrolizumab at least in the short term.

Subsequently, the ERG has identified a published paper by Velcheti et al which reports a post hoc analysis of time-on-treatment from KEYNOTE-024 and the PD-L1 ≥50% group in

KEYNOTE-042.[36] Whilst the KEYNOTE-024 time on treatment (ToT) data reported by Velcheti et al comes from the later data cut (median follow-up was 25.2 months) when comparable PFS data were not available, the reported ToT data for KEYNOTE-042 is directly comparable with the PFS data reported by Mok et al., 2019.[35] The ERG therefore extracted and compared data from the published curves on the proportion of patients remaining on treatment and the proportion progression free at set follow-up times (Table 4). Whilst this shows that time on treatment falls slightly below PFS in the first 6 months, it then crosses it and runs slightly above it from 12-21 months, before dropping off steeply just before 24 months when patients would complete their 35 cycles. Thus, the company's assumption of treatment continuing in line with PFS to 2 years for pembrolizumab is unlikely to bias the ICER substantially. Nevertheless, the ERG has tested the impact of adjusting pembrolizumab time on treatment relative to its derived PFS curve using the relative differences in the hazard of discontinuing and the hazard of progression or death between the extracted timepoints in Table 24.

Table 24. Extracted PFS and time on treatment data from KENOTE-042.

KEYNOTE 042 Time on Treatment		**KEYNOTE 042 Progression free survival**		**Model projection of Pembro PFS and ToT**	**Relative hazards by timepoint (Treatment discontinuation versus progression or death)***
Time (months)	Proportion	Time (months)	Proportion	Proportion	
0.0	1.000	0.0	1.000	[redacted]	
3.0	0.672	3.0	0.714	[redacted]	1.18
6.0	0.520	6.0	0.565	[redacted]	1.09
9.0	0.434	9.0	0.445	[redacted]	0.75
12.0	0.376	12.0	0.378	[redacted]	0.89
15.0	0.340	15.0	0.316	[redacted]	0.56
18.0	0.301	18.0	0.287	[redacted]	1.27
21.0	0.262	21.0	0.258	[redacted]	1.30
23.5	0.221	23.5	0.226	[redacted]	1.28
24.0	0.066	24.0	0.223	[redacted]	95.80

* Rate of treatment discontinuation over the rate of progression or death (PFS) between the extracted time points

3.2.7 Health related quality of life

This was presented in Section B.3.4 of Document B of the company submission, starting from page 108.

EQ-5D-3L was collected in the IMpower110 RCT. In the submission, values at baseline were provided for 97 TC3 or IC3 patients on atezolizumab (out of 107 randomised to this arm) and for 87 TC3 or IC3 patients on chemotherapy (of 98 randomised). In total there was a baseline value for 184 patients out of 205 randomised (90%).

The baseline utilities, using the UK tariff, were Provided in Table 40 of Document B (Reproduced in Table 25 below):

Table 25. Summary of baseline utilities (Source: Table 40 of the company submission, document B).

N	Min.	1st Qu.	Median	Mean	3rd Qu.	Max.
184	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Baseline and a follow-up EQ-5D observation were available for 84 patients on atezolizumab (of 107) and 79 patients on chemotherapy (of 98); combined, this gave data for 163 patients out of 205 (80%).

Post-baseline, 1528 observations were available in 163 patients (just over 9 observations per patient on average).

The ERG note that 21 patients have no EQ-5D-3L values at baseline (21/205, 10%). In terms of patients who had baseline and at least one follow-up, 42 patients were not included (205 minus 163) so it appears a further 21 patients had a baseline but no follow-up data. It was unclear what assumptions were made about missing data in the analyses. No reasons why data were missing were presented. There was no comparison of baseline characteristics of patients with and without EQ-5D (1) at baseline and (2) at follow-up.

In the company submission, three approaches to modelling utility values were considered, but one of these (the 'proximity to death' approach) was discarded because of wide, overlapping confidence intervals and counter-intuitive results.

The ERG accepts 'proximity to death' was not the best approach in this case given the diminishing numbers of patients contributing observations with increasing proximity to death, and the counterintuitive results generated.

The two models considered further were (1) pre-progression and post-progression, and (2) on treatment and off-treatment.

For the pre- and post-progression approach, data were available:

- Pre-progression for [redacted] patients on atezolizumab (of 107, [redacted]) and [redacted] patients on chemotherapy (of 98, [redacted]) patients
- Post-progression for [redacted] and [redacted] patients respectively

Results were presented in Table 42 of Document B (page 110), reproduced as Table 26 below.

Table 26. Health state utility values by progression status (Source: Table 42, Company submission, Document B)

Label	Estimate	SE	Lower limit 95% CI	Upper limit 95% CI
Pre progression				
Atezo (Arm A)	[redacted]	[redacted]	[redacted]	[redacted]
Chemo (Arm B)	[redacted]	[redacted]	[redacted]	[redacted]
Arm A and B pooled	[redacted]	[redacted]	[redacted]	[redacted]
Post progression				
Atezo (Arm A)	[redacted]	[redacted]	[redacted]	[redacted]
Chemo (Arm B)	[redacted]	[redacted]	[redacted]	[redacted]
Arm A and B pooled	[redacted]	[redacted]	[redacted]	[redacted]

The ERG notes that post-progression values in particular are based on small numbers with only [redacted] atezolizumab patients and [redacted] chemotherapy patients who progressed providing an EQ-5D value. Given the small numbers, the ERG also asked the company to present pre- and post-progression utilities for the wider population of IMpower110 at the clarification stage. The company provided this in their response (see company response to question B10 of the clarification letter), and it showed consistency with pooled results in Table 6.

Patients initially receiving atezolizumab appeared to have a higher post-progression utility value, although the p-value for the treatment by progression status interaction was not reported. This could, however, suggest that patients continue to derive some benefit after the RECIST criteria for progression in the RCT were met. This would support the idea that radiological progression and progression defined by symptom increase are not the same. The company, however, applied pulled values in the model, suggesting this to be conservative.

Using pooled values, progression of disease gave a decline in utility of [redacted]. There is some evidence that this [redacted].[37] This would also support the idea that radiological progression can occur before symptom increase in some patients.

The second approach to modelling utility values was by whether patients were on or off treatment; this was presented in Document B (section B.3.4.1.2). The results are reproduced in Table 27 below.

Table 27. Health state utility values by on/off treatment (Source: Table 44, Company submission, Document B)

Label	Estimate	SE	Lower limit 95% CI	Upper limit 95% CI
On treatment				
Atezo (Arm A)	[redacted]	[redacted]	[redacted]	[redacted]
Chemo (Arm B)	[redacted]	[redacted]	[redacted]	[redacted]
Arm A and B pooled	[redacted]	[redacted]	[redacted]	[redacted]
Off treatment				
Atezo (Arm A)	[redacted]	[redacted]	[redacted]	[redacted]
Chemo (Arm B)	[redacted]	[redacted]	[redacted]	[redacted]
Arm A and B pooled	[redacted]	[redacted]	[redacted]	[redacted]

As for the pre- and post-progression approach, some estimates are based on small numbers (off treatment there are values for [redacted] patients who had been on atezolizumab and [redacted] who had been on chemotherapy).

The ERG notes that point estimates of 'off treatment' utility appear more consistent between the treatment arms as compared to post-progression utility values, which could suggest greater homogeneity in the patient experience in the former compared to the latter.

Both approaches considered the stratification factors from the IMpower110 RCT in the models as potential explanatory variables (i.e. ECOG status, sex, histology). The company reports no statistically significant effects were seen for these variables.

The company selected the pre- and post-progression approach as their base-case. The justification was that although the main alternative, the on/off treatment approach, had the advantage of allowing for continued benefit after progression, it had the disadvantage of causing an artificial drop in utility when pembrolizumab reached its two-year maximum duration funded by NHS England.

The ERG agrees that this is an issue; however, the alternative approach of applying the utility drop associated with radiographic progression has its own limitations. It is possible that the observed post-progression values disproportionately reflect the health related quality of life of patients who have progressed radiographically but are yet to experience a significant deterioration in symptoms, which could result in the post-progression values overestimating average utility over time in the progressive disease state.

In addition, the drop in utility values from TA531 (NICE's guidance on pembrolizumab in this indication) was 0.11 on progression, (0.778 minus 0.668).[29] By contrast, the IMpower110 based figure gives a decline of [redacted]. The difference between pre- and post-progression for the two seemingly similar medicines suggests the true figure is uncertain. However, the company provided a scenario analysis that utilised the KENOTE-024 utility data, and this in fact moves the ICER in atezolizumab's favour.

It was assumed that any disutility from adverse events was captured in the EQ-5D data collected in IMpower110 (page 129, Document B). Whilst this is an uncertain assumption do the degree of missing data, it is unlikely to important consideration in the comparison between atezolizumab and pembrolizumab which are similarly well tolerated.

3.2.8 Resources and costs

Drug acquisition and administration

For pembrolizumab, the dosing assumed was 200mg every three weeks, with list price matching the one quoted in Section 2 of TA531 (£5,260 per cycle).

In terms of administration a cost was assumed for each infusion (hospital visit). This was the same as for TA531, at £183.54.
As an infusion takes 30 minutes, this seems plausible.

Adverse events

For adverse events, only grade 3 or 4 events were considered. For atezolizumab, any type of event with an incidence of 2% or more was included, but for pembrolizumab the threshold was higher: the incidence had to be 10% or more. This was because due to the way data from KEYNOTE-024 were presented.

It was unclear to the ERG why adverse event data were only taken from KEYNOTE-024, excluding the relevant patients from KEYNOTE-042.

Tables 56 and 57 of the company submission (Document B, page 125) show the number of events and the assumed treatment cost per event:

The company say the approach is conservative, since the definitions used include more adverse events for atezolizumab, but it would have been helpful to see a like-with-like comparison in the base case and the scenario described above as a sensitivity analysis. However, the ERG is generally satisfied with the approach, and would not expect differences in adverse event frequencies to be a substantial driver of the cost difference between the alternative medicines being compared.

Health care resource use

The company said that PD-L1 testing is part of routine practice and would not have a differential impact on the comparators being considered (would apply equally to atezolizumab and pembrolizumab), so the cost of testing was not included in the model (Document B, page 126).

The ERG agrees that the rationale (applies equally to all treatments) is sensible.

Resource use assumptions were set out for pre-progression and post-progression states per year and unit costs were then attached (Company submission, Tables 53 and 54, page 122, Document B). The assumed resource use either used data from TA531, the NICE Clinical Guideline on lung cancer diagnosis and a management (CG 121) or a Marie Curie report into the cost of end of life care.[29, 38, 39]

The data from TA531 seem relevant. The ERG is slightly concerned by the use of resource use assumptions from a clinical guideline because these could be seen as planned or aspirational levels rather than a description of the current service. In addition, the publication is now quite old, as is the Marie Curie report which was used to inform GP contact frequency in the progressive disease state. The ERG could not trace the company's number of 26.09 (fortnightly) GP home visits or occupational therapist visits per annum in the PD state from the references provided, and has some concern that these may not be applicable for the entire duration of time in the PD state.[39] The ERG's clinical advisor was also skeptical of the these assigned frequencies. However, having not been able to identify a better source for these parameters, the ERG explore the impact of reducing them by 25% and 50% in scenario analysis. Ideally, it would have been preferable to have some real world data on resource use frequencies or clinical validation for those health care resource use parameters obtained from older sources.

In addition to the health state costs, terminal care costs were applied in the model as a one of cost upon entry to the death state. These were applied equally in both arms of the model (only timing will affect any small differences between arms due to discounting).

The ERG agrees that this approach is reasonable and is consistent with other appraisals.

Subsequent therapy

For costing of subsequent therapies, the company used the same approach as in TA531, where the regimen received was assumed to be platinum-doublet chemotherapy (page 119, Document B). This was justified with reference the NICE's treatment pathway website and to usual care in the NHS.[40]

The assumed regimens were outlined in Table 48 of the company submission (Document B, page 120). 100% of progressed patients were assumed to receive one regimen of chemotherapy.

The ERG's clinical adviser has confirmed that assuming all patients who are subsequently treated receive platinum-doublet chemotherapy is plausible in the NHS. However, the ERG questioned the assumption that 100% of patients initially treated with first line immunotherapy will subsequently receive chemotherapy and asked the company to explore this further at the clarification stage. The company duly consulted three practicing oncologists who suggested that 50-70% of patients on first line IO monotherapy would receive subsequent treatment, and provided a scenario in response to the clarification letter that applied 50%. The impact on the ICER was minimal.

It can be noted that the subsequent treatments applied in the PD state of the model are not fully aligned with the treatments received following progression on atezolizumab in the IMpower110 trial. Of those receiving subsequent treatment in IMpower110 following progression on atezolizumab, the majority received chemotherapy, although subsequent immunotherapy and targeted therapies were reported for a small proportion of patients (Company submission, Table 12, document B). However, a similar picture was observed in the KENOTE trials of pembrolizumab. The ERG do not consider the differences in modelled subsequent treatments compared to the immunotherapy arms of the respective trials to be a major issues. Of potentially greater importance, for determining the comparative efficacy of permbrolizumab versus atezolizumab in the NMA, is the degree of crossover to immunotherapy from the chemotherapy arms of respective trials.

4 COST EFFECTIVENESS RESULTS

4.1 Company's cost effectiveness results

The company presented an incremental cost-effectiveness analysis and a cost comparison (assuming equal efficacy for atezolizumab and pembrolizumab) – both at list prices and including an approved patient access scheme (PAS) price for atezolizumab. Neither set of results is appropriate for decision making because a confidential PAS price is also available for permbrolizumab.

The company expressed a preference for the cost comparison approach given the lack of significant difference in efficacy from the NMA. This was supported by the clinical experts they consulted, who highlighted the lack of evidence to support a meaningful difference in efficacy or safety between atezolizumab and pembrolizumab in this indication.

Nevertheless, the confidence intervals on the hazard ratios from the NMA are relatively wide and do not rule out the possibility of a meaningful difference. Therefore, it is appropriate that the company have explored both approaches.

In the base case cost-effectiveness analysis at list prices (Company submission, document B, Table 60), atezolizumab offered slightly less QALYs [redacted].

Applying the PAS discount to atezolizumab reduced the lifetime cost in the pembrolizumab arm from [redacted] to [redacted] (Company submission, document B, Table 61). Pembrolizumab at list price cost an additional £47,059 for 0.08 additional QALYs, an ICER of £560,832, putting atezolizumab in the south west quadrant relative to permbrolizumab. The company submission estimates that the incremental cost per QALY (pembrolizumab versus atezolizumab) only falls below £30k if pembrolizumab is discounted by at least [redacted] and below £20k per QALY at a minimum discount of [redacted]

The QALY difference is driven primarily by a small difference of 0.14 life years favouring pembrolizumab. The cost difference is driven primarily by differences in drug acquisition costs, [redacted].

The company's cost comparison results are provided in Table 62 (at list prices) and Table 63 (including the atezolizumab PAS) of the company submission (document B).

The ERG questioned the small difference in progressive disease costs despite the stated assumption of equal efficacy.

In response to the clarification letter, the company indicated that this was due to subsequent treatment costs being conditioned on time to treatment discontinuation, for which atezolizumab has its own separate curve, whilst pembrolizumab time on treatment is assumed equal to PFS up to the two year stopping point.

Whilst it may be reasonable to assume that subsequent treatment occurs upon discontinuation of atezolizumab (allowing for some post-progression treatment), it may be less so in the longer term where the TTD curve falls below PFS. Furthermore, the application of further treatment costs upon stopping pembrolizumab at two years lacks clinical validity. In this context, it may be more appropriate use the PFS curve to determine the proportion of patients initiating further treatment over time. However, the company's method only affects the timing of subsequent treatment costs in the context of their model, and so the impact on the cost difference would be minimal. Nevertheless, the ERG explored the impact of conditioning the timing of subsequent treatment costs on the PFS curve for permbrolizumab beyond two years. Further, the ERG assessed the impact on the cost comparison of assuming that 50% (rather than 100%) of patients who commence treatment on atezolizumab or pembrolizumab receive subsequent chemotherapy. This is in line with the advice the company received from clinical experts at the clarification stage.

4.2 Company's sensitivity analyses

The company presented probabilistic sensitivity analysis for the cost-effectiveness base case. This indicated a high degree of uncertainty around the small incremental QALY, whilst the incremental cost was dependent on whether the list price or PAS price was applied to atezolizumab. The scatter plot and CEAC are provided for the PAS price case below. The probabilistic results with the appropriate PAS price included for pembrolizumab are provided

by the ERG in a confidential appendix. There was an error in the computation of the CEAC provided by the company in their submission, which they updated at the clarification stage. However, the probabilities of cost-effectiveness for the two treatments still did not sum to one in the updated figure. Therefore, the ERG has recomputed the CEAC provided below using 2,500 probabilistic iterations.

Figure 4. Incremental Cost-Effectiveness Plane (PAS price for atezolizumab) (Source: Figure 17 of the company's response to the clarification letter)

Figure 5. Cost-Effectiveness Acceptability Curves - (PAS price for atezolizumab)

The company further provided a large number of scenario analyses, which they added to at the clarification stage based on ERG requests, and updated the Table to include measures of net monetary benefit and net health benefits at cost-effectiveness thresholds of £20,000 and £30,000. The updated table using the PAS price for atezolizumab (list price for pembrolizumab) is provided as Table 28 below. Under all the scenarios explored, atezolizumab produced the highest net benefits at the applied thresholds.

Omissions from the scenario analyses were application of the time dependent hazard ratios from the fractional polynomial NMA, and variation in the assumed treatment effect duration for pembrolizumab. The ERG acknowledges the implausible extrapolations produced for pembrolizumab when applying the FP NMA HRs in the company model but explores the impact of extending the treatment effect duration of pembrolizumab in Chapter 5.

Table 28. Scenario analyses results pembrolizumab vs. atezolizumab* (PAS price) (Source: Table 13 of the company's response to the clarification letter)

Parameter	Value	Atezo Mono			Pembro mono			Pembro Mono vs. Atezo Mono						
		Life Years	QALYS	Costs	Life Years	QALYS	Costs	Inc. QALYs	Inc. Costs	ICER*	NMB* WTP £30K	NMB* WTP £20K	NHB* WTP £30K	NHB* WTP £20K
Base case		[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	0.08	47,059	560,832*	-44,542*	-45,381*	-1.5*	-2.3*
Distribution OS	Exponential	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	0.10	48,475	476,303*	-45,422*	-46,439*	-1.5*	-2.3*
	Log-normal	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	0.12	47,481	401,488*	-43,933*	-45,116*	-1.5*	-2.3*
	Gen Gamma	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	0.09	47,186	536,154*	-44,546*	-45,426*	-1.5*	-2.3*
	Log-logistic	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	0.12	47,445	405,563*	-43,935*	-45,105*	-1.5*	-2.3*
	Gompertz	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	0.29	48,869	170,602*	-40,276*	-43,140*	-1.3*	-2.2*
	KM with Exponential tail	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	0.10	48,235	461,996*	-45,103*	-46,147*	-1.5*	-2.3*
	KM with Weibull tail	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	0.08	47,010	565,197*	-44,514*	-45,346*	-1.5*	-2.3*
	KM with Log-normal tail	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	0.12	47,386	392,050*	-43,760*	-44,969*	-1.5*	-2.2*
	KM with Gamma tail	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	0.09	47,090	538,405*	-44,466*	-45,340*	-1.5*	-2.3*

	KM with Log-logistic tail	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	0.12	47,358	402,037*	-43,824*	-45,002*	-1.5*	-2.3*
	KM with Gompertz tail	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	0.29	48,746	170,678*	-40,178*	-43,034*	-1.3*	-2.2*
Distribution PFS	Exponential	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	0.09	59,018	645,357*	-56,275*	-57,189*	-1.9*	-2.9*
	Weibull	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	0.09	51,166	576,877*	-48,505*	-49,392*	-1.6*	-2.5*
	Log-normal	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	0.08	47,451	561,842*	-44,917*	-45,762*	-1.5*	-2.3*
	Log-logistic	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	0.08	46,549	552,459*	-44,022*	-44,864*	-1.5*	-2.2*
	Gompertz	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	0.08	46,559	563,118*	-44,079*	-44,906*	-1.5*	-2.2*
	KM with Exponential tail	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	0.09	45,394	507,668*	-42,711*	-43,606*	-1.4*	-2.2*
	KM with Weibull tail	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	0.09	45,574	523,873*	-42,964*	-43,834*	-1.4*	-2.2*
	KM with Log-normal tail	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	0.08	45,866	552,201*	-43,374*	-44,205*	-1.4*	-2.2*
	KM with Gamma tail	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	0.08	45,883	553,930*	-43,398*	-44,226*	-1.4*	-2.2*
	KM with Log-logistic tail	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	0.08	45,885	554,118*	-43,401*	-44,229*	-1.4*	-2.2*
	KM with Gompertz tail	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	0.08	45,925	558,277*	-43,457*	-44,280*	-1.4*	-2.2*
	Exponential	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	0.08	55,120	656,895*	-52,603*	-53,442*	-1.8*	-2.7*

Distribution TTD	Weibull	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	0.08	46,041	548,696*	-43,524*	-44,363*	-1.5*	-2.2*
	Log-normal	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	0.08	35,726	425,770*	-33,209*	-34,048*	-1.1*	-1.7*
	Log-logistic	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	0.08	35,866	427,431*	-33,348*	-34,188*	-1.1*	-1.7*
	Gompertz	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	0.08	37,358	445,211*	-34,840*	-35,679*	-1.2*	-1.8*
	KM with Exponential tail	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	0.08	57,250	682,279*	-54,733*	-55,572*	-1.8*	-2.8*
	KM with Weibull tail	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	0.08	46,510	554,282*	-43,992*	-44,832*	-1.5*	-2.2*
	KM with Log-normal tail	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	0.08	37,683	449,090*	-35,166*	-36,005*	-1.2*	-1.8*
	KM with Gamma tail	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	0.08	47,536	566,506*	-45,018*	-45,857*	-1.5*	-2.3*
	KM with Log-logistic tail	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	0.08	38,132	454,439*	-35,615*	-36,454*	-1.2*	-1.8*
	KM with Gompertz tail	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	0.08	36,104	430,267*	-33,586*	-34,425*	-1.1*	-1.7*
Pembro treatment duration assumption	Set it equal to atezo actual treatment duration up to two years, when pemro	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	0.08	51,873	618,203*	-49,356*	-50,195*	-1.6*	-2.5*

	is discontinued													
Utility method	IMpower110 (On/Off treatment)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	0.03	47,059	1,433,902*	-46,075*	-46,403*	-1.5*	-2.3*
	IMpower110 (Proximity to death)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	0.11	47,059	441,166*	-43,859*	-44,926*	-1.5*	-2.2*
	Chouaid et al. 2013	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	0.08	47,059	591,720*	-44,674*	-45,469*	-1.5*	-2.3*
	Nafees et al. 2008	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	0.00	47,059	22,209,162*	-46,996*	-47,017*	-1.6*	-2.4*
	KEYNOTE-024	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	0.05	47,059	864,808*	-45,427*	-45,971*	-1.5*	-2.3*
Time horizon	5 years	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	0.12	55,315	453,856*	-51,658*	-52,877*	-1.7*	-2.6*
	10 years	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	0.14	49,792	363,872*	-45,687*	-47,055*	-1.5*	-2.4*
	15 years	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	0.10	47,830	456,515*	-44,687*	-45,735*	-1.5*	-2.3*
NMA	FE model	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	0.06	37,862	677,054*	-40,811*	-41,442*	-1.4*	-2.1*
Administration schedule	Q6W vs. Q4W atezo	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	0.08	48,555	578,658*	-46,038*	-46,877*	-1.5*	-2.3*
Capping of treatment benefit	Atezo OS treatment effect capped at 96 months	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	0.14	47,464	345,711*	-43,345*	-44,718*	-1.4*	-2.2*

	Atezo OS treatment effect capped at 60 months	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	0.2	48,022	234,870*	-41,888*	-43,933*	-1.4*	-2.2*
# Pembro PFS cap	Pembro PFS and OS cap at 60 months	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	0.08	47,403	597,908*	-45,025*	-45,818*	-1.5*	-2.3*
# half cycle correction	No half-cycle correction for drug and administration costs in the progression-free state	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	0.08	47,554	566,728*	-45,037*	-45,876*	-1.5*	-2.3*
# % of patients receiving subsequent therapy	50% of patients receive subsequent therapy	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	0.08	46,768	557,358*	-44,251*	-45,090*	-1.5*	-2.3*
# Utilities	Utility values for the whole ITT WT population	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	0.07	47,059	636,699*	-44,842*	-45,581*	-1.5*	-2.3*
# half cycle correction, % of patients receiving	All three changes as suggested by	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	0.07	47,263	639,448*	-45,045*	-45,784*	-1.5*	-2.3*

subsequent therapy and utilities	the ERG and described in the previous three scenarios													

*pembro versus atezo: high ICER indicates atezo is worth funding; ICER, incremental cost-effectiveness ratio; LYs, life years; QALYs, quality-adjusted life years; KM, Kaplan Meier; NMA, network meta-analysis; HR, hazard ratio; FE, fixed effects; #, new scenario analyses provided

NMB, net monetary benefit, NMB is calculated as: *(incremental gain in QALYs x threshold) – incremental cost*. A positive incremental NMB indicats that the intervention is cost-effective compared with the alternative at the given willingness-to-pay threshold.;

NHB, net health benefit calculated as: *incremental gain in QALYs – (incremental cost / opportunity cost threshold).* A positive NHB implies that overall population health would be increased as a result of the new intervention

Negative NMB and negative NHB mean atezo is worth funding

4.3 Model validation and face validity check

As noted in previous sections, the company selected time to event curves using measures for statistical fit, visual inspection, and clinical plausibility based on consultation with experts. The company also note validation against all available evidence.

With respect to model quality control, the company note that this was carried out by an external consultancy, including cell by cell formula and reference checking, and model functionality checks.

In addition, the ERG has carried out its own formula and cell referencing checks and has identified no material errors. Further functionality checks were applied by the ERG, such as: setting hazard ratios to one and checking OS and PFS were equalised; setting all utilities to one to ensure QALYs equalled life years; and equalising all the parameters expected to drive differences in costs and effects (based on the model description) and confirming the model showed zero difference between treatments with these settings. These checks all generated results consistent with expectation. One minor bug was identified in the pembrolizumab cohort trace which seemed to allow PFS to exceed OS in the tails of the selected distribution. The ERG assessed the impact of overriding the PFS curve with the OS curve where this occurred, and it had minimal impact on the cost-effectiveness results.

The validity of the company's fitted survival curves was discussed in Chapter 3 above (see 3.2.6).

5 EVIDENCE REVIEW GROUP'S ADDITIONAL ANALYSES

5.1 Exploratory and sensitivity analyses undertaken by the ERG

Based on the arguments set out in the critique of the company's case (Chapter 3), the ERG conducted several further scenario analyses to explore the impact of remaining uncertainties on the company's cost effectiveness findings. The scenarios assessed are set our below.

List of cost-effectiveness analysis scenarios assessed by the ERG (see Table 29 for results):

1. Correcting pembrolizumab PFS to remain below OS at all times.
2. Increasing the treatment effect duration cap for pembrolizumab from 5 years, to 6, 7 and 8 years
3. Combination of 2 with selection of generalized gamma OS reference curve
4. Combination of 2 with selection of the log-logistic OS reference curve
5. Subsequent treatment costs conditioned on the PFS curve for pembrolizumab, rather than treatment discontinuation.
6. Pembrolizumab time on treatment adjusted relative to PFS using data from KENOTE-042
7. 25% and 50% reductions in progressive disease GP and therapist costs.
8. Application of pembrolizumab HRs from the random effects NMA using the Impower110 September 2018 data cut.

List of cost-comparison scenarios assessed by the ERG (see Table 30 for results):

1. Subsequent treatment costs conditioned on the PFS curve for pembrolizumab, rather than treatment discontinuation.
2. 50% (rather than 100%) of patients who commence treatment on atezolizumab or pembrolizumab receive subsequent chemotherapy.
3. 1 and 2 combined with efficacy equalized

5.2 Impact on the ICER of additional clinical and economic analyses undertaken by the ERG

The results of the further scenario analysis conducted by the ERG are provided in Table 29 (cost-utility model) and Table 30 (cost comparison) below. Atezolizumab continues to provide positive incremental net benefits at the thresholds of £20k and £30k across all scenarios explored (at PAS price for atezolizumab, list price for pembrolizumab). Of the

scenarios explored, the ICER and incremental net benefits are most sensitive to the assumed treatment effect durations for pembrolizumab and the Impower110 data cut used to inform the NMA. It can be noted that when the earlier cut from IMpower110 is used, the direction of the QALY difference switches in atezolizumab's favour. The ICER and net benefits are also modestly sensitive to the adjusted time on treatment for pembrolizumab as per scenario 6. The other scenarios result in only small changes to the ICER and incremental net benefits. The cost comparison results were insensitive to the additional scenarios explored by the ERG (Table 30).

Table 29. ERG scenario analyses results atezolizumab versus pembrolizumab* (PAS price)

Parameter	Value	Atezo Mono			Pembro mono			Atezo Mono vs. Pembro Mono						
		Life Years	QALYS	Costs	Life Years	QALYS	Costs	Inc. QALYs	Inc. Costs	ICER	Inc. NMB WTP £30K	Inc. NMB WTP £20K	Inc. NHB WTP £30K	Inc. NHB WTP £20K
Base case		[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	-0.08	-47,059	560,832	44,542	45,381	1.5	2.3
1. Pembrolizumab PFS	Adjusted to always remain below OS in the tail of the distribution	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	-0.084	-47,066	561,530	44,552	45,390	1.5	2.3
2. Pembrolizumab treatment effect duration cap	6 years	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	-0.132	-47,475	360,717	43,527	44,843	1.5	2.2
	7 years	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	-0.168	-47,795	284,012	42,746	44,429	1.4	2.2
	8 years	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	-0.197	-48,047	243,532	42,128	44,101	1.4	2.2
3. OS ggamma with Pembrolizumab treatment effect duration cap	6 years	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	-0.143	-47,661	333,588	43,375	44,803	1.4	2.2
	7 years	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	-0.186	-48,030	258,679	42,460	44,317	1.4	2.2
	8 years	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	-0.220	-48,327	219,549	41,723	43,924	1.4	2.2
4. OS log-logistic with Pembrolizumab treatment effect duration cap	6 years	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	-0.177	-47,956	271,668	42,660	44,425	1.4	2.2
	7 years	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	-0.222	-48,346	217,594	41,681	43,903	1.4	2.2
	8 years	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	-0.258	-48,655	188,291	40,903	43,487	1.4	2.2
5. Pembrolizumab time to subsequent therapy	Based on PFS curve rather than assumed TTD	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	-0.084	-46,770	557,388	44,253	45,092	1.5	2.3

6. Pembrolizumab time on treatment	Adjusted relative to PFS using data from KENOTE-042	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	-0.084	-44,221	527,006	41,704	42,543	1.4	2.1
	Adjusted relative to PFS using data from KENOTE-042 + removal of half cycle correction for time on treatment	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	-0.084	-45,024	536,580	42,507	43,346	1.4	2.2
7. PD health state costs.	25% reduction in PD GP and therapist costs.	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	-0.084	-46,615	555,537	44,098	44,937	1.5	2.2
	25% reduction in PD GP and therapist costs.	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	-0.084	-46,171	550,242	43,653	44,493	1.5	2.2
8. Pembrolizumab HRs	Random effects NMA, IMpower110 Sept 2018 data cut	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	0.441	-58,042	-131,592	71,274	66,864	2.4	3.3

ICER, incremental cost-effectiveness ratio; LYs, life years; QALYs, quality-adjusted life years; NMA, network meta-analysis; HR, hazard ratio; TTD, time to treatment discontinuation.

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.;

NHB, net health benefit calculated as: *incremental gain in QALYs – (incremental cost / opportunity cost threshold).* A positive NHB implies that overall population health would be increased as a result of the new intervention

Table 30. ERG cost comparison scenario analyses results atezolizumab versus pembrolizumab (atezolizumab PAS price)

Parameter	Value	Atezolizumab	Pembrolizumab	Atezolizumab vs. Pembrolizumab
		Costs	Costs	Incremental savings
Base case		[redacted]	[redacted]	(52,078)
1. Pembrolizumab time to subsequent therapy	Based on PFS curve rather than assumed TTD	[redacted]	[redacted]	(51,682)
2. Use of subsequent chemotherapy	50% rather than 100%	[redacted]	[redacted]	(£51,792)
3. 1 and 2 combined with		[redacted]	[redacted]	(£51,594)

5.3 ERG's preferred assumptions

The ERGs preferred assumptions for their base case are the same as the company's except for the following:

1. No half-cycle correction for treatment costs, to ensure all patients receive
2. Pembrolizumab PFS adjusted to remain below OS at all times
2. Pembrolizumab time to subsequent chemotherapy based on extrapolated PFS rather than applied to all who discontinue at the two-year stopping point
3. Pembrolizumab time on treatment adjusted relative to PFS using data from KEYNOTE-042
4. 50% receive subsequent therapy rather than 100%, in line with the company's clinical expert opinion.
5. 50% reduction in GP home visits and therapist visits in the progressive disease health state, given the ERGs inability to identify the companies applied frequencies in the stated sources and the ERGs own clinical expert advice.

The impact of applying these changes cumulatively is provided in Table 31 below. Whilst the changes reduce the ICER for pembrolizumab versus atezolizumab somewhat, it remains highly uncertain given the uncertainty surrounding the QALY gain which is driven by wide confidence intervals surrounding the hazard ratios from the NMA. The probabilistic output with the ERG base case settings are provided in Table 32, Figure 6, and Figure 7. Note, the ERG have not incorporated distributions for the adjustments made to the time on treatment curve for pembrolizumab relative to its PFS curve (these are applied deterministically).

Regarding the assumption of loss of efficacy for pembrolizumab relative to chemotherapy from 5 years onwards, this seems to be quite a pessimistic assumption in the context of the recently reported 5 year data from the KEYNOTE-024 study, where the reported HR for OS (versus chemotherapy) was 0.62 (0.48–0.81), compared with a hazard ratio of 0.63; 95% CI (0.47 to 0.86) reported at a median follow-up of 25 months (Reck 2019).[41, 42] This suggests no obvious loss in relative efficacy for pembrolizumab versus chemotherapy by 5 years follow-up, and so complete loss from 5 years would seem like an unlikely scenario. However, it can be noted that in KEYNOTE-024, patients randomized to pembro who completed two years of therapy or stopped pembrolizumab after achieving complete response and then had progressive disease, were eligible for a second course of pembrolizumab monotherapy. It is the ERG's understanding that such re-challenge would not be permitted in the NHS in England, and so the applicability of these results to the NHS is questionable. Thus, given the ongoing lack of certainty around the duration of treatment effect for pembrolizumab and atezolizumab, the ERG provides a range of scenarios below, using the ERG base case as the reference point in Table 33.

It can be noted that as the treatment effect duration for pembrolizumab increases, the QALY gain increases while the incremental cost remains relatively stable. However, the QALY difference remains highly uncertain in all these scenarios given the uncertainty around the HRs for permbrolizumab versus atezolizumab.

Table 31. Incremental changes leading to the ERGs base case (atezolizumab versus pembrolizumab)

Parameter	Value	Atezo Mono			Pembro mono			Atezo Mono vs. Pembro Mono						
		Life Years	QALYS	Costs	Life Years	QALYS	Costs	Inc. QALYs	Inc. Costs	ICER	Inc. NMB WTP £30K	Inc. NMB WTP £20K	Inc. NHB WTP £30K	Inc. NHB WTP £20K
Company base case		[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	-0.084	-47,059	560,832	44,542	45,381	1.5	2.3
+ Half cycle correction for time on treatment	removed	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	-0.084	-47,554	566,728	45,037	45,876	1.5	2.3
+Pembrolizumab PFS	Adjusted to remain below OS in the tail of the distribution	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	-0.084	-47,561	567,432	45,046	45,885	1.5	2.3
+Pembrolizumab time to subsequent therapy	Based on PFS curve rather than assumed TTD	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	-0.084	-47,278	564,058	44,764	45,602	1.5	2.3
+Pembrolizumab time on treatment	Adjusted relative to PFS using data from KENOTE-042	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	-0.084	-44,758	533,989	42,243	43,081	1.4	2.2
+Subsequent therapy	50% receive it rather than 100%	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	-0.084	-44,608	532,198	42,093	42,931	1.4	2.1
+ PD health state costs. (ERG base)	50% reduction in PD GP and therapist visits	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	-0.084	-43,715	521,544	41,200	42,038	1.4	2.1

ICER, incremental cost-effectiveness ratio; **LYs**, life years; **QALYs**, quality-adjusted life years; **TTD**, time to treatment discontinuation.

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.;

NHB, net health benefit calculated as: *incremental gain in QALYs – (incremental cost / opportunity cost threshold).* A positive NHB implies that overall population health would be increased as a result of the new intervention

Table 32. ERG base case – atezolizumab versus pembrolizumab (probabilistic)

	Total costs (£)	Total LY	Total QALYs	Incr. costs (£)	Incr. LY	Incr. QALYs	ICER (£/QALY)
Pembro	[redacted]	[redacted]	[redacted]	-43,080	-0.21	-0.14	309,723
Atezo	[redacted]	[redacted]	[redacted]				
ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years,							

*Caveat: PSA does not include distributions on the relative hazards used by the ERG to adjust the pembrolizumab time on treatment curve relative to its PFS curve

Figure 6. ERG base case cost-effectiveness scatter plot (atezolizumab versus pembrolizumab)

Figure 7. ERG base case cost-effectiveness acceptability curves

Table 33. Exploration of the duration of treatment effect with reference to the ERG base case (atezolizumab versus pembrolizumab)

Parameter	Value	Atezo Mono			Pembro mono			Atezo Mono vs. Pembro Mono						
		Life Years	QALYS	Costs	Life Years	QALYS	Costs	Inc. QALYs	Inc. Costs	ICER	Inc. NMB WTP £30K	Inc. NMB WTP £20K	Inc. NHB WTP £30K	Inc. NHB WTP £20K
ERG base		[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	-0.084	-43,715	521,544	41,200	42,038	1.4	2.1
Pembro treatment effect duration	6 years	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	-0.132	-44,000	334,336	40,052	41,368	1.3	2.1
	7 years	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	-0.168	-44,222	262,780	39,173	40,856	1.3	2.0
	8 years	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	-0.197	-44,397	225,034	38,478	40,451	1.3	2.0
Atezolizumab treatment effect duration	8 years	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	-0.137	-44,016	320,598	39,897	41,270	1.3	2.1
Atezolizumab and pembrolizumab treatment effect durations	Atezo 8; pembro 6	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	-0.185	-44,306	239,495	38,756	40,606	1.3	2.0
	Atezo 8; pembro 7	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	-0.222	-44,528	200,879	37,878	40,095	1.3	2.0
	Atezo 8; pembro 8	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	-0.251	-44,704	178,334	37,184	39,690	1.2	2.0

ICER, incremental cost-effectiveness ratio; LYs, life years; QALYs, quality-adjusted life years

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.;

NHB, net health benefit calculated as: *incremental gain in QALYs – (incremental cost / opportunity cost threshold).* A positive NHB implies that overall population health would be increased as a result of the new intervention

5.4 Conclusions of the cost effectiveness section

Overall, the ERG believes the company have presented a reasonable economic case given the lack of evidence to identify a meaningful difference in efficacy or safety between the medicines being compared. However, there are substantial uncertainties around the case, and a meaningful difference between the drugs cannot be ruled out based on the available evidence. Whilst changes to key parameters such as time on treatment and the assumed duration of treatment effect for pembrolizumab have a substantial effect on the ICER, the difference in QALYs remains highly uncertain in across all scenarios given the uncertainty surrounding the hazard ratios from the NMA.

Key issues in the cost-effectiveness case that would benefit from further scrutiny and discussion include:

1. The expected duration of treatment effects for pembrolizumab versus chemotherapy in the context of a two-year stopping rule and no re-challenge for progressive disease
2. The expected gains in treatment effect duration that might be achievable with atezolizumab with no stopping rule
3. The expected difference between time on treatment and progression free survival for pembrolizumab
4. The health care resource use frequencies and health state costs for the progressive disease state of the company model.

As the cost-effectiveness case or cost comparison case is predicated on the validity NMA, further clarity on the comparability of high PD-L1 cohorts identified using the SP142 assay (as per IMpower110) and the 22C3 assay (as per the KEYNOTE trials) would be beneficial.

6 END OF LIFE

Based on the evidence and modelling provided, it is unlikely that NICE end of life criteria will apply in the context of this appraisal, on the grounds that the [redacted]*, and there is insufficient evidence to support a meaningful difference in life expectancy between the two treatments.*

7 REFERENCES

1. Cancer Research UK. Lung cancer incidence. Available from: https://www.cancerresearchuk.org/health-professional/cancer-statistics/statistics-by-cancer-type/lung-cancer#heading-Zero.

2. Royal College of Physicians. NLCA annual report 2018 2020. Available from: https://www.rcplondon.ac.uk/projects/outputs/nlca-annual-report-2018.

3. Langer CJ, Besse B, Gualberto A, Brambilla E, Soria JC. The evolving role of histology in the management of advanced non-small-cell lung cancer. J Clin Oncol. 2010;28(36):5311-20.

4. Beckett P. National Lung Cancer Audit (NLCA) annual report 2018 2019. Available from: https://www.rcplondon.ac.uk/projects/outputs/national-lung-cancer-audit-nlca-annual-report-2018.

5. Blandin Knight S, Crosbie PA, Balata H, Chudziak J, Hussell T, Dive C. Progress and prospects of early detection in lung cancer. Open Biol. 2017;7(9).

6. Cancer Research UK. Lung cancer survival by stage at diagnosis 2019. Available from: https://www.cancerresearchuk.org/health-professional/cancer-statistics/statistics-by-cancer-type/lung-cancer/survival#heading-Three.

7. American Cancer Society. Lung Cancer Survival Rates 2020. Available from: https://www.cancer.org/cancer/lung-cancer/detection-diagnosis-staging/survival-rates.html.

8. Tishelman C, Degner LF, Rudman A, Bertilsson K, Bond R, Broberger E, et al. Symptoms in patients with lung carcinoma: distinguishing distress from intensity. Cancer. 2005;104(9):2013-21.

9. Cooley ME. Symptoms in adults with lung cancer. A systematic research review. J Pain Symptom Manage. 2000;19(2):137-53.

10. de Marinis F, Pereira JR, Fossella F, Perry MC, Reck M, Salzberg M, et al. Lung Cancer Symptom Scale outcomes in relation to standard efficacy measures: an analysis of the phase III study of pemetrexed versus docetaxel in advanced non-small cell lung cancer. J Thorac Oncol. 2008;3(1):30-6.

11. Shi Y, Sun Y, Yu J, Ding C, Wang Z, Wang C, et al. China experts consensus on the diagnosis and treatment of advanced stage primary lung cancer (2016 version). Asia Pac J Clin Oncol. 2017;13(1):87-103.

12. Muers MF, Round CE. Palliation of symptoms in non-small cell lung cancer: a study by the Yorkshire Regional Cancer Organisation Thoracic Group. Thorax. 1993;48(4):339-43.

13. Electronic Medicines Compendium. Tecentriq 1,200 mg concentrate for solution for infusion 2020. Available from: https://www.medicines.org.uk/emc/product/8442/smpc.

14. Meng X, Huang Z, Teng F, Xing L, Yu J. Predictive biomarkers in PD-1/PD-L1 checkpoint blockade immunotherapy. Cancer Treat Rev. 2015;41(10):868-76.

15. Dietel M, Savelov N, Salanova R, Micke P, Bigras G, Hida T, et al. Real-world prevalence of programmed death ligand 1 expression in locally advanced or metastatic non-

small-cell lung cancer: The global, multicenter EXPRESS study. Lung Cancer. 2019;134:174-9.

16. European Medicines Agency. Tecentriq 2020. Available from: https://www.ema.europa.eu/en/medicines/human/EPAR/tecentriq.

17. National Institute for Health and Care Excellence. Lung cancer: diagnosis and management [NG122] 2019. Available from: https://www.nice.org.uk/guidance/ng122.

18. Herbst RS, Giaccone G, de Marinis F, Reinmuth N, Vergnenegre A, Barrios CH, et al. Atezolizumab for first-line treatment of PD-L1-selected patients with NSCLC. N Engl J Med. 2020;383(14):1328-39.

19. Herbst RS, Giaccone G, de Marinis F, Reinmuth N, Vergnenegre A, Barrios CH, et al. Protocol for: Atezolizumab for first-line treatment of PD-L1-selected patients with NSCLC. N Engl J Med. 2020;383(14):1328-39.

20. Herbst RS, de Marinis F, Giaccone G, Reinmuth N, Vergnenegre A, Barrios CH, et al. LBA1 Clinical efficacy of atezolizumab (atezo) in biomarker subgroups by SP142, SP263 and 22C3 PD-L1 immunohistochemistry (IHC) assays and by blood tumour mutational burden (bTMB): Results from the IMpower110 study. Ann Oncol. 2019;30:xi62-xi3.

21. Spigel D, de Marinis F, Giaccone G, Reinmuth N, Vergnenegre A, Barrios CH, et al. IMpower110: Interim overall survival (OS) analysis of a phase III study of atezolizumab (atezo) vs platinum-based chemotherapy (chemo) as first-line (1L) treatment (tx) in PD-L1-selected NSCLC. Ann Oncol. 2019;30(Supplement 5):v915.

22. F. Hoffmann-La Roche Ltd. IMpower110 - Final Analysis (Data on File). 2020.

23. de Marinis F, Giaccone G, Herbst RS, Oprean C, Szczesna A, Boukovinas I, et al. Patient-reported outcomes (PROs) in the randomized, phase III IMpower110 study of atezolizumab (atezo) vs chemotherapy in 1L metastatic NSCLC. J Clin Oncol. 2020;38(15_Supp):9594.

24. Gadgeel S, Kowanetz M, Zou W, Hirsch FR, Kerr KM, Gandara DR, et al. Clinical efficacy of atezolizumab (Atezo) in PD-L1 subgroups defined by SP142 and 22C3 IHC assays in 2L1 NSCLC: Results from the randomized OAK study. Ann Oncol. 2017;28(Supplement 5):v460-1.

25. European Medicines Agency. Question and answer on adjustment for cross-over in estimating effects in oncology trials. London; 2018. Report No.: EMA/300567/2018.

26. Dias S, Welton NJ, Sutton AJ, Ades AE. NICE DSU technical support document 2: a generalised linear modelling framework for pairwise and network meta-analysis of randomised controlled trials. Sheffield: NICE Decision Support Unit; 2011.

27. Jansen JP. Network meta-analysis of survival data with fractional polynomials. BMC Med Res Methodol. 2011;11:61.

28. Turner RM, Jackson D, Wei Y, Thompson SG, Higgins JP. Predictive distributions for between-study heterogeneity and simple methods for their application in Bayesian meta-analysis. Stat Med. 2015;34(6):984-98.

29. National Institute for Health and Care Excellence. Pembrolizumab for untreated PD-L1-positive metastatic non-small-cell lung cancer [TA531] London/Manchester: National Institute

for Health and Care Excellence; 2018. Available from: https://www.nice.org.uk/guidance/ta531.

30. Pocock SJ, Clayton TC, Altman DG. Survival plots of time-to-event outcomes in clinical trials: good practice and pitfalls. Lancet. 2002;359(9318):1686-9.

31. Garon EB, Hellmann MD, Rizvi NA, Carcereny E, Leighl NB, Ahn MJ, et al. Five-Year Overall Survival for Patients With Advanced Non–Small-Cell Lung Cancer Treated With Pembrolizumab: Results From the Phase I KEYNOTE-001 Study. J Clin Oncol. 2019;37(28):2518-27.

32. Nanda S. KEYNOTE-024: 'Meaningful' OS improvement with pembrolizumab maintained at 5 years: Springer Healthcare; 2020. Available from: https://oncology.medicinematters.com/esmo-2020/lung-and-thoracic-tumors/keynote-024-pembrolizumab-nsclc/18448250.

33. European Medicines Agency. Keytruda: summary of product characteristics. London: European Medicines Agency.

34. Reck M, Rodríguez-Abreu D, Robinson AG, Hui R, Csőszi T, Fülöp A, et al. Pembrolizumab versus chemotherapy for PD-L1-positive non-small-cell lung cancer. N Engl J Med. 2016;375(19):1823-33.

35. 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. Lancet. 2019;393(10183):1819-30.

36. Velcheti V, Chandwani S, Chen X, Pietanza MC, Burke T. First-line pembrolizumab monotherapy for metastatic PD-L1-positive NSCLC: real-world analysis of time on treatment. Immunotherapy. 2019;11(10):889-901.

37. Pickard AS, Neary MP, Cella D. Estimation of minimally important differences in EQ-5D utility and VAS scores in cancer. Health Qual Life Outcomes. 2007;5:70.

38. National Institute for Health and Care Excellence. Lung cancer: diagnosis and management [CG121]. London/Manchester; 2011.

39. Taylor D, Carter S, Marie Curie Cancer Care. Understanding the cost of end of life care in different settings. University of London; 2004.

40. National Institute for Health and Care Excellence. NICE pathways: Treating non-small-cell lung cancer London/Manchester: National Institute for Health and Care Excellence; 2020. Available from: https://pathways.nice.org.uk/pathways/lung-cancer#path=view%3A/pathways/lung-cancer/treating-non-small-cell-lung-cancer.xml&content=view-index.

41. Brahmer JR, Rodriguez-Abreu D, Robinson AG, Hui R, Csőszi T, Fülöp A, et al. LBA51 KEYNOTE-024 5-year OS update: First-line (1L) pembrolizumab (pembro) vs platinum-based chemotherapy (chemo) in patients (pts) with metastatic NSCLC and PD-L1 tumour proportion score (TPS) ≥50%. Ann Oncol. 2020;31:S1181-2.

42. Reck M, Rodríguez-Abreu D, Robinson AG, Hui R, Csőszi T, Fülöp A, et al. Updated analysis of KEYNOTE-024: Pembrolizumab versus platinum-based chemotherapy for

advanced non-small-cell lung cancer with PD-L1 tumor proportion score of 50% or greater. J Clin Oncol. 2019;37(7):537-46.

National Institute for Health and Care Excellence

Centre for Health Technology Evaluation

ERG report – factual accuracy check and confidential information check

Atezolizumab monotherapy for untreated PD-L1 positive metastatic non-small-cell lung cancer [ID1678]

'*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 Friday 20 November 2020** 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

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Section 1.2 Background. page 1 Type error	Atezolizumab, is a humanized [redacted] monoclonal antibody, which attaches itself to the PD-L1 protein on cancer cells…	Atezolizumab is an IgG antibody not IgC	The typo has been amended
Section 1.2 Background. page 2 Type error	The company describes the management of metastatic squamous and non-squamous NSCLC, whose tumours have PD-L1 expression [redacted]	It should read PD-L1 expression ≥50% not >50%	The typo has been amended.
Section 1.3, Table 9, page 4 Type error	The CS addresses a narrower population than that specified in the NICE final scope and focuses on adult patients with metastatic non-squamous or squamous non-small cell lung cancer with high PD-L1 expression ([redacted]).	It should read [redacted] TC or ≥[redacted] IC not [redacted] tumour cells or [redacted] tumour-infiltrating immune cells	The typo has been amended.
Section 2.2.1 Included studies, page 11 Type error	In keeping with the marketing authorization for atezolizumab monotherapy in first-line NSCLC, the CS only considers data for IMpower110 patients with high PD-L1 expression, TC3 or IC3 ([redacted])	It should read [redacted] TC or [redacted] IC not [redacted] tumour cells or [redacted] tumour-infiltrating immune cells	The typo has been amended.
Section 2.2.1 Included studies, page 11 Type error	The CS, therefore, considers data for 107 patients randomised to atezolizumab and 98 patients randomised to chemotherapy in [redacted]	typo IMpower110 not IMpower100	The typo has been amended

3.2.6 Treatment effectiveness and extrapolation -Treatment duration Pg.49-50 Wrong reference and lack of information Subsequently, the ERG has identified a published paper by Velcheti et al which reports a post hoc analysis of time-on-treatment from KEYNOTE-024 and the PD-L1 ≥50% group in KEYNOTE-042.(36) [redacted]	It seems to refer to: Velcheti V, Chandwani S, Chen X, Pietanza MC, Burke T. First-line pembrolizumab monotherapy for metastatic PD-L1-positive NSCLC: real-world analysis of time on treatment. Immunotherapy. 2019 Jul;11(10):889-901. doi: 10.2217/imt-2019-0061. Epub 2019 Jun 11. PMID: 31181973. "…which reports a median time on treatment of *xx* and a 12-months on treatment rate of *yy*. This compares to the company model results and the Flatiron data provided…"	The mentioned Velcheti et al study seem to refer to a study in previously treated population. Please clarify which is the correct reference. For transparency, and to avoid confusion, it would be appreciated if the results of the cited study were reported and compared with the pembro values used in the model, as well as the Flatiron data provided.	Apologies, we linked the wrong reference. The correct reference is the following: *Velcheti V, Chandwani S, Chen X, Pietanza MC, Burke T. First-line pembrolizumab monotherapy for metastatic PD-L1-positive NSCLC: real-world analysis of time on treatment. Immunotherapy. 2019 Jul;11(10):889-901.* We have added a column to Table 24 of the ERG report to show the percentage of patients on treatment as predicted by the model. The data on ToT from Velcheti are provided in column 2 of that table for comparison. We are not sure what Flatiron data the company is referring to for time on treatment. Note, the ERG workings are provided in the 'ERG' sheet added to the company model. There may be more comprehensive ways to incorporate pembro ToT into the model which could be explored during technical engagement.
5.1 pg. 69 sub-heading ***List of cost-comparison scenarios assessed by the ERG (see [redacted] for results)***	*List of cost-comparison scenarios assessed by the ERG (see Table 30 for results)*	Seems to reference the wrong table	The typo has been amended.

Type / reference error			

Issue 2

Description of problem	Description of proposed amendment	Justification for amendment	
Factual inaccuracy 3.2.6 Treatment effectiveness and extrapolation -Treatment duration pg.48 Point 3 does not represent the company position. The company did not make claims regarding re-challenge vs continued treatment and is unaware of longer-term data on the matter The company submission did not use an equivalent 'stop rule' for atezolizumab for three reasons: 1. To impose a stop rule on atezolizumab would not be consistent with the IMpower110 RCT evidence 2. There is a lack of rationale for a stop rule at two years 3. [redacted]	The company submission did not use an equivalent 'stop rule' for atezolizumab for three reasons: 1. To impose a stop rule on atezolizumab would not be consistent with the IMpower110 RCT evidence 2. There is a lack of rationale for a stop rule at two years *3.* The company did identify re-challenge as the biggest unmet medical need and believes that extending the IO availability to allow (re-challenge or) continued treatment would be a valuable option for some patients. However, the company was not aware on any available data about re-challenge.	Please quote the company position. From pg.106 CS: "*It is hypothesized that the response might be persistent in many cases nonetheless, if the patient has been on treatment long enough. At the moment it is unknown if two years treatment is long enough to trigger what has been described as persistent "immunological memory" however. The biggest unmet clinical need was highlighted for patients who relapse after stopping treatment and do not have further immunotherapy options available. This is not in licence and out of scope for this submission. For some patients it could be very important to continue treatment beyond two years, however the numbers of patients needing to continue treatment beyond that time point was described by clinicians as very small."* We appreciate that the ERG mentioned a long-term follow-up for pembrolizumab allowing re-challange.	We accept the amendment and have changed point 3, as suggested.

Issue 3

Description of problem	Description of proposed amendment	Justification for amendment	
Factual inaccuracy Pg: 71, 75, 78 Table 29. ERG scenario analyses results pembrolizumab vs. atezolizumab* (PAS price) : subheading within the table says "[redacted], while heading says pembro vs.atezo NMB and NHB are positive, footnotes state: "[redacted]" Table 31. Incremental changes leading to the ERGs base case Table 33. Exploration of the duration of treatment effect with reference to the ERG base case	We suggest changing the subheading within the table to "pembro mono vs atezo mono **and making NMB and NHB negative values**, in line with the legend, and **making the incremental QALY as positive,** indicating pembro has a QALY gain. Any other option is fine, as long as confusion is avoided.	Please check tables and legends as negative QALY difference, positive NMB/NHB, legend and/or ICERs might need correcting	Apologies for inconsistencies. We have brought these in line with the subheading and the way results have been presented within the Tables: atezo versus pembro. Changes to headings and footnotes made to Table 29, 31, 32 and 33.

Confidential marking

Location of incorrect marking	Description of incorrect marking	Amended marking	
Section 2.4.1 Results of the NMA, page 33	Table 20: HR results should be marked AIC instead of CIC	[redacted]	Marked as AIC as requested.
Section 3.2.3 population pg.39	The modelled population is in line with the TC3 or IC3 subgroup of IMpwer110 trial, [redacted] outlined in company submission (Document B, Table 1) needs to be marked CIC	The modelled population is in line with the TC3 or IC3 subgroup of IMpower110 trial, [redacted] outlined in company submission (Document B, Table 1): "Adult patients with [redacted]."	Changes accepted and made.
Section 3.2.3 population pg.39	The company submission pointed out [redacted]	The company submission pointed out that the [redacted] so further sub-groups	Changes accepted and made

	[redacted] needs to be marked CIC.	within this biomarker are not presented.	
Section 3.2.3 population pg.39	[redacted]	[redacted]	Changes accepted and made

NICE National Institute for Health and Care Excellence

Technical engagement response form

Atezolizumab monotherapy for untreated PD-L1 positive metastatic non-small-cell lung cancer [ID1678]

As a stakeholder you have been invited to comment on the ERG report for this appraisal. The ERG report and stakeholders' responses are used by the appraisal committee to help it make decisions at the appraisal committee meeting. Usually, only unresolved or uncertain key issues will be discussed at the meeting.

We need your comments and feedback on the key issues below. You do not have to provide a response to every issue. The text boxes will expand as you type. Please read the notes about completing this form. We cannot accept forms that are not filled in correctly. Your comments will be included in the committee papers in full and may also be summarised and presented in slides at the appraisal committee meeting.

Deadline for comments **5pm on Monday 11 January 2021**

Thank you for your time.

NICE National Institute for Health and Care Excellence

Please log in to your NICE Docs account to upload your completed form, as a Word document (not a PDF).

Notes on completing this form

- Please see the ERG report which summarises the background and submitted evidence, and presents the ERG's summary of key issues, critique of the evidence and exploratory analyses. This will provide context and describe the questions below in greater detail.
- Please ensure your response clearly identifies the issue numbers that have been used in the executive summary of the ERG report. If you would like to comment on issues in the ERG report that have not been identified as key issues, you can do so in the 'Additional issues' section.
- If you are the company involved in this appraisal, please complete the 'Summary of changes to the company's cost-effectiveness estimates(s)' section if your response includes changes to your cost-effectiveness evidence.
- Please do not embed documents (such as PDFs or tables) because this may lead to the information being mislaid or make the response unreadable. Please type information directly into the form.
- Do not include medical information about yourself or another person that could identify you or the other person.
- Do not use abbreviations.

- Do not include attachments such as journal articles, letters or leaflets. For copyright reasons, we will have to return forms that have attachments without reading them. You can resubmit your form without attachments, but it must be sent by the deadline.
- If you provide journal articles to support your comments, you must have copyright clearance for these articles.
- Combine all comments from your organisation (if applicable) into 1 response. We cannot accept more than 1 set of comments from each organisation.
- Please underline all confidential information, and separately highlight information that is submitted under 'commercial in confidence' in turquoise, all information submitted under 'academic in confidence' in yellow, and all information submitted under 'depersonalised data' in pink. If confidential information is submitted, please also send a second version of your comments with that information replaced with the following text: 'academic/commercial in confidence information removed'. See the Guide to the processes of technology appraisal (sections 3.1.23 to 3.1.29) for more information.

We reserve the right to summarise and edit comments received during engagement, or not to publish them at all, if we consider the comments are too long, or publication would be unlawful or otherwise inappropriate.

Comments received during engagement are published in the interests of openness and transparency, and to promote understanding of how recommendations are developed. The comments are published as a record of the comments we received, and are not endorsed by NICE, its

officers or advisory committees.

About you

Your name	**Sergio Sciuto**
Organisation name – stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder please leave blank)	**Roche Products Ltd**
Disclosure Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	**None**

Key issues for engagement

Please use the table below to respond to questions raised in the ERG report on key issues. You may also provide additional comments on the key issue that you would like to raise but which do not address the specific questions.

Key issue	Does this response contain new evidence, data or analyses?	Response
Key issue 1: Narrower population than that specified in the NICE final scope and choice of comparator	YES	The ERG have highlighted a concern regarding the appropriate comparator for the appraisal, based on differences in diagnostic tests between IMpower110 (SP142, measuring tumour cells [TC] and immune cells [IC]) and the KEYNOTE trials (22C3, measuring tumour proportion score [TPS]). As some issues are interrelated, we structure the response as follows: In response to issue 1: 1. We present a breakdown of the TC3-wild type (WT) and IC3-WT subpopulations for OS and discuss the IC3-only subpopulation (provided in this section)

		In response to issue 2: 2. We present the KM for the 22C3 TPS ≥ 50% subgroup of IMpower110 and the resulting time varying HRs from the fractional polynomial NMA In response to issue 3: 3. We discuss the point estimates for the HRs (Random Effect) resulting network meta-analysis (NMA) update for the 22C3 TPS ≥ 50% subgroup

		Breakdown of TC3 and IC3 populations **Summary:** ● We observe a similar OS and PFS benefit with atezolizumab in the TC3 (any IC) WT and IC3 (only) WT subpopulations regardless of follow up time. We note the small patient numbers involved in the subgroups with [redacted] classified as TC3 (any IC) WT and [redacted] classified as IC3 (only) WT and the different outlooks shown for these patients ● Overall, [redacted] of the PD-L1 high patients identified using the SP142 were also identified using 22C3. ● About [redacted] of the patients identified as IC3 only by the SP142 assay were also detected as TPS>50% by the 22C3 assay, ● In total, [redacted] patients identified as IC3 only had a TPS <50% using the 22C3 assay, representing [redacted] of the total PD-L1 high population [redacted] as identified by SP142 ● There are no available data to confirm how these patients identified as IC3 only with TPS <50% using the 22C3 assay are currently being treated in the UK, although given that atezolizumab's magnitude of treatment benefit is maintained regardless of whether the patients are TC3 or IC3 and whichever assay is used, there is a strong equity case to include these patients in any reimbursement recommendation ● We therefore believe the SP142 cost-effectiveness analysis (CEA) is appropriate

		Ad hoc exploratory subgroup analysis of the IC3 or TC3 subpopulation **An ad hoc exploratory subgroup analysis was performed on the primary analysis (15.7 month median follow up) to assess efficacy in patients with high IC expression (IC3) by the SP142 assay (Figure 1). Within the SP142-selected high–PD-L1 expression (TC3 or IC3 WT) subpopulation, [redacted] were classified as TC3 (any IC) WT and [redacted] were classified as IC3-only WT. [redacted] was observed with atezolizumab compared to chemotherapy in the TC3 (any IC) WT and IC3-only WT subpopulation (Figure 1). The IC3-only patients appeared to [redacted] compared with the TC3 (any IC) patients with the baseline characteristics showing no untoward biases when compared to the overall TC3 or IC3 WT subpopulation (Table 13 in Appendix A). A similar trend of progression-free survival (PFS) benefit with atezolizumab was also observed in both subpopulations (** **Figure 2) and this treatment effect was [redacted]) (** Figure 3). Overall, high PD-L1 expression as evaluated by either TC (TC3 [any IC] WT) or IC (IC3 [not TC3] WT) [redacted] to the observed treatment effect of atezolizumab vs chemotherapy.

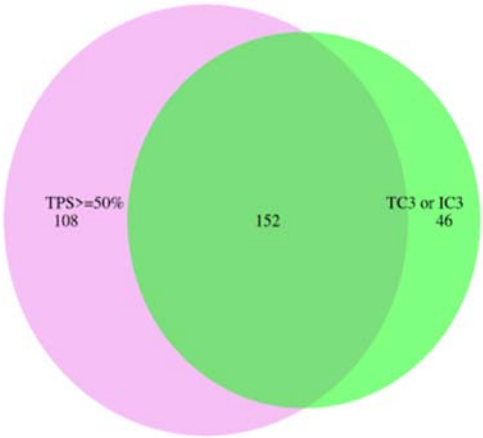
		Figure 1: Subgroup analysis of OS in the TC3 or IC3 WT subpopulation (median follow up 15.7 months) as identified by the SP142 essay  atezo, atezolizumab; chemo, chemotherapy; HR, hazard ratio. [a] Unstratified HRs for all subgroups.

		Figure 2: Subgroup analysis of PFS in the TC3 or IC3 WT Population (median follow up 15.7 months) as identified by the SP142 essay  The vertical dashed lines indicates the HR for all patients. The diameter of the circle is proportional to the square root of the total number of events.

		Figure 3: Subgroup analysis of OS in the TC3 or IC3 WT Population (median follow up 31.3 months) as identified by the SP142 essay  The vertical dashed lines indicates the HR for all patients. The diameter of the circle is proportional to the square root of the total number of events.

		Patients identified using the SP142 or 22C3 assay We agree that, when comparing to pembrolizumab, it is useful to consider the TPS ≥50% subgroups identified using the 22C3 assay, which is the same assay used in the KEYNOTE-024 and -042 studies. As presented in our responses to the clarification questions, the 22C3 assay does not consider immune cells, but gives a TPS based on the percentage of viable tumour cells showing partial or complete membrane staining. We also know that the sensitivity of the assays differ between 22C3 and SP142 (1, 2). The estimation of the number of IC3-only patients (as defined by the SP142 assay) that were not identified when using the 22C3 assay can be deduced by looking at data from the population identified as high PD-L1 expressors using the SP142 assay and for whom both the SP142 and the 22C3 assay results are available (n=198 patients): 1. Of the total 198 patients, 152 patients were also identified as ≥50% by the 22C3 assay, while 46 patients were identified by SP142 only (Figure 4), also shared in the response to A11 of the clarification questions. 2. Of the total 198 patients, [redacted] were identified as IC3 only (not TC3) by SP142 assay. Of these, [redacted] patients were also identified to have a PD-L1 ≥50% by the 22C3 assay, while the remaining [redacted] IC3-only patients were identified by the SP142 only. Of note, there is a [redacted] of IC3-only patients as compared to the numbers presented in Figure 1, since [redacted] as defined by SP142 were not evaluable using the 22C3 assay. 3. From points 1 and 2, we can conclude that of the total 46 patients who were identified using the SP142 only, [redacted] were IC3 only (not TC3). This equates to [redacted] of the total PD-L1 high population [redacted] as identified by SP142, who were IC3-only with a TPS <50% as identified using the 22C3 assay.

Figure 4: Overlap between the SP142 and 22C3 assays in the PD-L1-high subgroups (median follow-up 31.3 months) (3)



Number of patients defined as PD-L1 high by assay: SP142 (green) and 22C3 (pink)

Discussion

There are only [redacted] patients, with a TPS <50% using the 22C3 assay, representing [redacted] of the total PD-L1 high population. These patients are unlikely to be detected in current routine NHS practice, as the most widely used assay (based on insights gathered from 27 centres) is 22C3 and typically only one assay is used

		(4). As such, these patients could fall into PDL-1 low or PD-L1 negative expressors. Whilst there are a number of options for these patients, the most likely comparator for PD-L1 low and negative expressors in both non-squamous and squamous could be pembrolizumab + carboplatin + pemetrexed or pembrolizumab + carboplatin + paclitaxel, respectively. However, there are currently no data available to perform such comparison. Approximately [redacted] the IC3-only patients identified by the SP142 assay are also identified by the 22C3 assay; we therefore believe pembrolizumab is the right comparator for atezolizumab. We understand that 1L NSCLC trials so far have been (mostly) based on the 22C3 assay and that this is the first evidence available looking at outlooks and treatment effects for IC3-only patients in 1L NSCLC. While the outlook of these patients with chemo-combinations/other products is unknown, we observe that atezolizumab's magnitude of treatment benefit [redacted] of whether the patients are TC3 or IC3. However, the small patient numbers make it difficult to draw definitive conclusion. Exploring a different cost-effectiveness case with the [redacted] would be inappropriate and unfeasible when, for any treatment, no other efficacy data are available and these patients are highly unlikely to be detected in clinical practice. We believe there is a strong equity case to include these patients in our recommendation, as atezolizumab is the only treatment showing a maintained treatment benefit in a potentially difficult to treat population, based on an exploratory analysis with small patient numbers. Furthermore, it would not be feasible to collect additional data through the NHS post-reimbursement, as 22C3 followed by SP263 are the most predominantly used assays in clinical practice. To do so, would require

		changing how clinicians currently request testing, as well as ensuring all current central and in-house pathology laboratories are equipped to accommodate these requests. We therefore believe the analysis versus pembrolizumab is the most appropriate, providing a strong case for cost-effectiveness and cost comparison that optimises NHS resources, when atezolizumab is compared to pembrolizumab.
Key issue 2: Atezolizumab effect over time	**YES**	The ERG pointed out how, from the Fractional Polynomial (FP) approach in relation to the atezolizumab-pembrolizumab comparison, the direction of the effect increasingly appears to favour pembrolizumab over time: *"However, the comparison is complicated by different durations of follow up in the respective trials, dwindling sample sizes with increasing follow up, varying degrees of cross-over in the comparator arms of the different trials, and possibly varying degrees of immunotherapy re-challenge in the treatment arms of the trials. The above issues make it very difficult to determine if or how the relative efficacy of pembrolizumab and atezolizumab changes over time. […]The ERG is of the opinion that without additional and more homogeneous data between the two treatments, this uncertainty cannot be solved."* There is uncertainty around the efficacy of atezolizumab and pembrolizumab over time. This uncertainty is due to limited trial follow-ups, heterogeneity of the trials, censoring later in the trial, cross-over therapy or subsequent lines of therapies and re-challenge in the pembrolizumab trials. We agree with the ERG that "*there is insufficient evidence to support a meaningful difference in life expectancy between the two treatments*" (e.g., page 80 of the ERG report).

		Here, we provide additional overall survival (OS) data from the 2018 and 2020 data cuts based on the 22C3 assay and show that the benefit of atezolizumab holds regardless of the trial follow-up and the assay used. We discuss landmark OS data from clinical trials that confirm the sustained treatment benefit of atezolizumab over time, as well similar effect over time between the two products. We also discuss the NMA results and its limitations. Setting the level I evidence from the OS landmark analysis aside, when interpreting the Fractional Polynomial NMA results, we agree with the ERG that: "*without additional and more homogeneous data between the two treatments, this uncertainty cannot be solved*." There is no evidence to support a meaningful difference between the two treatments; this observation supports the approach of a cost minimisation analysis. ***Efficacy data for atezolizumab over time with the 22C3 assay*** **Summary:** **Clinical trial evidence** ● IMpower110 data show no observable loss of efficacy and sustained treatment benefit over time for atezolizumab, regardless of FU times and assay used to determine eligibility to treatment ● The landmark OS data show little difference between atezolizumab and pembrolizumab: RCT and clinical opinion supports the equivalence of atezolizumab and pembrolizumab in 1L NSCLC **Indirect Treatment Comparison**

- The FP NMA results for the 22C3 population indicate improved HRs for atezolizumab; analysis including the updated KEYNOTE-024 data cut confirm that differences in trial FU affect the NMA: All highlight the lack of evidence for either intervention performing better over time
- The larger and more comparable KEYNOTE-042 trial, which given the sample size has a bigger impact on the FP NMA results, lacks of adequate FU
- KEYNOTE-024 had a more stringent selection for trial inclusion than IMpower110 and allowed re-challenge; this is in contrast with IMpower110 and not reflective of NHS clinical practice, and importantly, impacts the NMA
- The small patient numbers, dwindling sample sizes and difference in FU times of IMpower110 compared with the KEYNOTE studies impact the reliability of the FP NMA results

Clinical trial evidence

As highlighted in response to the ERG clarification question A6, from the clinical trial we do not observe a decrease of atezolizumab's effect over time, irrespective of the assay used to determine eligibility to treatment. The median duration of survival for the TC3 or IC3 WT subpopulation (based on the SP142 assay) between the two data cuts remained the same for patients treated with atezolizumab: [redacted] However, with the extended follow up, the median duration of survival in the chemotherapy arm changed from [redacted].

In addition, looking at the data based on the 22C3 assay (22C3-based Kaplan-Meier [KM] curves in Figure 5 and Figure 6), we notice how the median duration of survival for atezolizumab improved between the two data

		cuts from [redacted] to [redacted] This confirms the treatment benefit over time, regardless of the assay used to determine eligibility to treatment. Even in the median OS values, we observe a bigger improvement for the chemotherapy arm, from [redacted]

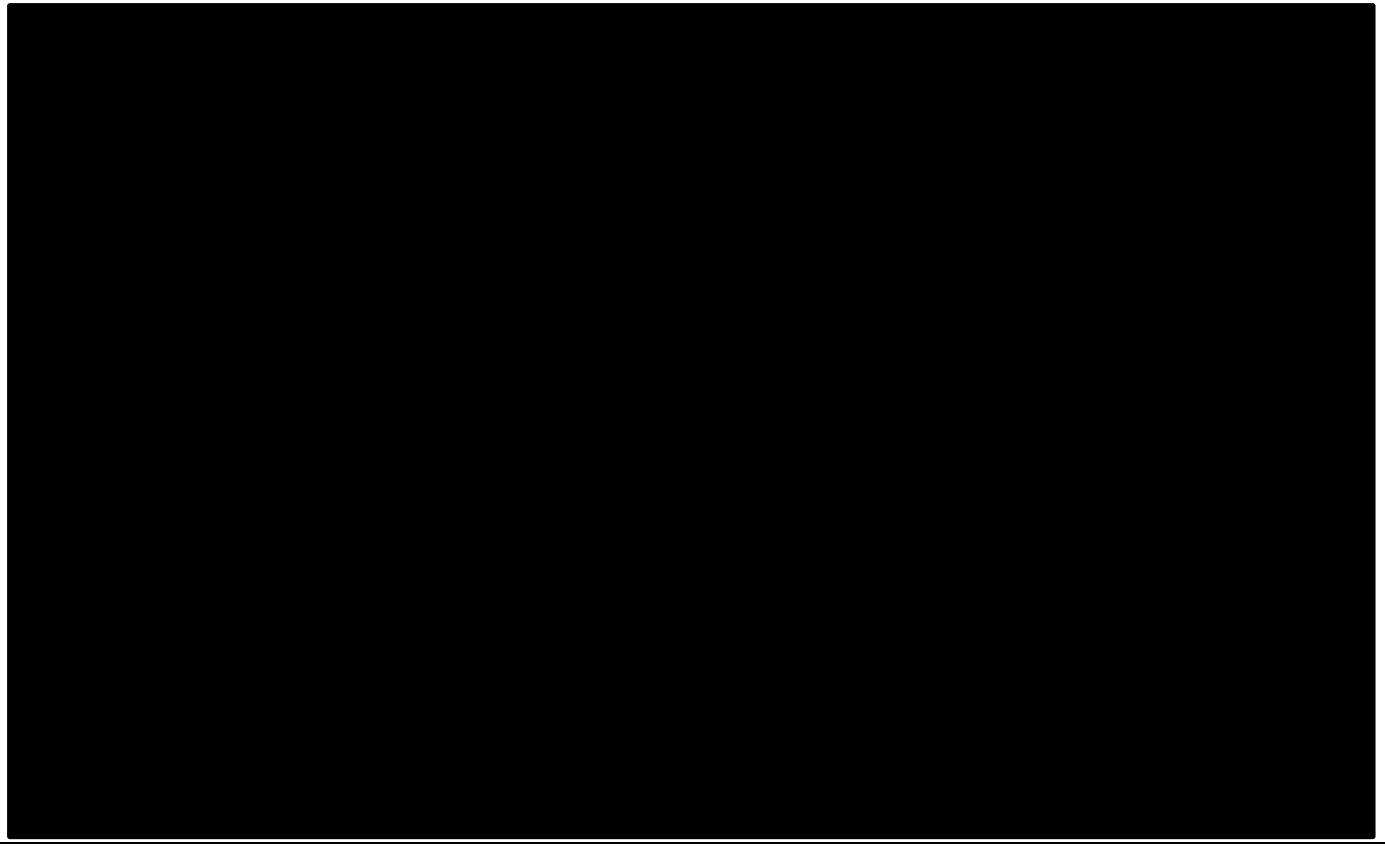
		Figure 5: Kaplan-Meier plot of OS (22C3 assay), PD-L1 status ≥50%, CCOD 10th September 2018 

		Figure 6: Kaplan-Meier plot of OS (22C3 assay), PD-L1 status ≥50%, CCOD 4th February 2020 

		Looking at the KM curves based on the clinical cut-off data (CCOD) 4th February 2020 and using the 22C3 assay, we observe the chemotherapy arm plateauing at 22-24 months, probably due to the effect of subsequent lines of cancer immunotherapies ([redacted] of patients in the chemotherapy arm received subsequent immunotherapy [I/O]). While this could arguably reflect clinical practice, it becomes a tangible issue when compared to the KEYNOTE studies through the NMA, which have a shorter FU. This could influence the effect over time against pembrolizumab observed in the fractional polynomial (FP) NMA. The [redacted] from the 22C3 assay data when comparing to the SP142 data, as well as from the IC3 (non-TC3) and TC3 subpopulations, confirms indeed that atezolizumab is an effective treatment regardless of the assay used to screen patients and that the magnitude of benefit is maintained across subpopulations. **Landmark OS data** To add further clarity around the efficacy over time, we believe that for I/Os in general, and specifically in this case, the landmark OS are useful data points. This is because, as the ERG states: "*the comparison is complicated by different durations of follow up in the respective trials, dwindling sample sizes with increasing follow up, varying degrees of cross-over in the comparator arms of the different trials, and possibly varying degrees of immunotherapy re-challenge in the treatment arms of the trials*". In Table 1, we present the 22C3-based median follow up, HRs and landmark OS at 12 and 24 months for the PD-L1 ≥50% or TC3/IC3 subpopulation, comparing the IMpower110 and KEYNOTE studies. It highlights how

minimal difference is observable between the two products. In fact, we believe it is not possible to distinguish between the two products based on the data from the RCTs.

Table 1: Impower110 and KEYNOTE studies, 22c3-TPS>50% population: Median follow up, HR and landmark OS

Study	Median FU	22C3 based HR vs chemotherapy	22C3 based 12-month OS rate	22C3 based 24-month OS rate
IMpower110 (CCOD Sep 2018) (3)	15.7 months	[redacted]	[redacted]	[redacted]
KEYNOTE-042 (CCOD Sept 2018) (5, 6)	14.0 months	0.69 (0.56 - 0.85)*	64% (TPS ≥50%) vs 51% (Chemotherapy)*	45% (TPS ≥50%) vs 30% (Chemotherapy)

		IMpower110 (CCOD Feb 2020) (7)	[redacted]	[redacted]	[redacted]	[redacted]
		KEYNOTE-024 (CCOD Jul 2017) (8)	25.2 months	0.63 (0.47-0.86)*	70.3% (62.3-76.9) vs 54.8 (46.4 to 62.4 (chemotherapy)	52% (TPS ≥50%) vs 35% (chemotherapy)

*Estimated from KM curves in Mok et al. 2019 (5)

Comparing to pembrolizumab using the NMA

Based on the 22C3 TPS≥50%, the forest plots from the NMA indicate an improved HR (random effect model [RE]), compared to the company base case. Figure 7 is based on the 2018 data cut, Figure 8 is based on the 2020 data cut (FU=[redacted]

HRs (RE) vs pembrolizumab from the NMA:

- 2018 primary analysis HR – 22C3 HR:[redacted]) *vs. SP142:* [redacted])

		• 2020 exploratory analysis HR – 22C3 HR: [redacted] *vs. SP142:* [redacted] – *base case HR* Please refer to issue 3 for the forest plots. We note that the highest of all the available HRs (HR: 1.13; CI 0.66, 1.97) is used in the company base case. **Fractional polynomial NMA results** The FP time dependent HRs based on the 22C3 assay (Figure 7 and Figure 8 below) do not highlight any significant changes from the ones presented previously based on the SP142 assay.

		Figure 7: OS hazard ratios of atezolizumab relative to pembrolizumab between 1 and 60 months. for the random effects FP model, order 1, P1=0 (Weibull) (CCOD 10th September 2018) - 22C3 assay 

		Figure 8: OS hazard ratios of atezolizumab relative to pembrolizumab between 1 and 60 months. for the random effects FP model, order 1, P1=0 (Weibull) (CCOD 4th February 2020) - 22C3 assay 

		When comparing to pembrolizumab though the NMA, we agree with the ERG regarding the uncertainty in the comparison. Not only is the comparison uncertain, but also the difference from the NMA is very small and clinically non-significant. This confirms clinical opinion, once again, namely that the two products can be deemed as clinically equivalent in this indication. **FP NMA analysis with the updated KEYNOTE-024 data cut** Here, we present the FP NMA results using the updated data cut for the KEYNOTE-024 study (8). The previous KEYNOTE-024 May 2016 data cut (9) was used in the company submission, but the update to the SLR has led to us to also having the KEYNOTE-024 update available. This update confirms that the lack of FU in the KEYNOTE studies impacts the results of the FP NMA. For completeness, we present the FP time varying HR for the 22C3 population when including the extended FU for the KEYNOTE-024 study and compare them with the results based on the earlier KEYNOTE-024 data cut. A downward shift in the HRs over time vs pembrolizumab is noticeable, when the latest data cut for KEYNOTE-024 is used (Figure 9). This confirms the impact the lack of FU of the KEYNOTE studies has on the FP NMA results. Of note, KEYNOTE-042 has a bigger sample size, so an updated cut-off would influence results more, however, the more comparable KEYNOTE-042 study is lacking any recent update with longer follow up.

		Figure 9: OS hazard ratios of atezolizumab relative to pembrolizumab between 1 and 60 months. for the random effects FP model, order 1, P1=0 (Weibull) (CCOD 10th September 2018 and 4th February 2020) 

		Conclusion In summary, no loss of efficacy is observable for atezolizumab over time. RCT evidence and clinical opinion currently supports the equivalence of the two products in this same population. The following 3 points summarise the FP NMA evidence we provide above to support our reasoning: 1. **Plateau in the 2020 exploratory analysis of the IMpower110 chemotherapy arm and difference in trials FU** The NMA estimate is impacted by the prolonged follow up time of the Impower110 trial: this applies to both the comparison to chemotherapy and compared to the KEYNOTE studies. As we have seen, the HR of the IMpower110 trial is impacted by subsequent therapies for patients on the chemotherapy arm. From circa 20 months, a plateau in the Impower110 chemotherapy arm from the exploratory analysis is observable from the KM curves presented in Figure 5 and Figure 6. This is also reflected in all unadjusted FP results presented. It would be helpful to have updated data from KEYNOTE-042 as it has the biggest sample size, updated results with longer follow-up time and would have more influence on the FP NMA. As shown in the company submission, the point estimate HR based on the 2018 data cut, of similar maturity to KEYNOTE-042, slightly favours atezolizumab 2. **Small numbers and dwindling sample sizes** We observe how the patients numbers are small and diminishing over time. The chemotherapy arms, on which this comparison is anchored, suffers from small numbers, evident at 6-12 months. The numbers at risk at different time points is presented in Appendix B

		3. The KEYNOTE-024 results are unmatched by other KEYNOTE studies and impact the NMA We recall that the NMA network includes both the KEYNOTE-042 and the KEYNOTE-024 studies and highlight: IMpower110 and KEYNOTE-042 required patients to have PD-L1≥ 1% at enrolment, whereas KEYNOTE-024 required patients to have PD-L1≥ 50%. IMpower110 and KEYNOTE-042 studies are more homogenous in patient inclusion criteria. We heard at an advisory board held in December 2020 that KEYNOTE-024 required a more stringent selection for trial inclusion, particularly when the PD-L1 results were not clear and/or around the PD-L1 ≥ 50% cut-off. Of note, KEYNOTE-024 allowed patients to be re-challenged with pembrolizumab after stopping treatment at 2 years, if they progressed after having responded to therapy (10). As shown in response to issue 4, re-challenge is an efficacious strategy: circa 80% of patients respond to re-challenge. Re-challenge is not permitted in the NHS, leading to questions over its relevance and applicability to this decision problem. Including KEYNOTE-024 in the NMA network could introduce a bias in the NMA results towards pembrolizumab. These two factors might also contribute to explain why the KEYNOTE-024 trial shows results unmatched by the KEYNOTE-042 trial. Overall, the inclusion of updated data from the KEYNOTE-024 study indeed not only support this argument, but also highlight how the hazard ratio over time from the FP NMA of atezolizumab vs. pembrolizumab improves if prolonged FU data for the KEYNOTE studies become available. This is observed, even if in KEYNOTE-024 re-challenge is allowed (not currently permitted in the NHS). Furthermore, the FP NMA results confirm there is no evidence favouring one product over another. This interpretation of the FP NMA is in line with the more robust evidence derived from the RCTs, namely the landmark OS results (presented in Table

		1). We believe that the landmark OS is useful in this case and highlight how no difference is observable between the two products, supporting the case for a cost minimisation analysis. The difference between the two products in long-term treatment effect beyond the observed period is more likely to depend on the implementation of a stopping rule or the lack of it. We will discuss this further in issue 4.
Key issue 3: Assays comparability	**YES**	Here, we provide a sensitivity analysis using the 22C3 TPS ≥ 50% subgroup (or TC3 subgroup) of IMpower110 in the NMA in response to the ERG's comment: "*Acknowledging the double selection issue for IMpower110, the ERG believes selection of participants to inform the NMA could have been based on similar criteria (preferably the 22C3 assay given it is the more commonly used) or, if not possible, the proportions of both the TC3 and IC3 patients should have been given.*"

		Sensitivity analysis using the 22C3 TPS ≥ 50% subgroup (or TC3 subgroup) of IMpower110 in the NMA

Summary

- A sensitivity analysis using the 22C3 TPS >=50% subgroup (or TC3 subgroup) of IMpower110 in the NMA showed improved HR compared with the company base case based on the SP142 assay (NMA using 2020 data cut and 22C3 assay: OS HR(RE)=[redacted] vs SP142 assay: [redacted]). The original company base case used the highest of all available HRs and are conservative
- When comparing the 12 and 24 month landmark OS from IMpower110 using 22C3 or SP142 assays and 2018 or 2020 data cuts, the results were comparable
- In all appropriate cost-effectiveness scenarios based on the 22C3 assay results, atezolizumab without a stopping rule gains more QALY and potentially dominates pembrolizumab: regardless of the parametrisation, utilities, pembrolizumab ToT extrapolation etc. (Table 12). This further support our assumption that the interventions are equivalent
- The option of atezolizumab for 1L NSCLC will allow some patients to be treated beyond 2 years

Sensitivity analysis - OS

Based on the 22C3 TPS≥50%, the forest plots from the NMA indicate an improved HR (RE), compared to the company base case using the SP142 assay. Figure 10 is based on the 2018 primary analysis data cut,

		Figure 11 shows the results based on the 2020 exploratory analysis data cut (FU=[redacted], Figure 12 is based on the 2020 exploratory analysis data cut (FU=[redacted] using the updated KEYNOTE-024 data. HRs (RE) vs pembrolizumab from the NMA: ● 2018 primary analysis 22C3 HR:[redacted]) (Figure 10) *vs. SP142:* [redacted]) (Section B.2.9. CS) ● 2020 exploratory analysis 22C3 HR: [redacted]) (Figure 11) *vs*. *SP142:* [redacted] (Section B.2.9. CS) ● 2020 exploratory analysis 22C3 including new KN-024 3 year follow up data HR (Figure 12): [redacted]

		Figure 10: OS hazard ratio based on hazard ratio data for treatments relative to atezolizumab, using the random effects model (CCOD 10th September 2018) - 22C3 assay- 

		Figure 11: OS hazard ratio based on hazard ratio data for treatments relative to atezolizumab, using the random effects model(CCOD 10th February 2020) - 22C3 assay- 

		Figure 12: OS hazard ratio based on hazard ratio data for treatments relative to atezolizumab, using the random effects model(CCOD 10th February 2020) - 22C3 assay- with latest KEYNOTE-024 data cut 

As Table 2 shows, OS HR point estimates and landmark results are similar across assays, when comparing to chemotherapy.

Table 2: Impower110 22c3 vs SP142 results TPS>50% population: Median follow up, HR and landmark OS

Study	Median FU	HR vs chemotherapy	based 12 months OS rate	based 24 months OS rate
22C3 IMpower110 (CCOD Sep 2018) (data on file)	15.7 months	[redacted]	[redacted]	[redacted]
SP142 IMpower110 (CCOD Sep 2018) (3))	15.7 months	0.58 (C.I.: 0.40-0.89)	64.9% vs 50.6% (chemotherapy)	[redacted] vs [redacted] (chemotherapy)

		22C3 IMpower110 (CCOD Feb 2020) (data on file)	[redacted]	[redacted]	[redacted]	[redacted]
		SP142 IMpower110 (CCOD Feb 2020) (7)	[redacted]	[redacted]	[redacted]	[redacted]

Sensitivity analysis - PFS

As far as assay comparability is concerned, we do not notice a difference that is large enough to raise concerns on the topic. The same insight is confirmed by the PFS forest plots presented below (Figure 13 and Figure 14).

		Figure 13: PFS hazard ratio based on hazard ratio data for treatments relative to atezolizumab, using the random effects model (CCOD 10th February 2020) - 22C3 - 

		Figure 14: PFS hazard ratio based on hazard ratio data for treatments relative to atezolizumab, using the random effects model (CCOD 10th February 2020) - 22C3 - with latest KEYNOTE-024 data cut 

		Conclusion We note how the highest of all the available OS HRs is used in the company base case and how the cost effectiveness results using the 22C3 assay favour atezolizumab: patients on atezolizumab gain more QALYs than patients on pembrolizumab (please see Table 12, where the cost-effectiveness analysis is presented). In all cost-effectiveness scenarios based on the 22C3 assay results, atezolizumab gains more QALY and potentially dominates pembrolizumab: regardless of the parametrisation, utilities, pembrolizumab ToT extrapolation etc.. This further support our assumption that the interventions are equivalent. We therefore believe a strong cost-effectiveness and cost comparison case has been put forward that would optimise NHS resources, while allowing an area of unmet need to be covered: some patients that might need treatment after two years. Please refer to issue 4 for more details on benefit of treating beyond 2 years.
Key issue 4: Relative duration of treatment effects for the technology and its comparator	**NO**	In this response, we provide further discussion around the treatment benefit cap at 5 years and the benefit of continuing treatment beyond 2 years. The ERG points out how this: *"is not an easy point to resolve given lack of longer term data available, but a more considered discussion of the assumption in light of all the available evidence and expert opinion may help to better inform the validity of the assumption".*

		Duration of treatment effect **Summary** ● The question around the duration of treatment effect has come up in many past appraisals. In particular, the very recent Nivolumab FAD (CDF review of TA484/ID1572 Sept 2020) (11), the committee pointed out how "*there was no new robust evidence on the overall duration of the continued benefit. So, the assumption accepted in the original guidance had not changed" (12),* confirming the 5 year treatment benefit assumption ● Evidence links treatment duration to patient benefit; there is no evidence that stopping treatment at two years is the best strategy for all patients. I/O therapy can be effective beyond two years and pembrolizumab re-treatment data are not only an example of this, but also introduce bias in the NMA ● Atezolizumab is cost effective without a stopping rule and dominant based on 22C3 analyses (Table 12). The extremely low number of patients (Appendix C) and the high unmet need in need of treatment beyond 2 years in clinical practice, we believe there is little justification for applying a stopping rule ● This TA represents a real opportunity for patients in need and an opportunity for the NHS to improve clinical practice while optimising the use of limited resources

		Capping of the pembrolizumab treatment effect: Consistency with previous appraisals Duration of treatment effect is an area of uncertainty for immunotherapies and has arisen as a discussion item in many past appraisals (Table 3). We acknowledge the precedent set in past appraisals are a key consideration when answering this question. We have searched for these appraisals where the treatment effect was assumed to last 5 years from treatment initiation: TA520, TA525, TA531, TA557, TA584, TA655, and TA661 (12-18). Committee decisions on other immunotherapy appraisals express uncertainty around the treatment effect duration, but the treatment effect is assumed to last at least 5 years. In particular, in the very recent nivolumab FAD (CDF review of TA484/ID1572 Sept 2020) (12), the committee states "when nivolumab is stopped at 2 years, it is acceptable to assume an additional survival benefit for at least 3 more years." Most importantly, the committee also concluded that: "*the exact duration of treatment benefit was unclear, but it was likely to be at least 3 years after treatment had stopped*" (12). It also points out, however, "*there was no new robust evidence on the overall duration of the continued benefit. So, the assumption accepted in the original guidance had not changed"* (12). To our knowledge no further evidence since this was published in September 2020 is available that justifies revising this statement. Therefore, 5-year treatment effect duration with a 2-year stopping rule can be seen as a appropriate treatment benefit assumption for pembrolizumab.

Table 3: List of immunotherapies from NICE TAs which discuss the treatment effect duration and stopping rule

Immunotherapy	Indication	With treatment cap?	With 2 year stopping rule?	Appraisal number
Atezolizumab	Locally advanced or metastatic non-small-cell lung cancer after chemotherapy	The committee considered that the treatment effect was unlikely to last more than 5 years after treatment had stopped.	Yes	TA520 (2018) (13)
	Locally advanced or metastatic urothelial carcinoma after platinum-	The committee considered it implausible that the treatment effect for atezolizumab	Yes	TA525 (2018) (14)

Technical engagement response form

			containing chemotherapy	would continue life long after stopping treatment and included a treatment effect cap at 3 years after stopping treatment			
			In combination with bevacizumab, carboplatin and paclitaxel for treating metastatic non-squamous non-small-cell lung cancer	Although treatment effect duration is uncertain, a 3-year treatment effect from when treatment is stopped was deemed	Yes	TA584 (2019) (17)	

				appropriate for decision making			
			With carboplatin and etoposide for untreated extensive-stage small-cell lung cancer	60-month treatment duration was plausible but uncertain due to short follow up	No	TA638 (2020) (19)	
			With nab-paclitaxel for untreated PD-L1-positive, locally advanced or metastatic, triple-negative breast cancer	Although there is uncertainty regarding the treatment-effect duration, incorporating a treatment waning effect was not	No	TA639 (2020) (20)	

				considered appropriate			
		Pembrolizumab	Untreated PDL1-positive metastatic non-small-cell lung cancer	The company presented 3- and 5- year scenarios which were taken into account for decision-making	Yes	TA531 (2018) (15)	
			PD-L1-positive non-small-cell lung cancer after chemotherapy	The company presented 3-, 5- and 10- year scenarios and the committee noted the lack of evidence to agree on a single clinically	Yes	TA428 (2017) (21)	

				plausible scenario			
			With pemetrexed and platinum chemotherapy for untreated, metastatic, non-squamous non-small-cell lung cancer	Scenarios including a treatment effect between 3 and 5 years from the start of treatment were used for decision making	Yes	TA557 (2019) (16)	
			Untreated metastatic or unresectable recurrent head and neck squamous cell carcinoma	The committee concluded that assuming a 5-year treatment effect duration was appropriate	Yes	TA661 (2020) (18)	

		Nivolumab	Advanced squamous non-small-cell lung cancer after chemotherapy	The committee concluded that survival benefit was likely to continue for at least 3 years after treatment had stopped.	Yes	TA655 (2020) (12)

Continuing treatment beyond 2 years

In this cohort of patients, the small number of patients potentially treated beyond 2 years (See Appendix C), the high unmet need, the cost-effectiveness of atezolizumab without a stopping rule and the efficacy of further treatment does not, in our opinion, justify restricting treatment with atezolizumab without clinical trial evidence.

"*The ERG agrees that atezolizumab is likely to have a longer treatment duration than pembrolizumab, but relative benefits versus pembrolizumab beyond five years remain an area of uncertainty*" (page 47 ERG report). The longer treatment duration will be the case, if no stopping rule is implemented for atezolizumab. Indeed, Velcheti et al. (22), states: "*Some authors have suggested that time on treatment (TTD) could serve as a practical surrogate to measure the benefits of therapy, with preliminary evidence suggesting correlations with overall survival (OS) (23) and progression-free survival (PFS) (24). Indeed, the results of a recently published analysis of 18 randomized clinical trials of patients with metastatic NSCLC indicate that TTD is*

		associated with PFS across therapeutic classes when studied at the patient level (25)." Not imposing a stopping rule on atezolizumab would deliver additional benefits to patients. Under current modelling assumptions, atezolizumab is cost effective without a stopping rule in place versus pembrolizumab with a stopping rule. The TA638 and TA639 NICE appraisals (Table 3) have already allowed continuing treatment beyond two years in line with atezolizumab's trial evidence. Furthermore, it is implausible and inconsistent with previous committee conclusions that a treatment effect cap should be imposed whilst patients are still on and therefore benefiting from treatment. Allowing continuation of treatment with atezolizumab, is [redacted], and patients can clinically benefit from treatment as needed. As noted by NHS England and NHS Improvement during the TA639 appraisal, "*Impassion130 did not have a stopping rule and hence patients will be potentially treated until disease progression. NHS E and NHS I therefore do not understand why a treatment waning effect has been applied in the absence of a stopping rule either in the design of the trial or as a plan by the company to limit the duration of treatment to a fixed time."* (20). Additional confirmation of the link between time on treatment and benefit to patients comes from the CheckMate153 trial: Following important questions regarding the optimal duration of treatment with PD-1 and PD-L1 inhibitors, CheckMate153 was the first randomised study to evaluate the impact of treatment duration. Patients were randomised to receive continuous nivolumab, or discontinue after 1 year, with retreatment allowed at PD. Results were presented at ESMO, Madrid in September 2017 and demonstrated patients who

		discontinue treatment have a statistically significant increased risk of progression, and numerically increased risk of death (26). CheckMate 153 evaluated continuous treatment versus 1-year fixed-duration treatment with nivolumab in patients with advanced NSCLC. Preliminary results suggested that continuous treatment beyond 1 year was beneficial, with improved PFS (HR 0.42) and a trend toward improved OS (26). These observations suggest that cessation at 1 year is too early. However, the question remains whether patients could potentially stop after a longer treatment duration, or if treatment should be continued as long as the drug is tolerated. It is still unclear if 2 years is long enough to trigger "immunological response" for all patients. In conclusion, given patients' variability, arbitrarily capping treatment at two years risks penalising patients who need treatment the most. **Retreatment data** We recently became aware of retreatment data with pembrolizumab that have been published (27). We believe these data could inform the discussion and highlight that an unmet clinical need can be met with the approval of atezolizumab. Whether continuing treatment beyond two years or restarting the treatment after a treatment holiday when it is needed, some patients will need the option of further treatment. In addition to highlighting how treatment is effective beyond two years, the studies below point out how effectiveness of pembrolizumab in the NHS is less than the efficacy observed in the clinical trials, due to the stopping rule. This also creates bias in the NMA results: o The updated information from KEYNOTE-010 (second-line treatment in PD-L1 positive (TPS ≥ 1%) NSCLC) provides insight into the effectiveness of retreatment: 79% responded to re-

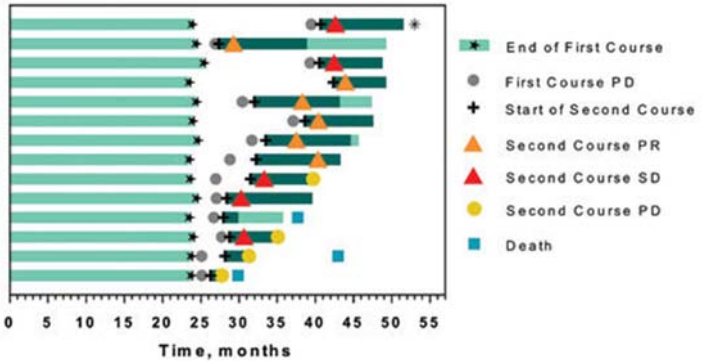
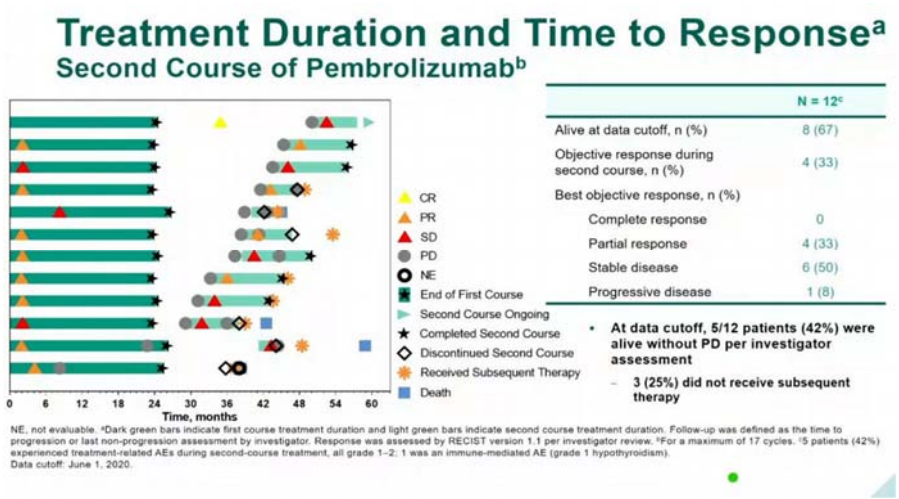
		treatment: Of the 14 patients who went on to get a second course of treatment after progression, six had a partial response, and five had stable disease during second treatment course; all 11 (79%) who responded or had stable disease were alive at the time of analysis (Figure 15) o KEYNOTE-024 data (28) confirms what we observed from the KEYNOTE-010 conclusions, namely that rechallenge post progression is an efficacious strategy. Of the 12 patients that received re-treatment, 83% responded: 4 PR (33%) and 6 SD (50%) (Figure 16). At data cut-off 5/12 patients (42%) were alive without PD per investigator assessment. o For melanoma, updated results of KEYNOTE-006 demonstrated that among patients who had disease progression after two years, the majority responded to retreatment (29)“ (30) **Figure 15: Outcomes of patients who received a second course of treatment - KEYNOTE-010** 

Figure 16: Outcomes of patients who received a second course of treatment - KEYNOTE-024



Given the efficacy of rechallenge, with about 80% of patients responding well to treatment, we believe that the KEYNOTE-024 results introduce bias in the NMA. Such results can be seen as more representative of efficacy results achievable with an I/O treatment without a stopping rule in place (30).

Through a recent advisory board, we heard it is hypothesised that the response to I/O therapies might be persistent in many cases, if the patient has been on treatment long enough. Currently. it is unknown if two year's treatment is long enough for everyone to trigger what has been described as persistent "immunological memory" for all the patients. The biggest unmet clinical need was highlighted for patients who relapse after stopping treatment and do not have further immunotherapy options available. For those patients it could be

		very important to continue treatment beyond two years, however the numbers of patients needing to continue treatment beyond that time point was described by clinicians as “very small” (See Appendix C). **Conclusion** There is no new evidence justifying the revision of the treatment effect cap at 5 years with a 2-year stopping rule for pembrolizumab. Atezolizumab’s evidence base does not include a stopping rule and there is no evidence that prematurely stopping treatment does not have a detrimental benefit on health outcomes, for patients who still benefit of treatment. Evidence links treatment duration to patient benefit and shows that treatment after two years can be efficacious when needed. In addition, retreatment in the KEYNOTE-024 trial could introduce bias in the NMA. We note how the highest of all the available HRs is used in the company base case and that the cost effectiveness results using the 22C3 assay favour atezolizumab: patients on atezolizumab gain more QALYs than patients on pembrolizumab (Table 12). In brief, atezolizumab without a stopping rule potentially dominates pembrolizumab with a stopping rule. In this cohort of patients, the small patient number, the high-unmet need and the efficacy of further treatment does not, in our opinion, justify restricting treatment with atezolizumab without clinical trial evidence and when atezolizumab is cost-effective without a stopping rule in place. This TA represents a real opportunity for patients in need and an opportunity for the NHS to improve clinical practice while optimising the use of limited resources.

Key issue 5: Time on treatment with pembrolizumab relative to its PFS curve	YES	ERG requested exploration of more formal methods for comparing pembrolizumab PFS and time on treatment data, such as curve fitting to reconstructed patient level data in order to investigate the relationship between the two outcomes and provide a more precise approach for the model. We provide further data below in response to this. ***Time on treatment data with pembrolizumab relative to its PFS curve*** **Summary** ● We explore two additional methods: o Fit parametric curves to the digitalised KM curves for both ToT and PFS of KEYNOTE-042 and calculate the HR with a monthly interval from the extrapolations. o Construct a ToT curve by parametrically extrapolating the KEYNOTE-042 and the KEYNOTE-024 digitalised KM curves and applying a weighted average to the extrapolations based on the number of patients at risk ● We also provide RWE data from Flatiron, equivalent to Velcheti et al. (22), but with longer follow-up. These data confirm that circa 10% of patients reach 2 years of treatment in clinical practice and that some patients need to continue treatment beyond two years (5% at 30 months).

		Fitting parametric curves to KEYNOTE-024 data The ERG identified a published paper by Velcheti et al (22) which reports a post hoc analysis of ToT from KEYNOTE-024 and the PD-L1 ≥50% group in KEYNOTE-042. The ERG calculated the relative hazard by time points in the KEYNOTE-042 trial, with a 3 months' time point interval and applied this hazard to the pembrolizumab's PFS function in the model. With this as a starting point, we have tried to build on ERG's approach and suggest alternative possible solutions. We digitalised the pembrolizumab ToT and PFS data from the Velcheti paper (22) for the KEYNOTE-024 and KEYNOTE-042 data, although the KEYNOTE-024 and KEYNOTE-042 curves overlap a lot in the publication and are not easy to digitalise. We then checked the 6- and 12-month survival proportions versus the plots in the paper, and they are reasonably close. We first assessed reducing the 3-month time interval to a monthly interval; when using ToT and PFS KM curves, the time intervals between events do not match and reducing the interval to monthly led to problems. The resulting hazard was extremely high in the first month and when applied to the modelled PFS function, it resulted in 36% of patients discontinuing treatment within the first month. This is clearly not realistic and not in line with clinical data. As such, this method was discharged and alternative methods were explored. In addition to the ERG approach, we present two alternative methods to explore ToT on pembrolizumab, each with its own limitations and assumptions:

1. "Parametric Extrapolation method"

Here, we fitted parametric curves to the digitalised KM curves for both ToT and PFS of KEYNOTE-042 and for ToT from KEYNOTE-024 and calculated the HR with a monthly interval from the extrapolations (See Appendix D for the parametric extrapolations). This is in line with the ERG suggestion: "*exploration of more formal methods of comparing available pembrolizumab PFS and time on treatment data, such as curve fitting to reconstructed patient level data".*

In Table 4, we provide the AIC/BIC statistics and show the fit of the best fitting models to the time to event curves. The selected functions for KEYNOTE-042 based on fit are: for PFS Log-Normal and for TOT Weibull and Gamma as an alternative (**Figure 17**, **Figure 18**, and

Figure 19). Generalised Gamma could be an alternative to Log-Normal for PFS, but we could not fit it for ToT. Additional figures are provided as a separate document.

Table 4: AIC/BIC statistics for the "Parametric Extrapolation Method" - KEYNOTE-042 PFS and KN-042 ToT

KEYNOTE-042 PFS			**KEYNOTE-042 ToT**		
AIC	**BIC**	**Dist**	**AIC**	**BIC**	**Dist**
1526.60	**1534.00**	**lnorm**	**1346.80**	**1354.00**	**weibull**
1527.30	1538.40	gengamma	**1349.20**	**1356.40**	**gamma**

		1532.30	1539.70	llogis	1350.20	1357.40	llogis
		1538.00	1545.40	gompertz	1353.30	1360.50	lnorm
		1552.60	1560.00	weibull	1363.30	1370.50	gompertz
		1558.50	1562.20	exponential	1395.30	1398.90	exponential
		1556.50	1563.90	gamma	-	-	-

		Figure 17: PFS parametric extrapolations for KEYNOTE-042 – Log normal as base case 

		Figure 18: TTOT parametric extrapolations for KEYNOTE-042 – Weibull (base case) 

		Figure 19: TTOT parametric extrapolations for KEYNOTE-042 – Gamma 

2. "Weighted average method"

Here, we have constructed a ToT curve by applying a weighted average to parametrically extrapolated KEYNOTE-042 and the KEYNOTE-024 digitalised KM curves of ToT, based on the number of patients in each study. This method is more simple and intuitive; it uses all the available data, including the KEYNOTE-024 data (Figure 20). We provide all parametric extrapolations for pembrolizumab ToT as an attachment. Here, we will only show the best fitting based on the AIC/BIC statistics – log normal.

Table 5: AIC/BIC statistics for KEYNOTE-024 ToT functions

KEYNOTE-024 TOT		
AIC	**BIC**	**Dist**
795.50	**801.60**	**lnorm**
802.10	808.10	llogis
803.20	809.30	gompertz
810.00	816.00	weibull
812.90	818.90	gamma
818.40	821.40	exponential

		Figure 20: TTOT parametric extrapolations for KEYNOTE-024 – Log-Normal 

		Figure 30 and Figure 31 in Appendix D, show how the different methods have similar results and how the weighted average method, unsurprisingly gives results in between the observed ToT KM curves from the KEYNOTE trials, although at times runs over the PFS function from the model. **Pembrolizumab Time on Treatment: ICER impact (Table 12)** • Baseline ICER from the PFS approach (ICER £561,530, Total pembrolizumab treatment costs £[redacted]) • 5 a ERG approach: Changes: ICER £-33,864, pembrolizumab treatment cost difference £-2,733 • 5 b Extrapolation method: ToT Weibull Change: ICER £-42,870 pembrolizumab treatment costs £-3,359 • 5 c Extrapolation method: ToT Gamma Change: ICER £-29,982 pembrolizumab treatment costs £-2,317 • 5 d Weighted Average of ToT for KN-042 and KN-024 Change: ICER £+4,742 pembrolizumab treatment costs £+479 Very small variations in costs have a relatively big impact on the ICER, given the very small QALY difference. This confirms once again the appropriateness of the cost comparison analysis for decision making in this case, over the cost effectiveness analysis. We notice how the ERG approach (and the company base case based on PFS) rank in between the extrapolation method using the Weibull function and the Weighted Average method, using all the data from

		the RCTs, in terms of ICERs. Each approach relies on several assumptions and all estimates are approximations. We will choose the most conservative extrapolation method, the Weibull function for ToT of KEYNOTE-042 and Log-Normal for the PFS function (Figure 18), for the case presented here. Even in this worst-case ToT extrapolation scenario, driven by a marginal difference in pembrolizumab's treatment costs, we believe a strong cost-effectiveness and cost comparison scenario has been put forward. **Real world evidence data** In addition, we have extracted data from pembrolizumab time to last treatment administration's ToT matching the trial population, following Velcheti's methodology from Flatiron (22). Flatiron is the same source of information that was used by Velcheti, with these updated Flatiron data having the advantage of a longer observation period, until COVID-19 censor date 2020-03-01 (22). Real world data are available for a descriptive comparison. Only the resulting KM curve is presented here, the full report is provided as an attachment. Overall, [redacted] patients with a diagnosis of advanced NSCLC, ECOG 0 or 1, Squamous or Non-squamous histology and PD-L1 expression greater or equal to 50% started pembrolizumab as monotherapy. The median follow-up time from the start of pembrolizumab until death or last activity in the database was 17.5 months. From Figure 21 we can see that, at 12 and 24 months, [redacted] were still on treatment. After 30 months, [redacted] were still on treatment.

		This data confirm two important points that we also heard from clinicians: ● At 24 months, a maximum of 10% of patients are still on treatment and, ● few patients are in need and continue to be treated beyond 24 months **Figure 21: Flatiron data for patients treated with pembrolizumab** 

Key issue 6: The validity of certain resource use frequencies in the progressive disease state of the model	**YES**	The company referenced sources for GP home visits and occupational therapist visits in the progressive disease state of the model, which the ERG has been unable to trace. In addition, the ERGs clinical advisor felt that these seemed very high at 26.06 per year for application throughout time spent time in the PD state. These costs have an impact on the ICER resulting from differences in PFS between the alternatives. Those in the pembrolizumab arm spend a greater duration of time in this state of the model. **Summary** ● GP home visit frequency was discussed at an advisory board and Roche agree with the ERG in reducing the visits by 50%. We also reduced the Therapist visits accordingly. ● The GP home visit frequency was eventually traced back to Appendix 1 of NICE Guideline CG81 (31) **Adjustment to GP home and therapist visit frequency** No real world data are available on GP contact frequency, but we discussed the GP home visit frequency at an Advisory Board and we it was agreed that the reduction of 50% of this value is appropriate. **Investigation into origin of data source** This original GP contact frequency in the submission was derived from Table 53 (*Resource use frequency for progression-free and progressed health states)* in the company submission of the TA531 (15), which was

		based on Table 62 (*Estimated health-care resource use per patient for disease monitoring and supportive care in PFS, PPS and during the terminal phase)* of Brown et al study (32): • GP home visit 26.09 per annum (fortnightly) Marie Curie report • Therapist visit 26.09 per annum (fortnightly) Appendix 1 of NICE Guideline CG81 The Marie Curie report was referenced in the company submission and appear to have been derived from a study from Professor David Taylor and Sarah Carter of the School of Pharmacy, University of London, to examine how people's preferences to die at home might be realised: *Valuing Choice—Dying at Home: A case for the more equitable provision of high quality support for people who wish to die at home, 2004 (33)* Nonetheless, we were unable to trace back this reference, also mentioned in "House of Commons Health Committee Palliative Care Fourth Report of Session 2003–04 Volume I" (34). Eventually, the same frequency is traceable to Appendix 1 of NICE Guideline CG81 (31), specifically Package 2, which is described as follows: "*The second package of care describes an average level of supportive and palliative care a patient receiving the 'no chemotherapy' intervention might be expected to receive until the last two weeks of life. This package of care is also included for the patient that follows the strategies in the model with three lines of chemotherapy, from the time of progression until the two weeks before death. Unlike the care given in package 1, all elements of the care delivered in package 2 are time-related. The packages are artificial constructs designed for use in the model. There is no assumption that each individual will receive*

		precisely this pattern of care, rather this was an attempt to estimate the costs of supportive care in general at different points in the patient pathway." Impact on the ICER: 50% reduction of PD HS home visit frequency: Change: £-9,956

Additional issues

Please use the table below to respond to additional issues in the ERG report that have not been identified as key issues. Please do **not** use this table to repeat issues or comments that have been raised at an earlier point in this appraisal (e.g. at the clarification stage).

Does this response contain new evidence, data or analyses? **Issue from the ERG report**	**Response**

Relevant section(s) and/or page(s)	
ADDITIONAL ISSUE 1: Utilities for the whole ITT WT population	
NO new evidence 3.2.7 Health related quality of life, page 51-53 ERG's clarification question B10 Following ERG's clarification question B10 we	Utilities for the ITT WT population, requested by the ERG in the clarification question Question B10, are more robust, have more than double observations, double number of patients and similar baseline utility values. As such, these should be used for the base case. As noted in the ERG report, "*using pooled values, progression of disease gave a decline in utility of* [redacted]. *There is some evidence that this* [redacted]*." (pg.53).* Indeed, these more robust values solve this issue as well, to our understanding. Summary from the response to Question B10: In the whole ITT WT population, 475 had a baseline utility value (Table 6). The following table summarises the baseline utility for the whole ITT WT population and by TC3 or IC3 subgroup. The ITT WT population has a higher number of observations and similar baseline utility values.

analysed the quality of life data for the whole ITT WT population. Only the TC3 or IC3-WT subpopulation was initially considered for the estimation of utility.

Table 6: Baseline utility values

	TC3 or IC3	TC1/2/3 or IC1/2/3 excluding TC3 or IC3	ITT WT
N	[redacted]	[redacted]	[redacted]
Median	[redacted]	[redacted]	[redacted]
Mean	[redacted]	[redacted]	[redacted]

We believe it is more appropriate to use the whole ITT WT population.

A subset of 425 patients has available baseline utility and at least a post-baseline utility measurement. The number of patients and observations available by progression status and TC3 or IC3 subgroup is presented in Table 7 below for the 4th February 2020 data-cut:

Table 7: Number of patients and observations (CCOD 4th February 2020)

Treatment arm	Number of patients	Number of observations
Pre-progression	[redacted]	[redacted]
TC3 or IC3	[redacted]	[redacted]
TC1/2/3 or IC1/2/3 excluding TC3 or IC3	[redacted]	[redacted]
Post-progression	[redacted]	[redacted]
TC3 or IC3	[redacted]	[redacted]
TC1/2/3 or IC1/2/3 excluding TC3 or IC3	[redacted]	[redacted]

The utility values for pre and post progression were estimated separately for each TC3 or IC3 subgroup and are presented in Table 8.

Table 8: Utility values for pre and post progression

Label	Estimate	SE	Lower limit 95% CI	Upper limit 95% CI
Pre progression				
TC3 or IC3	[redacted]	[redacted]	[redacted]	[redacted]
TC1/2/3 or IC1/2/3 excluding TC3 or IC3	[redacted]	[redacted]	[redacted]	[redacted]
ITT WT	[redacted]	[redacted]	[redacted]	[redacted]

	Post progression				
	TC3 or IC3	[redacted]	[redacted]	[redacted]	[redacted]
	TC1/2/3 or IC1/2/3 excluding TC3 or IC3	[redacted]	[redacted]	[redacted]	[redacted]
	ITT WT	[redacted]	[redacted]	[redacted]	[redacted]

Using these, more robust values is more favourable to atezolizumab: impact on the ICER: £+77,217.

Even without these utility values, the 22C3 scenario analysis shows atezolizumab gains more QALY than pembrolizumab. The swings in the ICER direction confirm that the two products are comparable and the cost comparison is an appropriate tool for decision-making.

ADDITIONAL ISSUE 2: Cost-Effectiveness of Atezolizumab in 22C3 selected patients TPS>=50% – Scenario analysis	
YES new analyses 22C3 subgroup analysis We hereby provide an overview of base case selected for the 22C3 based	We have aligned the 22C3 assay scenario analysis with the new base case presented in Table 12 for the SP142 data. We have applied all ERG's amendments and applied the worst-case pembrolizumab's ToT extrapolation. We have also used the full utility data set as described above in Additional Issue 2. In Figure 22, we present the parametric extrapolations chosen for the 22C3 assay scenario. We ran extensive scenario analyses and none of the inputs changes the picture: atezolizumab gains slightly more QALY than pembrolizumab and potentially dominates it. These results are in line with the analyses based on the 2018 primary analysis data cut based on the SP142 assay. The only scenario where atezolizumab is not dominating, is assuming extended treatment effect for pembrolizumab. While we have already discussed how there is no evidence to justify such an assumption, we notice that even assuming lifetime treatment benefit for pembrolizumab, the ICERs would be aligned with the company chosen SP142 base case. Given the extremely small QALY difference, we interpret this cost effectiveness result as a further confirmation of the equivalence of the two products in this indication. **AEs** There has been small amendments on Treatment Related Grade 3, Grade 4, Grade 5 and Serious AEs by treatment. The AEs table can be found in Appendix E, Table 15. The cut-off for inclusion in the economic model did not change.

scenario analysis.

Further parametric extrapolations and information are sent through separate files and available in the economic model

Utilities

In line with the new base case, we have chosen the ITT WT population utility values. The conclusion does not change when TC3/IC3 WT-only utilities are used. Atezolizumab gains more QALYs than pembrolizumab.

Parametric Extrapolations

We hereby provide an overview of base case selected for the 22C3 based scenario analysis.

Further parametric extrapolations and information are sent through separate files and available in the economic model. Given the time constraint and given that in all scenarios, atezolizumab gains more QALYs and potentially dominates pembrolizumab regardless of the parametrisation, utilities, pembrolizumab's ToT extrapolation used etc., we will not engage in a lengthy discussion on the appropriateness of the selected model.

Time on Treatment

Table 9: Time on treatment AIC/BIC statistics

Distribution	AIC	BIC
Weibull	530.47	536.26
Gamma	532.46	541.15
Log-logistic	533.34	539.14

Log-normal	540.65	546.45
Gompertz	541.26	547.05
Exponential	578.90	581.79

Figure 22: Selected Extrapolation – Weibull; as described using the "parametric extrapolation method" for pembrolizumab

Overall Survival

Table 10: Overall Survival AIC/BIC statistics

Distribution	AIC	BIC
Exponential	393.96	396.86
Weibull	394.90	400.70
Gompertz	395.30	401.09
Gamma	396.80	405.49
Log-logistic	397.55	403.35
Log-normal	403.09	408.88

	Selected OS Extrapolation **Figure 23: Overall Survival - Weibull extrapolation** 

Alternative OS Extrapolations

Figure 24: Overall Survival - Exponential extrapolation

	Figure 25: Overall Survival Gompertz extrapolation 

Progression Free Survival

Table 11: PFS AIC/BIC statistics

Distribution	AIC	BIC
Gompertz	452.17	457.97
Log-normal	452.72	458.52
Gamma	453.44	462.13
Log-logistic	454.76	460.56
Weibull	467.10	472.90
Exponential	479.93	482.83

Selected PFS Extrapolation

Figure 26: PFS – Log-Normal extrapolation

Alternative PFS Extrapolations

Figure 27: PFS – Gamma extrapolation

Figure 28: PFS – Log-Logistic extrapolation

Figure 29: PFS – Gompertz extrapolation

22C3 scenario analysis

Table 12: 22C3 assay based analyses atezolizumab vs. pembrolizumab. Base case aligned with the base case below (5b+1+2+3+4+6): All ERG amendments applied + worst case ToT extrapolation scenario used. (PAS price)

Parameter	Value	Atezo Mono			Pembro mono			Atezo Mono vs. Pembro Mono		
		Life Years	QALYS	Costs	Life Years	QALYS	Costs	Inc. QALYs	Inc. Costs	ICER
Base case		**2.49**	[redacted]	[redacted]	**2.48**	[redacted]	[redacted]	**0.03**	**-38,112**	**Dominant**
Distribution OS	Exponential	2.36	[redacted]	[redacted]	2.37	[redacted]	[redacted]	0.02	-39,427	Dominant
	Log-normal	3.56	[redacted]	[redacted]	3.44	[redacted]	[redacted]	0.12	-37,113	Dominant
	Gen Gamma	2.41	[redacted]	[redacted]	2.41	[redacted]	[redacted]	0.02	-38,958	Dominant
	Log-logistic	3.38	[redacted]	[redacted]	3.27	[redacted]	[redacted]	0.11	-37,169	Dominant
	Gompertz	2.81	[redacted]	[redacted]	2.74	[redacted]	[redacted]	0.08	-37,313	Dominant
	KM with Exponential tail	2.30	[redacted]	[redacted]	2.32	[redacted]	[redacted]	0.01	-39,547	Dominant

	KM with Weibull tail	2.43	[redacted]	[redacted]	2.43	[redacted]	[redacted]	0.03	-38,224	Dominant
	KM with Log-normal tail	3.35	[redacted]	[redacted]	3.26	[redacted]	[redacted]	0.10	-37,215	Dominant
	KM with Gamma tail	2.35	[redacted]	[redacted]	2.36	[redacted]	[redacted]	0.02	-39,099	Dominant
	KM with Log-logistic tail	3.20	[redacted]	[redacted]	3.12	[redacted]	[redacted]	0.09	-37,244	Dominant
	KM with Gompertz tail	2.74	[redacted]	[redacted]	2.67	[redacted]	[redacted]	0.07	-37,338	Dominant
Distribution PFS	Exponential	2.49	[redacted]	[redacted]	2.48	[redacted]	[redacted]	0.02	-50,968	Dominant
	Weibull	2.49	[redacted]	[redacted]	2.48	[redacted]	[redacted]	0.03	-37,507	Dominant
	Gen Gamma	2.49	[redacted]	[redacted]	2.48	[redacted]	[redacted]	0.04	-37,709	Dominant
	Log-logistic	2.49	[redacted]	[redacted]	2.48	[redacted]	[redacted]	0.03	-36,240	Dominant
	Gompertz	2.49	[redacted]	[redacted]	2.48	[redacted]	[redacted]	0.04	-35,001	Dominant

	KM with Exponential tail	2.49	[redacted]	[redacted]	2.48	[redacted]	[redacted]	0.02	-38,285	Dominant
	KM with Weibull tail	2.49	[redacted]	[redacted]	2.48	[redacted]	[redacted]	0.03	-38,354	Dominant
	KM with Log-normal tail	2.49	[redacted]	[redacted]	2.48	[redacted]	[redacted]	0.04	-38,425	Dominant
	KM with Gamma tail	2.49	[redacted]	[redacted]	2.48	[redacted]	[redacted]	0.04	-38,430	Dominant
	KM with Log-logistic tail	2.49	[redacted]	[redacted]	2.48	[redacted]	[redacted]	0.04	-38,428	Dominant
	KM with Gompertz tail	2.49	[redacted]	[redacted]	2.48	[redacted]	[redacted]	0.04	-38,434	Dominant
Distribution TTD	Exponential	2.49	[redacted]	[redacted]	2.48	[redacted]	[redacted]	0.03	-46,064	Dominant
	Log-normal	2.49	[redacted]	[redacted]	2.48	[redacted]	[redacted]	0.03	-33,554	Dominant
	Gen Gamma	2.49	[redacted]	[redacted]	2.48	[redacted]	[redacted]	0.03	-37,933	Dominant
	Log-logistic	2.49	[redacted]	[redacted]	2.48	[redacted]	[redacted]	0.03	-33,817	Dominant

	Gompertz	2.49	[redacted]	[redacted]	2.48	[redacted]	[redacted]	0.03	-34,770	Dominant
	KM with Exponential tail	2.49	[redacted]	[redacted]	2.48	[redacted]	[redacted]	0.03	-48,535	Dominant
	KM with Weibull tail	2.49	[redacted]	[redacted]	2.48	[redacted]	[redacted]	0.03	-39,886	Dominant
	KM with Log-normal tail	2.49	[redacted]	[redacted]	2.48	[redacted]	[redacted]	0.03	-35,964	Dominant
	KM with Gamma tail	2.49	[redacted]	[redacted]	2.48	[redacted]	[redacted]	0.03	-39,704	Dominant
	KM with Log-logistic tail	2.49	[redacted]	[redacted]	2.48	[redacted]	[redacted]	0.03	-36,324	Dominant
	KM with Gompertz tail	2.49	[redacted]	[redacted]	2.48	[redacted]	[redacted]	0.03	-34,908	Dominant
	Actual treatment duration	2.49	[redacted]	[redacted]	2.48	[redacted]	[redacted]	0.03	-51,121	Dominant
	Until progression	2.49	[redacted]	[redacted]	2.48	[redacted]	[redacted]	0.03	-38,112	Dominant

Utility method	TC3/IC3 WT	2.49	[redacted]	[redacted]	2.48	[redacted]	[redacted]	0.03	-38,112	Dominant
	IMpower110 (On/Off treatment)	2.49	[redacted]	[redacted]	2.48	[redacted]	[redacted]	0.08	-38,112	Dominant
	IMpower110 (Pre/Post progression)	2.49	[redacted]	[redacted]	2.48	[redacted]	[redacted]	0.03	-38,112	Dominant
	IMpower110 (Proximity to death)	2.49	[redacted]	[redacted]	2.48	[redacted]	[redacted]	0.01	-38,112	Dominant
	Chouaid et al. 2013	2.49	[redacted]	[redacted]	2.48	[redacted]	[redacted]	0.03	-38,112	Dominant
	Nafees et al. 2008	2.49	[redacted]	[redacted]	2.48	[redacted]	[redacted]	0.08	-38,112	Dominant
	KEYNOTE-024	2.49	[redacted]	[redacted]	2.48	[redacted]	[redacted]	0.05	-38,112	Dominant
TTD half cycle correction	No	2.49	[redacted]	[redacted]	2.48	[redacted]	[redacted]	0.03	-38,653	Dominant
Time horizon	5	2.09	[redacted]	[redacted]	2.16	[redacted]	[redacted]	-0.03	-45,081	1,1380,226
	10	2.42	[redacted]	[redacted]	2.45	[redacted]	[redacted]	0.00	-39,852	Dominant

	15	2.48	[redacted]	[redacted]	2.48	[redacted]	[redacted]	0.03	-38,406	Dominant

Summary of changes to the company's cost-effectiveness estimate(s)

Company: If you have made changes to the company's preferred cost-effectiveness estimate(s) in response to technical engagement, please complete the table below to summarise these changes.

First submitted base case (PAS price)		**£560,832**
ERG's accepted corrections (PAS price)		
1 PFS ≤OS	ERG amendment accepted and included for atezolizumab	**£561,530 (always included in the changes below)** Change: £+698
2 50% of patients who progress receive subsequent chemotherapy	ERG amendment accepted	£558,052 Change: £-2,780
3 Post pembro therapy cost follows PFS	ERG amendment accepted	£558,156 Change: £-2,676

4 Reduction of 50% of PD HS home visit frequency	ERG amendment accepted	£550,876 Change: £-9,956
Pembrolizumab Time on Treatment		
***5 a** ERG approach*		*£527,666* *Change: £-33,864*
5 b Extrapolation method: Weibull for ToT KN42	Most pessimistic Time on Treatment extrapolation – Base case	£518,660 Change: £-42,870
***5 c** Extrapolation method: Gamma for ToT KN42*	*Intermediate scenario*	*£531,548* *Change: £-29,982*
5 d Weighted Average of KN-042 and KN-024	*More optimistic scenario*	*£566,271* *Change: £+4,742*

<table>
<tr><td colspan="4">Utilities</td></tr>
<tr><td>6 Use of the whole utility set for the ITT WT population</td><td>Initially the company submission was based only on observations for the TC3/IC3 WT population.

Following the ERG request we have analysed utilities for the whole ITT WT population</td><td>Use of the whole utility set for the ITT WT population, as described above in the first additional issue, is more appropriate, as the data set includes more observations</td><td>£638,049* Change: +77,217</td></tr>
<tr><td colspan="4">Company’s preferred base case following technical engagement</td></tr>
<tr><td colspan="4">Base Case cost effectiveness analysis (PAS price)</td></tr>
<tr><td>Basecase

(5b+1+2+3+4+6)

ToT: Extrapolation – Weibull - Most conservative Time on Treatment extrapolation</td><td colspan="3">
<table>
<tr><th colspan="7">Atezo mono versus Pembro mono</th></tr>
<tr><th>Inc. QALYs</th><th>Inc. Costs</th><th>ICER*</th><th>NMB* WTP £30K</th><th>NMB* WTP £20K</th><th>NHB* WTP £30K</th><th>NHB* WTP £20K</th></tr>
<tr><td>-0.07</td><td>-42,263</td><td>572,939</td><td>40,050</td><td>40,788</td><td>1.34</td><td>2.04</td></tr>
</table>
</td></tr>
</table>

Base Case Cost comparison analysis results (PAS price)

Basecase

(5b+1+2+3+4)

	Atezo Mono (£)	Pembro mono (£)	Incremental costs (£)
Mean cost of PFS	[redacted]	[redacted]	[redacted]
Mean cost of progression	[redacted]	[redacted]	[redacted]
Terminal/palliative care cost	[redacted]	[redacted]	[redacted]
Mean total cost (£)	[redacted]	[redacted]	[redacted]

Scenarios varying pembrolizumab Time on Treatment modelling (PAS price)

(5a+1+2+3+4+6)

ToT: ERG approach

Atezo mono versus Pembro mono

Inc. QALYs	Inc. Costs	ICER*	NMB* WTP £30K	NMB* WTP £20K	NHB* WTP £30K	NHB* WTP £20K
-0.07	-42,911	581,724	40,698	41,436	1.36	2.07

(5c+1+2+3+4+6)

ToT: Extrapolation - Gamma

Atezo mono versus Pembro mono

Inc. QALYs	Inc. Costs	ICER*	NMB* WTP £30K	NMB* WTP £20K	NHB* WTP £30K	NHB* WTP £20K
-0.07	-43,342	587,556	41,128	41,866	1.37	2.09

(5d+1+2+3+4+6)

ToT: Weighted average method

Atezo mono versus Pembro mono

Inc. QALYs	Inc. Costs	ICER*	NMB* WTP £30K	NMB* WTP £20K	NHB* WTP £30K	NHB* WTP £20K
-0.07	-46,236	626,799	44,023	44,761	1.47	2.24

References

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1. Hirsch FR, McElhinny A, Stanforth D, Ranger-Moore J, Jansson M, Kulangara K, et al. PD-L1 immunohistochemistry assays for lung cancer: results from phase 1 of the blueprint PD-L1 IHC assay comparison project. 2017;12(2):208-22.
2. Tsao MS, Kerr KM, Kockx M, Beasley MB, Borczuk AC, Botling J, et al. PD-L1 Immunohistochemistry Comparability Study in Real-Life Clinical Samples: Results of Blueprint Phase 2 Project. Journal of thoracic oncology : official publication of the International Association for the Study of Lung Cancer. 2018;13(9):1302-11.
3. Herbst RS, Giaccone G, de Marinis F, Reinmuth N, Vergnenegre A, Barrios CH, et al. Atezolizumab for First-Line Treatment of PD-L1–Selected Patients with NSCLC. New England Journal of Medicine. 2020;383(14):1328-39.
4. Santini FC, Rudin CM. Atezolizumab for the treatment of non-small cell lung cancer. Expert Rev Clin Pharmacol. 2017;10(9):935-45.
5. 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.
6. Mok TSK, Wu YL, Kudaba I, Kowalski DM, Cho BC, Turna HZ, et al. Final analysis of the phase III KEYNOTE-042 study: Pembrolizumab (Pembro) versus platinum-based chemotherapy (Chemo) as first-line therapy for patients (Pts) with PD-L1-positive locally advanced/metastatic NSCLC. Annals of Oncology. 2019;30(Suppl 2):ii38.
7. Data on File (Greco). IMpower110 - Final Analysis. 2020.
8. Reck M, Rodriguez-Abreu D, Robinson AG, Hui R, Csoszi T, Fulop A, et al. Updated Analysis of KEYNOTE-024: Pembrolizumab Versus Platinum-Based Chemotherapy for Advanced Non-Small-Cell Lung Cancer With PD-L1 Tumor Proportion Score of 50% or Greater. Journal of clinical oncology : official journal of the American Society of Clinical Oncology. 2019;37(7):537-46.
9. Reck M, Rodríguez-Abreu D, Robinson A, Hui R, Cs?szi T, Fülöp A, et al. Pembrolizumab versus Chemotherapy for PD-L1-Positive Non-Small-Cell Lung Cancer. New England journal of medicine. 2016;375(19):1823-33.
10. Reck M, Rodríguez-Abreu D, Robinson A, Hui R, Csoszi T, Fülöp A, et al. Pembrolizumab versus chemotherapy for PD-L1-positive non-small-cell lung cancer - PROTOCOL. New England journal of medicine. 2016;375(19):1823-33.

11. National Institute for Health and Care Excellence. Nivolumab for previously treated locally advanced or metastatic non-squamous non-small-cell lung cancer (CDF review TA484) [ID1572] 2020 [Date Accessed 4th January 2021]. Available from: https://www.nice.org.uk/guidance/indevelopment/gid-ta10513.
12. National Institute for Health and Care Excellence. Nivolumab for advanced squamous non-small-cell lung cancer after chemotherapy [TA655]. 2020.
13. National Institute for Health and Care Excellence. Atezolizumab for treating locally advanced or metastatic non-small-cell lung cancer after chemotherapy [TA520] 2018 [Date Accessed 3rd September 2020]. Available from: https://www.nice.org.uk/guidance/ta520.
14. National Institute for Health and Care Excellence. Atezolizumab for treating locally advanced or metastatic urothelial carcinoma after platinum-containing chemotherapy [TA525]. 2018.
15. National Institute for Health and Care Excellence. Pembrolizumab for untreated PD-L1-positive metastatic non-small-cell lung cancer [TA531] 2018 [Date Accessed 18th February 2020]. Available from: https://www.nice.org.uk/guidance/ta531.
16. National Institute for Health and Care Excellence. Pembrolizumab with pemetrexed and platinum chemotherapy for untreated, metastatic, non-squamous non-small-cell lung cancer [TA557] 2019 [Date Accessed 1st September 2020]. Available from: https://www.nice.org.uk/guidance/ta557.
17. National Institute for Health and Care Excellence (NICE). Atezolizumab in combination with bevacizumab, paclitaxel and carboplatin for the first-line treatment of adult patients with metastatic non-squamous NSCLC [online] Available at: https://www.nice.org.uk/guidance/ta584/documents/committee-papers [TA584]. 2019.
18. National Institute for Health and Care Excellence. Pembrolizumab for untreated metastatic or unresectable recurrent head and neck squamous cell carcinoma [TA661] 2020 [Available from: https://www.nice.org.uk/guidance/ta661.
19. National Institute for Health and Care Excellence. Atezolizumab with carboplatin and etoposide for untreated extensive-stage small-cell lung cancer [TA638] 2020 [Date Accessed 2nd September 2020]. Available from: https://www.nice.org.uk/guidance/ta638.
20. National Institute for Health and Care Excellence. Atezolizumab with nab-paclitaxel for untreated PD-L1-positive, locally advanced or metastatic, triple-negative breast cancer [TA639] 2020 [Date Accessed 2nd September 2020]. Available from: https://www.nice.org.uk/guidance/ta639.
21. National Institute for Health and Care Excellence. Pembrolizumab for treating PD-L1-positive non-small-cell lung cancer after chemotherapy [TA428]. 2017.

22. Velcheti V, Chandwani S, Chen X, Pietanza MC, Burke T. First-line pembrolizumab monotherapy for metastatic PD-L1-positive NSCLC: real-world analysis of time on treatment. Immunotherapy. 2019;11(10):889-901.
23. Friends of Cancer Research. Establishing a framework to evaluate real-world endpoints. 2018.
24. Gong Y, Kehl KL, Oxnard GR, Khozin S, Mishra-Kalyani PS, Blumenthal GM. Time to treatment discontinuation (TTD) as a pragmatic endpoint in metastatic non-small cell lung cancer (mNSCLC): A pooled analysis of 8 trials. Journal of Clinical Oncology. 2018;36(15_suppl):9064-.
25. Blumenthal GM, Gong Y, Kehl K, Mishra-Kalyani P, Goldberg KB, Khozin S, et al. Analysis of time-to-treatment discontinuation of targeted therapy, immunotherapy, and chemotherapy in clinical trials of patients with non-small-cell lung cancer. Annals of oncology : official journal of the European Society for Medical Oncology. 2019;30(5):830-8.
26. Spigel DR, McLeod M, Hussein MA, Waterhouse DM, Einhorn L, Horn L, et al. Randomized results of fixed-duration (1-yr) vs continuous nivolumab in patients (pts) with advanced non-small cell lung cancer (NSCLC). Annals of Oncology. 2017;28:v461.
27. Herbst RS, Garon EB, Kim DW, Cho BC, Perez-Gracia JL, Han JY, et al. Long-Term Outcomes and Retreatment Among Patients With Previously Treated, Programmed Death-Ligand 1–Positive, Advanced Non–Small-Cell Lung Cancer in the KEYNOTE-010 Study. Journal of clinical oncology : official journal of the American Society of Clinical Oncology. 2020;38(14):1580-90.
28. Brahmer JR, Rodriguez-Abreu D, Robinson AG, Hui R, Csőszi T, Fülöp A, et al. LBA51 KEYNOTE-024 5-year OS update: First-line (1L) pembrolizumab (pembro) vs platinum-based chemotherapy (chemo) in patients (pts) with metastatic NSCLC and PD-L1 tumour proportion score (TPS) ≥50%. Annals of Oncology. 2020;31:S1181-S2.
29. Long GV, Schachter J, Ribas A, Arance AM, Grob J-J, Mortier L, et al. 4-year survival and outcomes after cessation of pembrolizumab (pembro) after 2-years in patients (pts) with ipilimumab (ipi)-naive advanced melanoma in KEYNOTE-006. Journal of Clinical Oncology. 2018;36(15_suppl):9503-.
30. IASLC. KEYNOTE-010: Long-Term Outcomes and Results of Retreatment 2019 [Date Accessed 21st December 2020]. Available from: https://www.iaslc.org/iaslc-news/ilcn/keynote-010-long-term-outcomes-and-results-retreatment.
31. National Institute for Health and Care Excellence. Advanced breast cancer: diagnosis and treatment [CG81] 2009 [Date Accessed 4th January 2020]. Available from: https://www.nice.org.uk/guidance/cg81/evidence/full-guideline-pdf-242246995.
32. Brown T, Pilkington G, Bagust A, Boland A, Oyee J, Tudur-Smith C, et al. Clinical effectiveness and cost-effectiveness of first-line chemotherapy for adult patients with locally advanced or metastatic non-small cell lung cancer: a systematic review and economic evaluation. Health technology assessment (Winchester, England). 2013;17(31):1-278.
33. David Taylor, Sarah Carter. Valuing Choice – Dying at Home. A care for the more equitable provision of high
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quality support for people who wish to die at home. An economic and social policy opinion commissioned by Marie Curie Cancer Care. School of Pharmacy, University of London,. 2004.
34. House of Commons Health Committee. Palliative Care. Fourth Report of Session 2003–04 2004.

Appendix A – Patient baseline characteristics from IMpower110

Table 13: Patient baseline characteristics from IMpower110 of the 22C3, SP142, and IC3 only PD-L1 high subpopulations (CCOD 10th September 2018)

	22C3 subpopulation Atezolizumab [redacted]	**22C3 subpopulation** Chemotherapy [redacted]	**SP142 IC3 or TC3 subpopulation** Atezolizumab (N=107)	**SP142 IC3 or TC3 subpopulation** chemotherapy (N=98)	**SP142 IC3 not TC3 subpopulation** [redacted]	**SP142 IC3 not TC3 subpopulation** [redacted]
Age (Years)						
Mean (SD)	[redacted]	[redacted]	63.3 (9.1)	64.2 (9.0)	[redacted]	[redacted]
Median	[redacted]	[redacted]	63	65.5	[redacted]	[redacted]
Min - Max	[redacted]	[redacted]	33-79	33-87	[redacted]	[redacted]
Age Group (Years)						
< 65	[redacted]	[redacted]	59 (55.1%)	43 (43.9%)	[redacted]	[redacted]
>= 65	[redacted]	[redacted]	48 (44.9%)	55 (56.1%)	[redacted]	[redacted]
Age Group (Years)						
< 65	[redacted]	[redacted]	59 (55.1%)	43 (43.9%)	[redacted]	[redacted]
65 to 74	[redacted]	[redacted]	33 (30.8%)	47 (48.0%)	[redacted]	[redacted]

75 to 84	[redacted]	[redacted]	15 (14.0%)	7 (7.1%)	[redacted]	[redacted]
>= 85	[redacted]	[redacted]	0	1 (1.0%)	[redacted]	[redacted]
Sex						
Male	[redacted]	[redacted]	79 (73.8%)	64 (65.3%)	[redacted]	[redacted]
Female	[redacted]	[redacted]	28 (26.2%)	34 (34.7%)	[redacted]	[redacted]
Race						
Asian	[redacted]	[redacted]	20 (18.7%)	15 (15.3%)	[redacted]	[redacted]
White	[redacted]	[redacted]	87 (81.3%)	82 (83.7%)	[redacted]	[redacted]
Unknown	[redacted]	[redacted]	0 (0%)	1 (1.0%)	[redacted]	[redacted]
Ethnicity						
Hispanic or Latino	[redacted]	[redacted]	9 (8.4%)	5 (5.1%)	[redacted]	[redacted]
Not Hispanic or Latino	[redacted]	[redacted]	98 (91.6%)	91 (92.9%)	[redacted]	[redacted]
Not Stated	[redacted]	[redacted]	0 (0%)	2 (2.0%)	[redacted]	[redacted]

Baseline Weight (kg)						
Mean (SD)	[redacted]	[redacted]	69.43 (14.99)	67.93 (14.33)	[redacted]	[redacted]
Median	[redacted]	[redacted]	69.00	66.73	[redacted]	[redacted]
Min - Max	[redacted]	[redacted]	32.9 - 98.4	39.4 - 111.0	[redacted]	[redacted]
Baseline ECOG per eCRF						
0	[redacted]	[redacted]	35 (32.7%)	38 (38.8%)	[redacted]	[redacted]
1	[redacted]	[redacted]	72 (67.3%)	60 (61.2%)	[redacted]	[redacted]
Baseline ECOG from IxRS						
0	[redacted]	[redacted]	33 (30.8%)	38 (38.8%)	[redacted]	[redacted]
1	[redacted]	[redacted]	74 (69.2%)	60 (61.2%)	[redacted]	[redacted]
Tobacco Use History						
never	[redacted]	[redacted]	9 (8.4%)	15 (15.3%)	[redacted]	[redacted]
current	[redacted]	[redacted]	20 (18.7%)	29 (29.6%)	[redacted]	[redacted]
previous	[redacted]	[redacted]	78 (72.9%)	54 (55.1%)	[redacted]	[redacted]
Histology from IxRS						

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non-squamous	[redacted]	[redacted]	-	-	[redacted]	[redacted]
squamous	[redacted]	[redacted]	-	-	[redacted]	[redacted]
PD-L1 Expression from IxRS						
TC0 and IC1/2/3	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
TC1/2/3 and Any IC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Appendix B – The number of patients at risk at different time points

Table 14: OS; HR and numbers at risk for 22C3 patients

Time (months)	Chemo	PEMB	IMp110_ATZ	IMp110_Chemo	KN024_Chemo	KN024_PEMB	KN042_Chemo	KN042_PEMB
3	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
6	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
12	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
18	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
24	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

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36	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
48	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
60	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Second column: The first number indicates the median posterior estimate, while the numbers in brackets indicate the 95% posterior credible interval.

Appendix C – Patient numbers treated beyond 2 years

Number of patient treated beyond two years

We believe the patient cohort in need of treatment beyond two years is very small and could be as small as 15 patients. Below we perform some basic calculations:

- Patients receiving 2 years of treatment: From the IMpower110 KM, 26% of patient receive 2 years of treatment (28% from parametric extrapolation), from KEYNOTE-024, 25% reached two years of treatment, from KEYNOTE-010 11% (second line trial allowing re-treatment). It is clinical estimation that in clinical practice less than 10% of patients reach two years of treatment. This value is also

confirmed by the RWE data presented in response to issue 5. We will use 10% for illustrative purposes here, but would welcome data from NHSE about the percentage of patients that achieve 2 years of full treatment in clinical practice.

- Retreatment rates: From KEYNOTE-024, 36% of patients who reached two years of treatment where retreated, in KEYNOTE-010 18% of patients who completed 2 years or 35 cycles went on to have retreatment with pembrolizumab. We think that in clinical practice the retreatment rates could be somewhere in between a first line clinical study (36%) and a second line study including more advanced patients (18%). We will use 30%–36%.

Assuming 10% of the 1656 patients (Blueteq data from NHSE) who currently access pembrolizumab receive 2 years of therapy, this would equal to 166 patients. If, of those patients 30% - 36% would need further treatment beyond two years (KEYNOTE re-treatment rates), the patient cohort under consideration in the NHS is between 50 to 60 patients.

- We also know from KEYNOTE-024 (Figure 18) that 50% of patients stopped re-treatment before 1 year

As such, of the 60 patients in NHS clinical practice in need of receiving further treatment beyond two years, only 30 patients would potentially reach 1 further year of treatment (or more).

Market share would inform the rest of the calculation: 15 would receive 1 further year of treatment or more, if deemed clinically appropriate. As mentioned by clinicians, the patient numbers in need of receiving further treatment beyond two years in the NHS is extremely small.

Appendix D – Alternative parametric extrapolations

Figure 30: Parametric distribution used for the "weighted method and "extrapolation method" (ToT Weibull; PFS Log-normal) compared to KEYNOTE ToT KM and the PFS from the model

Figure 31: Parametric distribution used for the "weighted method and "extrapolation method" (ToT Gamma; PFS Log-normal) compared to KN KM ToT and the PFS from the model

Appendix E – AEs by treatment based on 22C3 assay

Table 15: Treatment Related Grade 3, Grade 4, Grade 5 and Serious AEs

AEs	atezolizumab		chemotherapy	
	%	n AEs	%	n AEs
Alanine aminotransferase increased	[redacted]	[redacted]	[redacted]	[redacted]
Amylase increased	[redacted]	[redacted]	[redacted]	[redacted]
Anaemia	[redacted]	[redacted]	[redacted]	[redacted]
Arthralgia	[redacted]	[redacted]	[redacted]	[redacted]
Aspartate aminotransferase increased	[redacted]	[redacted]	[redacted]	[redacted]
Asthenia	[redacted]	[redacted]	[redacted]	[redacted]
Cerebral ischaemia	[redacted]	[redacted]	[redacted]	[redacted]
Colitis	[redacted]	[redacted]	[redacted]	[redacted]
Constipation	[redacted]	[redacted]	[redacted]	[redacted]
Decreased appetite	[redacted]	[redacted]	[redacted]	[redacted]
Diarrhoea	[redacted]	[redacted]	[redacted]	[redacted]

Erythema	[redacted]	[redacted]	[redacted]	[redacted]
Fatigue	[redacted]	[redacted]	[redacted]	[redacted]
Febrile neutropenia	[redacted]	[redacted]	[redacted]	[redacted]
Gastroenteritis	[redacted]	[redacted]	[redacted]	[redacted]
General physical health deterioration	[redacted]	[redacted]	[redacted]	[redacted]
Hyperglycaemia	[redacted]	[redacted]	[redacted]	[redacted]
Hyperkalaemia	[redacted]	[redacted]	[redacted]	[redacted]
Hypoalbuminaemia	[redacted]	[redacted]	[redacted]	[redacted]
Hyponatraemia	[redacted]	[redacted]	[redacted]	[redacted]
Immune system disorder	[redacted]	[redacted]	[redacted]	[redacted]
Influenza like illness	[redacted]	[redacted]	[redacted]	[redacted]
Infusion related reaction	[redacted]	[redacted]	[redacted]	[redacted]
Leukopenia	[redacted]	[redacted]	[redacted]	[redacted]
Liver function test abnormal	[redacted]	[redacted]	[redacted]	[redacted]
Nausea	[redacted]	[redacted]	[redacted]	[redacted]

Neutropenia	[redacted]	[redacted]	[redacted]	[redacted]
Neutrophil count decreased	[redacted]	[redacted]	[redacted]	[redacted]
Oedema peripheral	[redacted]	[redacted]	[redacted]	[redacted]
Pancytopenia	[redacted]	[redacted]	[redacted]	[redacted]
Petechiae	[redacted]	[redacted]	[redacted]	[redacted]
Platelet count decreased	[redacted]	[redacted]	[redacted]	[redacted]
Pneumonia	[redacted]	[redacted]	[redacted]	[redacted]
Pneumonia bacterial	[redacted]	[redacted]	[redacted]	[redacted]
Pneumonitis	[redacted]	[redacted]	[redacted]	[redacted]
Pyrexia	[redacted]	[redacted]	[redacted]	[redacted]
Rash	[redacted]	[redacted]	[redacted]	[redacted]
Rash erythematous	[redacted]	[redacted]	[redacted]	[redacted]
Rash maculo-papular	[redacted]	[redacted]	[redacted]	[redacted]
Renal failure	[redacted]	[redacted]	[redacted]	[redacted]
Sepsis	[redacted]	[redacted]	[redacted]	[redacted]

Stomatitis	[redacted]	[redacted]	[redacted]	[redacted]
Syncope	[redacted]	[redacted]	[redacted]	[redacted]
Thrombocytopenia	[redacted]	[redacted]	[redacted]	[redacted]
Thrombocytosis	[redacted]	[redacted]	[redacted]	[redacted]
Thrombophlebitis	[redacted]	[redacted]	[redacted]	[redacted]
Toxic skin eruption	[redacted]	[redacted]	[redacted]	[redacted]
Transaminases increased	[redacted]	[redacted]	[redacted]	[redacted]
Vasculitis	[redacted]	[redacted]	[redacted]	[redacted]
Vomiting	[redacted]	[redacted]	[redacted]	[redacted]
Weight decreased	[redacted]	[redacted]	[redacted]	[redacted]
White blood cell count decreased	[redacted]	[redacted]	[redacted]	[redacted]

NICE National Institute for Health and Care Excellence

Clinical expert statement & technical engagement response form

Atezolizumab monotherapy for untreated PD-L1 positive metastatic non-small-cell lung cancer [ID1678]

Thank you for agreeing to comment on the ERG report for this appraisal, and for providing your 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. The ERG report and stakeholder responses are used by the appraisal committee to help it make decisions at the appraisal committee meeting. Usually, only unresolved or uncertain key issues will be discussed at the meeting.

Information on completing this form:

- In **part 1** we are asking you to complete questions where we ask for your views on this technology. You do not have to answer every question – they are prompts to guide you. The text boxes will expand as you type.
- In **part 2** we are asking you to give your views on key issues in the Evidence Review Group (ERG) report that are likely to be discussed by the committee. An overview of the key issues are summarised in the executive summary at the beginning of the ERG report.
- The key issues in the ERG report reflect the areas where there is uncertainty in the evidence, and because of this the cost effectiveness of the treatment is also uncertain. In part 2 of this form we have included any of the issues raised by the ERG where we think having a clinical perspective could help either:
- resolve any uncertainty that has been identified
  OR
- provide missing or additional information that could help committee reach a collaborative decision in the face of uncertainty that cannot be resolved.

In **part 3** we are asking you to provide 5 summary sentences on the main points contained in this document.

Please return this form by **5pm** on **Monday 11 January 2021**

Completing this form

Part 1 can be completed anytime. We advise that the final draft of part 2 is completed after the expert engagement teleconference (if you are attending/have attended). This teleconference will briefly summarise the key issues, any specific questions we would like you to answer and the type of information the committee would find useful.

Important information on completing this expert statement

- 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 want to include **journal articles** in your submission you must have copyright clearance for these articles. We can accept journal articles in NICE Docs.
- Do not include medical information about yourself or another person that could identify you or the other person.
- Please underline all confidential information, and separately highlight information that is submitted under 'commercial in confidence' in turquoise, all information submitted under 'academic in confidence' in yellow.If confidential information is submitted, please also send a second version of your comments with that information replaced with the following text: 'academic/commercial in confidence information removed'. See the Guide to the processes of technology appraisal (sections 3.1.23 to 3.1.29) for more information.

PART 1 – Treating a patient with this condition and current treatment options	
About you	
1. Your name	**Yvonne Summers**
2. Name of organisation	**The Christie Hospital and Manchester University NHS Foundation Trusts**
3. Job title or position	**Consultant Medical Oncologist**
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):
5. Do you wish to agree with your nominating organisation's submission? (We would encourage you to complete this form even if you agree with your nominating organisation's submission)	☐ yes, I agree with it ☐ no, I disagree with it ☐ I agree with some of it, but disagree with some of it **X**☐ other (they didn't submit one, I don't know if they submitted one etc.)

6. If you wrote the organisation submission and/ or do not have anything to add, tick here. (If you tick this box, the rest of this form will be deleted after submission.)	☐ yes
7. Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	**nil**
The aim of treatment for this condition	
8. What is the main aim of treatment? (For example, to stop progression, to improve mobility, to cure the condition, or prevent progression or disability.)	Aim of the treatment is: • To reduce or stabalise cancer • To improve survival • To improve symptoms and maintain quality of life

9. What do you consider a clinically significant treatment response? (For example, a reduction in tumour size by x cm, or a reduction in disease activity by a certain amount.)	A significant response is one which improves progression free survival (PFS) by a clinically meaningful period of time (3 months or more). This response needs to be put into the context of how tolerable the treatment is, eg 3 months extra life may be less valuable if the treatment is very toxic and impairs quality of life. Response is assessed by RECIST criteria in oncology trials which means that absolute measurements are not taken into account - response is a shrinkage of >30% of target lesions measured, Progression is growth by 20% or more of target lesions measured and stable disease falls in between. Prolonged disease stability (>6months) is also clinically meaningful
10. In your view, is there an unmet need for patients and healthcare professionals in this condition?	Although survival is improving for patients with advanced NSCLC, there is still unmet need in terms of: • There is currently only one immunotherapy agent (pembrolizumab) available for this indication in patients with high PD-L1 expressing NSCLC • Although outcomes and toxicity are similar, choice and competition in the market is valuable for the NHS
What is the expected place of the technology in current practice?	
11. How is the condition currently treated in the NHS?	Patients are treated in keeping with NICE guidance: • The majority of patients with advanced NSCLC with PD- L1>49% are treated with single agent pembrolizumab • A smaller proportion are treated with histology specific chemotherapy combined with pembrolizumab (ID1584 and TA600). This treatment would be considered in those with bulky disease or disease impinging on critical central structures eg main airways
• Are any clinical guidelines used in the treatment of the condition, and if so, which?	ESMO recommends Atezolizumab as a promising alternative to Pembrolizumab in PD-L1 high patients, but Atezolizumab was not approved at the time of issue To a lesser degree ASCO, NCCN

• Is the pathway of care well defined? Does it vary or are there differences of opinion between professionals across the NHS? (Please state if your experience is from outside England.)	The pathway is well defined. Treatment with Pembrolizumab alone for PD-L1>49% is very well established. Treatment with Chemotherapy/Immunotherapy combination is more variably used because the increased toxicity of combination treatment is of note. Some clinicians and patients prefer to avoid the use of chemotherapy (probably less than 20% of patients in this category will have combination chemo/immunotherapy treatment)
• What impact would the technology have on the current pathway of care?	There would be no change in the pathway. Atezolizumab would be an alternative to Pembrolizumab
12. Will the technology be used (or is it already used) in the same way as current care in NHS clinical practice?	Yes it is already used in post platinum second line setting. The use will potentially be moved up to 1st line for those with PD-L1>49%
• How does healthcare resource use differ between the technology and current care?	The phase 3 RCT for both atezolizumab and pembrolizumab were 3 weekly treatment schedules ie the same. However, in clinical practice, particularly during COVID, many centres have changed pembrolizumab treatment to double dose every 6 weeks to reduce hospital visits
• In what clinical setting should the technology be used? (For example, primary or secondary care, specialist clinics.)	Secondary care – oncology out-patient setting
• What investment is needed to introduce the technology? (For example,	Nil in addition to standard care

for facilities, equipment, or training.)	
13. Do you expect the technology to provide clinically meaningful benefits compared with current care?	Benefits similar to Pembrolizumab
• Do you expect the technology to increase length of life more than current care?	no
• Do you expect the technology to increase health-related quality of life more than current care?	no
14. Are there any groups of people for whom the technology would be more or less effective (or appropriate) than the general population?	no
The use of the technology	
15. Will the technology be easier or more difficult to use for patients	Very similar technology. No robust differences in toxicity or efficacy (given limitations of cross trial comparisons)

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.)	
16. Will any rules (informal or formal) be used to start or stop treatment with the technology? Do these include any additional testing?	Whether a 2 year stopping rule should be introduced must be considered (as is the case with Pembrolizumab). The trial was designed to continue until progressive disease (PD) or toxicity. There would be some benefit in allowing treating until PD as this only applies to a small group of patients and, at present, patients cannot be retreated with immunotherapy on PD even if they have had substantial benefit.
17. Do you consider that the use of the technology will result in any substantial health-related benefits that are unlikely to be included in the quality-adjusted life year (QALY) calculation?	no

18. Do you consider the technology to be innovative in its potential to make a significant and substantial impact on health-related benefits and how might it improve the way that current need is met?	1st line immunotherapy is innovative, however atezolizumab itself, in this setting, could not be considered innovative as there is already a similar agent (pembrolizumab) available in this indication.
• Is the technology a 'step-change' in the management of the condition?	no
• Does the use of the technology address any particular unmet need of the patient population?	no
19. How do any side effects or adverse effects of the technology affect the management of the condition and the patient's quality of life?	The side effects are very similar to the current standard of care, Pembrolizumab. Adverse effect management is the same.
Sources of evidence	

20. Do the clinical trials on the technology reflect current UK clinical practice?	Yes, and the UK contributed to the trial. There are the usual caveats about clinical trial patients being younger and fitter that the standard NSCLC population
• 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?	Standard outcome measures of PFS, ORR and OS are important, however, PFS does not correlate particularly well with long term survival for immunotherapy treatments and PFS improvements are often less than OS improvements. Landmark analysis at 1,2,3 and eventually 5 years are important in addition to overall survival. For those patients who achieve a response to therapy, duration of response gives a good indication of the treatment efficacy.
• If surrogate outcome measures were used, do they adequately predict long-term clinical outcomes?	na
• Are there any adverse effects that were not apparent in clinical trials but have come to light subsequently?	no

21. Are you aware of any relevant evidence that might not be found by a systematic review of the trial evidence?	no
22. Are you aware of any new evidence for the comparator treatment(s) since the publication of NICE technology appraisal guidance TA531?	no
23. How do data on real-world experience compare with the trial data?	Real world data on 1st line pembrolizumab demonstrates similar outcomes to the trial data. I am unaware of any real world data for 1st line atezolizumab
Equality	
24a. Are there any potential equality issues that should be taken into account when considering this treatment?	no

24b. Consider whether these issues are different from issues with current care and why.	
Topic-specific questions	
28a. Approximately how many GP home visits would you expect people with untreated NSCLC to receive annually? Do you consider fortnightly visits to be realistic or an overestimation? Please consider your answers in the context of patients who are relatively young (aged ~63 – 65 years) and who are physically fit (ECOG status 0 or 1).	As discussed separately by e-mail, fortnightly visits would be unlikely except perhaps in the last few months of life. I would expect less than 5 home visits in a year.
28b. Approximately how many occupational therapist visits would you expect people with untreated NSCLC to receive annually? Do you consider fortnightly visits to be realistic or an overestimation?	No more than 1-2

Please consider your answers in the context of patients who are relatively young (aged ~63 – 65 years) and who are physically fit (ECOG status 0 or 1).	

PART 2 – Technical engagement questions for clinical experts	
Issues arising from technical engagement	
We welcome your response to the questions below, but you do not have to answer every question. If you think an issue that is important to clinicians or patients has been missed in the ERG report, please also advise on this in the space provided at the end of this section. The text boxes will expand as you type. Your responses to the following issues will be considered by the committee and may be summarised and presented in slides at the appraisal committee meeting. For information: the professional organisation that nominated you has been sent a technical engagement response form (a separate document) which asks for comments on each of the key issues that have been raised in the ERG report, these will also be considered by the committee.	
Key issue 1: Narrower population than that specified in the NICE final scope and choice of comparator	
Key issue 2: Atezolizumab effect over time	
Key issue 3: Assays comparability	

Key issue 4: Relative duration of treatment effects for the technology and its comparator	
Key issue 5: Time on treatment with pembrolizumab relative to its PFS curve	
Key issue 6: The validity of certain resource use frequencies in the progressive disease state of the model	
Are there any important issues that have been missed in ERG report?	

PART 3 -Key messages

16. In up to 5 sentences, please summarise the key messages of your statement:

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-

-
-
-

Thank you for your time.

Please log in to your NICE Docs account to upload your completed document, declaration of interest form and consent form.

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Atezolizumab monotherapy for untreated advanced non-small-cell lung cancer [ID1678]

ERG critique of the company response to the technical engagement report

Produced by Aberdeen HTA Group

Date completed: 22 January 2021

Contains [redacted] and [redacted] information.

In response to the technical engagement (TE) report, the company addressed each of the points raised and submitted some revised modelling and additional evidence to support a revised base case analysis.

This short commentary critiques the company's response to each of the main issues raised:

1. Narrower population than that specified in the NICE final scope and choice of comparator.
2. Atezolizumab effect over time
3. Assays comparability
4. Relative duration of treatment effects for the technology and its comparator
5. Time on treatment with pembrolizumab relative to its PFS curve
6. The validity of certain resource use frequencies in the progressive disease state of the model

This commentary should be read in conjunction with the company's response to technical engagement document.

1. Narrower population than that specified in the NICE final scope and choice of comparator

This related to the ERGs concern that the subgroup of focus in the company submission, IC3 (infiltrating immune cell PD-L1 expression >10%) or TC3 (tumour cell PD-L1 expression ≥50%) based on the SP142 assay, may include a subset of patients (IC3 only) who would not currently be considered eligible for pembrolizumab monotherapy according to NICE guidance (TA531). The ERG suggested that the company should have provided a breakdown of the SP142 TC3 and IC3 subpopulations of IMPOWER110, and also suggested a sensitivity analysis in the NMA using the subgroup of patients with TPS ≥ 50% as defined by the 22C3 assay (used to determine PD-L1 expression in the KEYNOTE trials included in the NMA).

The company have carried out an extensive and fair assessment of the situation showing that:

- [redacted] of the 205 SP142 TC3 or IC3 subgroup were classed as IC3 only.
- [redacted] of IC3 only on SP142, were identified as TPS <50% on the 22C3 assay; [redacted] of the SP142 TC3 or IC3 subgroup evaluable on both assays ([redacted]).

The company note that 22C3 is the most commonly used assay in clinical practice, and the ERG agrees with this statement. Thus, it is unlikely that the group of patients identified as IC3 only (on SP142), with TPS <50% on the 22C3 assay, would be identified in practice, and the company note there is no data to confirm how they are currently being treated in the UK.

The company have helpfully provided a new subgroup analysis according the SP142 split, TC3 (any IC3) and IC3 (only), which shows that the magnitude of relative OS and PFS benefit for atezolizumab versus chemo [redacted]. Thus, the company argue that there is a strong equity case to include these patients in any reimbursement recommendation for atezolizumab.

The ERG agrees that the IC3 (only) subgroup with TPS <50% on 22C3 is too small to inform an alternative comparison and acknowledge the unavailability of data for the most likely routine comparators according to NHS treatment pathways. It is, however, reassuring that the company's additional subgroup analysis [redacted] for the TC3 and IC3 (only) subgroups of IMPOWER110 as identified by the SP142 assay.

2. Atezolizumab effect over time

This related to the ERGs observation that the company's Fractional Polynomial (FP) NMA, accommodating possible changing relative hazards between the treatments over time, appeared to generate hazard ratios for OS that increasingly favoured pembrolizumab over time. The ERG believed that without more homogeneous comparative data between the two treatments, this uncertainty cannot be resolved.

The company have conducted several further sensitivity analyses in relation to this issue which they believe help explain the observed trend in the the original analysis, and further confirms a lack of evidence to support the superiority of either intervention (pembrolizumab or atezolizimab) over the other in this population. This included sensitivity analysis of the fractional polynomial NMA using the 22C3 TPS ≥ 50% subgroup of IMPOWER110, which improved the HRs for atezolizumab.

The company also illustrate how different durations of follow-up may bias the FP NMA. Plateauing was observed in the chemotherapy arm of IMPOWER110 with longer follow-up, which the company suggest is a probably the result of subsequent lines of cancer immunotherapies having time to impact on the OS curve. This resulted in a reduced HR for atezolizumab versus chemotherapy compared with the earlier primary analysis data cut. The problem lies in the fact that the larger of the pembrolizumab trials (KEYNOTE-042) only has follow-up data in line with the earlier IMPOWER110 data cut (see Figures 5 and 6, and Table 1 of the company's response to technical engagement), which could bias in favour of pembrolizumab in the NMA. The company also make the point here, that despite longer term follow-up reducing the relative treatment effect for atezolizumab versus chemotherapy, the landmark survival proportions at 12 months and 24 months remain stable and remain similar for pembrolizumab and atezolizumab,

[redacted].

Another similar point in relation to the above is made with the latest OS analysis of KEYNOTE-024 (1), which the company used in another sensitivity analysis of the FP NMA. When including the longer follow-up data from this smaller pembrolizumab study, the HRs improved slightly for atezolizumab, highlighting the importance of follow-up duration. Further, the company point out that rechallenge with pembrolizumab was allowed in

KEYNOTE-024 for patients who responded to treatment but subsequently progressed after stopping at two years. This would not be allowed currently according to NHS practice, and thus inclusion of KEYNOTE-024 in the NMA could bias in favour of pembrolizumab.

Again, the ERG acknowledges the company's full assessment and discussion of the issue. It is reassuring to note that all the sensitivity analyses improved the HRs for atezolizumab. The ERG also agrees that the allowance of rechallenge in KEYNOTE-024 has the potential to bias the indirect comparison in favour of pembrolizumab in the context of NHS practice where rechallenge is not currently allowed.

Nevertheless, the ERG believe substantial uncertainty remains in the NMA comparison between pembrolizumab and atezolizumab. While there is no evidence to support a meaningful difference in treatment effect over time between atezolizumab and pembrolizumab, nor can one be ruled out with confidence. The differences in assay-based selection criteria and durations of follow-up so far precludes this. As the company acknowledged in their response to the clarification letter, the comparison with pembrolizumab based on the 22C3 ≥ 50% subgroup of IMPOWER110 has its own limitations, as this represents a doubly selected group positive on both SP142 and 22C3 assays. The greater sensitivity of the 22C3 assay that the company allude to (2,3) also means that we cannot be sure the exact PD-L1 expressions levels in those with PD-L1 ≥ 50% are comparable between the studies. However, the company's further analyses have provided reassurance that their base case approach is the most conservative from the options available with the current data.

3. Assays comparability

This point is closely related to issues 1 and 2 above, stemming from the fact that IMpower110 used assay SP142 to select IC3 (infiltrating immune cell PD-L1 expression ≥10%) or TC3 (tumour cell PD-L1 expression ≥ 50%) patients while the KEYNOTE trials used assay 22C3 to select patients with tumour proportion score ≥50%.

Acknowledging the double selection issue, the ERG suggested that a sensitivity analysis could have been conducted using the 22C3 TPS ≥50% subgroup of IMpower110 to inform the NMA. As discussed above, the company performed this using the fractional polynomial

approach, and they also performed it for the random effects NMA and applied the estimated hazard ratios in further economic modelling scenarios.

The random effects hazard ratios are presented in Figures 10-14 of the company's response document, all of which improved slightly for atezolizumab, indicating that the company has used the most conservative estimates available in their base case.

To illustrate the impact on the economic modelling, the company also provided a new set of curve fits for the 22C3 TPS ≥50% subgroup of Impower110, and then applied the random effects HRs from the NMA informed by 22C3 TPS ≥50% subgroup of Impower110 (10th February 2020 data cut). They also incorporated other amendments in this alternative base case, and provided a full set of scenarios around it (described in detail under Additional Issue two, page 75, of the company response document). In all the additional scenarios informed by the 22C3 TPS ≥50% subgroup of Impower110, atezolizumab generated more QALYs and potentially dominated pembrolizumab.

This provides further reassurance that the company's original approach offers the most conservative given the data available. But as indicated above, the lack of evidence to support a meaningful difference in PFS or OS cannot rule out the possibility that one exits. However, on balance the ERG believes that the company have provided a fair account of the data, and there is potential for bias to work in both directions in the NMA; shorter follow-up of KEYNOTE-042 and the allowance of immunotherapy rechallenge in KEYNOTE-024 potentially biasing in favour of pembrolizumab, and the lower sensitivity of SP142 and the 22C3 TPS >50% subgroup of IMpower110 being double selected, which could bias in favour of atezolizumab. The ERG believes that the uncertainties cannot be fully resolved without long-term comparative data on patients selected on the same assay. However, it should also be noted that the clinical expert opinion seems to support the comparability of these drugs for the current indication.

4. Relative duration of treatment effects for the technology and its comparator

The company has acted on the suggestions made by the ERG and has provided a more detailed discussion of the issue. The issue was the assumed duration of treatment effect with pembrolizumab (5 years with a stop rule at 2 years). The ERG noted that the modelling assumed a lifetime treatment benefit for atezolizumab (no stop rule). The fundamental

problem is a lack of follow-up data over the long-term in the context of the two-year stopping rule that applies to pembrolizumab and rechallenge not currently being permitted in the NHS treatment pathway. So the ERG acknowledged that the issue cannot be fully resolved.

The company's discussion included precedents in modelling of similar medicines in previous STAs; and a defense of not using a stop rule for atezolizumab.

A third section included by the company noted the number of patients who were re-treated and benefited from rechallenge in the KEYNOTE-024 study of pembrolizumab, which casts doubt on the applicability of the five-year follow-up data from this trial for informing treatment effect duration in the NHS where rechallenge is not permitted. The company also note that its inclusion in the NMA may bias in favour of pembrolizumab in this context. However, it can be noted that only 12 patients were re-treated out of 154 randomised to pembrolizumab in KEYNOTE-024, and so the extent of any bias is unclear and has not been established.

In terms of the precedents, the ERG believes NSCLC should have been considered separately from other STAs as there may be issues in generalising across all types of cancer. The ERG accepts that the assumption used in the company's base-case of 5-year duration of effect with pembrolizumab is consistent with some previous STAs in NSCLC. However, as the table provided by the company shows, in NSCLC 3 years and 10 years has also been considered by NICE appraisal committees.

The ERG suggests that while this establishes the company's assumption is in line with previous STAs, the Appraisal Committee will still wish to see a range of treatment effect durations used for pembrolizumab, which the ERG provided in its report.

The company also makes the case for why treatment with atezolizumab should not have a stop-rule imposed. To clarify, the ERG did not intend to make the case for such a stopping rule, the point made was that the lifetime benefit from atezolizumab was also an assumption. The ERG acknowledges the company's case that a lifetime benefit assumption is consistent with previous STAs when there is no stop rule. The ERG questions some of the other evidence presented such as the interpretation of the correlation of treatment duration and OS,

where the implication the company draws seems to be that more treatment always produces more OS. This has not been proven and is questionable.

5. Time on treatment with pembrolizumab relative to its PFS curve

The company has acted on the suggestions made by the ERG.

The ERG identified a paper that gave further information on the time to treatment discontinuation with pembrolizumab in KEYNOTE-042 and KEYNOTE-024. This suggested that equating ToT with PFS, as per the company's original base case, may overestimate pembrolizumab treatment costs. The company has acknowledged this and have supplied three alternative scenarios that allow the ToT curve for pembrolizumab to diverge from its PFS curve in the model.

The results of these further analyses are summarised on page 64 of the company response. This was helpful and shows the impact on the ICER results is modest.

The first two methods involved fitting preferred parametric curves to the digitized PFS and ToT Kaplan-Meier data from KEYNOTE-042, and using the relationship between the fitted curves to generate relative adjustments (hazard ratios) that can be applied to the PFS curve in the model to generate an adjusted ToT curve for pembrolizumab. The first alternative assumed a Weibull function for the ToT data in KEYNOTE-042, and the second assumed a gamma curve. For estimating adjustment HRs, both were compared to the company's preferred lognormal curve for KEYNOTE-042 PFS. The ERG believes that both these approaches offer a plausible approximation for ToT in the company's model and prefers them the company's third approach which directly applied the weighted average of the fitted ToT curves from KEYNOTE-042 in the model. The problem with the latter approach is that the PFS curve for pembrolizumab in the model is derived by applying the hazard ratio from the NMA to the PFS curve for atezolizumab, and so it is not directly comparable with the independently fitted curves for ToT in the KEYNOTE trials. Of the three different approaches, the company has applied the most conservative in their revised base case. Given the uncertainties, the ERG believes that either of the company's first two approaches, or the ERGs original adjustment which lies between them in terms of impact on the ICER, offer plausible alternatives.

6. The validity of certain resource use frequencies in the progressive disease state of the model

The company has acted on the suggestions made by the ERG.

The problem here was the face validity of the frequencies used for certain elements of resource use in the progressive disease state of the company's model. The company's base case assumed that when a patient was alive with progressed disease, a GP carried out a home visit every two weeks and an occupational therapist carried out a home visit every two weeks. These assumptions did not appear to be supported by data in the references provided for them.

From the baseline characteristics of IMpower 110, the median age of patients was [redacted] in one treatment arm and [redacted] in the other, and ECOG performance status in all cases was 0 or 1; therefore, patients were [redacted] and physically fit at the outset and are likely to have active family or carers. In the company's base case, patients spend approximately [redacted] years alive with progressive disease following progression on atezolizumab and pembrolizumab respectively, and have a utility value of [redacted] (updated to [redacted] in the company's revised base case). Intuitively, this does not sound like the characteristics of a patient who would be receiving home visits from their GP (or an OT) every two weeks.

The company has helpfully tracked down the source of the values used (Appendix 1 of NICE Guideline CG81). Although an original source study was not retrievable, from its title it seems to be a study of patients in the final (terminal) stage of disease, rather than a set of resource assumptions that could be applied [redacted] months from death.

The company note that they discussed the frequencies at an advisory board. However, rather that providing a new estimate based on clinical expert opinion, the company note they agree with the ERG in reducing the frequencies by 50%. It is not clear if their clinical experts explicitly advocated this reduction in the context of their modelling. The ERG applied it as a stopgap and acknowledged it could benefit from more clinical validation during technical engagement, and so it is not rooted in actual data. Reducing the PD costs does not have a large impact on the ICER, but it does act in favour of pembrolizumab when applying the the company's base case HRs in their cost-utility model.

Additional amendments

Updating of utility estimates

In the ERG report, attention was drawn to the fact utility values were based on a small number of patients, particularly for the PD state (ERG Report Section 3.2.7). The relatively small drop in utility between the pre-progression and progressive disease states was also noted. Given the small numbers and uncertainty arising from missing data, the ERG asked the company in the clarification letter to provide a comparison of values by progression status with the non-TC3-IC3 patients in Impower110. These showed general consistency. In their response to technical engagement, the company has used utility values for the ITT population of IMpower110 rather than those [redacted]. This results in a slightly higher pre-progression utility and slightly lower post progression utility, and hence a larger decrement associated with progression.

Whilst the ERG does not generally support the use of utility data from [redacted], in this case the utility values for progression free and progressive disease may have better face validity. It is also the case that utility values derived by progression status in TA531, based on KEYNOTE-024, resulted in an even greater drop in utility between the progression free and progressive disease states.

As the ERG's original report makes clear, the issues that were being highlighted with the original comments were (1) the extent to which utility data were missing, with no explanation of analysis, creating a risk of bias (such as patients in poor health being less likely to complete a questionnaire) and (2) the limited follow-up period of the RCT for valuing the progressive disease state in particular. Whilst this is not resolved by including patients [redacted], the ERG accepts that the company's updated values, derived from the ITT population of Impower110, do produce a drop in utility for the PD state that has better face validity and is more consistent with previous NSCLC appraisals.

Company's updated base case

Following consideration of the issues raised, the company has updated their base case to include several changes as outlined in Table 6 of their response document. The ERG believes that in general this offers a fair representation given the data available to inform the model. The ERG still has reservations about the comparability if the IMpower110 and KEYNOTE

studies but accepts that this cannot be resolved without long-term comparative data using the same assays and selection criteria to identify patients for both drugs. Such data is not available. It is acknowledged that given the available data, the company base case uses the most conservative hazard ratios, and also applies the most conservative assumption regarding the altertnative adjustments of time on treatment for pembrolizumab. Duration of treatment benefit for immunotherapy versus chemotherapy in the context of a two-year stopping rule, and no stopping rule, remains an area of uncertainty, but the company's base case assumptions are in line with previous NSCLC appraisals.

The ERG will provide an updated confidential appendix for all the company's further analyses, with the confidential PAS discount for pembrolizumab applied.

1. Brahmer JR, Rodriguez-Abreu D, Robinson AG, Hui R, Csőszi T, Fülöp A, et al. LBA51 KEYNOTE-024 5-year OS update: First-line (1L) pembrolizumab (pembro) vs platinum-based chemotherapy (chemo) in patients (pts) with metastatic NSCLC and PD-L1 tumour proportion score (TPS) ≥50%. Annals of Oncology. 2020;31:S1181-S2.
2. Hirsch FR, McElhinny A, Stanforth D, Ranger-Moore J, Jansson M, Kulangara K, et al. PD-L1 immunohistochemistry assays for lung cancer: results from phase 1 of the blueprint PD-L1 IHC assay comparison project. 2017;12(2):208-22.
3. Tsao MS, Kerr KM, Kockx M, Beasley MB, Borczuk AC, Botling J, et al. PD-L1 Immunohistochemistry Comparability Study in Real-Life Clinical Samples: Results of Blueprint Phase 2 Project. Journal of thoracic oncology : official publication of the International Association for the Study of Lung Cancer. 2018;13(9):1302-11.

Atezolizumab monotherapy for untreated advanced non-small-cell lung cancer [ID1678]

Post technical engagement addendum to the ERG report

Produced by Aberdeen HTA Group

Date completed: 29/01/21

Version: 1

Contains [redacted]

This post technical engagement addendum to the ERG report includes the following analysis:

1. Table A1: A corrected version of the company's new base case cost comparison analysis (to replace Table 11 from the company's response to technical engagement). The original mistakenly did not equalise efficacy.
2. Table A2: An alternative ERG base case which retains all the assumptions of the previous ERG base case but applies the progression free and progressive disease utilities from the ITT- wild type population of IMpower110, which the company applied in their updated bas case.
3. Table A3: Scenarios exploring different treatment effect durations as per Table 33 of the original ERG report, are provided for this alternative ERG base case which utilises the progression free and progressive disease utilities from the ITT- wild type population of IMpower110.

All the analyses are conducted using the confidential PAS discount for atezolizumab and the list price for pembrolizumab. The results including the confidential PAS price for pembrolizumab are provided in the updated cPAS appendix.

Table A1 ERG corrected - company post-technical engagement cost comparison analysis results (PAS price) – replaces Table 11 from the company's response to technical engagement

	Atezo Mono (£)	Pembro mono (£)	Incremental costs (£)
Mean cost of PFS	[redacted]	[redacted]	[redacted]
Mean cost of progression	[redacted]	[redacted]	[redacted]
Terminal/palliative care cost	[redacted]	[redacted]	[redacted]
Mean total cost (£)	[redacted]	[redacted]	[redacted]

Note: the company's cost comparison provided in the response to the technical engagement adopted incorrect model settings, presenting cost differences for the base case cost-utility analysis rather than cost differences when assuming equal efficacy. The analysis provided above provides the corrected CMA analysis with the appropriate confidential PAS discount on pembrolizumab.

Table A2 - Alternative ERG base case with updated utility parameters (ITT WT for progression free and progressive disease states)

Parameter	Value	Atezo Mono			Pembro mono			Atezo Mono vs. Pembro Mono						
		Life Years	QALYS	Costs	Life Years	QALYS	Costs	Inc. QALYs	Inc. Costs	ICER	Inc. NMB WTP £30K	Inc. NMB WTP £20K	Inc. NHB WTP £30K	Inc. NHB WTP £20K
ERG base	TC3-IC3 ET Utilities	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	-0.084	-43,715	521,544	41,200	42,038	1.4	2.1
ERG base case	ITT WT Utilities	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	-0.07	-43,715	592,614	41,502	42,239	1.38	2.11

ICER, incremental cost-effectiveness ratio; **LYs**, life years; **QALYs**, quality-adjusted life years; **TTD**, time to treatment discontinuation.

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.;

NHB, net health benefit calculated as: *incremental gain in QALYs – (incremental cost / opportunity cost threshold).* A positive NHB implies that overall population health would be increased as a result of the new intervention

Table A3. Exploration of the duration of treatment effect with reference to the alternative ERG base case with utilities based on the ITT WT populaiton (atezolizumab versus pembrolizumab) – alternative to Table 33 of the ERG report

Parameter	Value	Atezo Mono			Pembro mono			Atezo Mono vs. Pembro Mono						
		Life Years	QALYS	Costs	Life Years	QALYS	Costs	Inc. QALYs	Inc. Costs	ICER	Inc. NMB WTP £30K	Inc. NMB WTP £20K	Inc. NHB WTP £30K	Inc. NHB WTP £20K
ERG base		[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	-0.084	-43,715	521,544	41,200	42,038	1.4	2.1
Pembro treatment effect duration	6 years	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	-0.12	-44,000	365,348	40,387	41,592	1.35	2.08
	7 years	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	-0.16	-44,222	283,071	39,535	41,097	1.32	2.05
	8 years	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	-0.18	-44,397	240,610	38,862	40,707	1.30	2.04
Atezolizumab treatment effect duration	8 years	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	-0.13	-44,016	348,467	40,226	41,489	1.34	2.07
Atezolizumab and pembrolizumab treatment effect durations	Atezo 8; pembro 6	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	-0.17	-44,306	256,325	39,120	40,849	1.30	2.04
	Atezo 8; pembro 7	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	-0.21	-44,528	213,438	38,270	40,356	1.28	2.02
	Atezo 8; pembro 8	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	-0.24	-44,704	188,686	37,596	39,965	1.25	2.00

ICER, incremental cost-effectiveness ratio; LYs, life years; QALYs, quality-adjusted life years

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.;

NHB, net health benefit calculated as: *incremental gain in QALYs – (incremental cost / opportunity cost threshold).* A positive NHB implies that overall population health would be increased as a result of the new intervention

Atezolizumab monotherapy for untreated advanced non-small-cell lung cancer [ID1678]

Second addendum of the ERG report

Produced by Aberdeen HTA Group

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Contains [redacted]

This second post technical engagement addendum to the ERG report uses updated annual resource use estimates for GP and occupational therapist home visits in the progressive disease state of the model. Based on feedback from clinical experts, these are set at 5 per year for GP home visits and 2 per year for OT home visits.

This revised addendum also provides results using alternative dosing schedules for atezolizumab and pembrolizumab. The main company and ERG analyses applied the dosing schedules used in the trials informing the model efficacy inputs: 1,200mg every 3 weeks (Q3W) for atezolizumab, and 200mg every 3 weeks (Q3W) for pembrolizumab. The ERGs clinical expert has advised that these were used as standard pre-COVID, but that since COVID-19, alternative dosing schedules of 1,680mg every 4 weeks (Q4w) for atezolizumab and 400mg every 6 weeks (Q6W) for pembrolizumab are being used more frequently. Therefore, this addendum now provides results for the key analyses using the original (Q3W) and the alternative dosing assumptions:

1. Table A1: The company's post-technical engagement revised base case and alternative analysis with gamma extrapolation of pembrolizumab time on treatment.
2. Table A2: The ERGs original and post-technical engagement revised base case analysis
3. Table A3: The ERG scenarios exploring different treatment effect durations as per Table 33 of the original ERG report - using the ERGs post-technical engagement revised base case which uses the progression free and progressive disease utilities from the ITT- wild type population of IMpower110.
4. Table A4: As per Table A3 but applying the alternative dosing frequencies of 1,680mg every 4 weeks for atezolizumab and 400mg every 6 weeks for pembrolizumab.

Tables A3 and A4 provide further analysis at the request of NICE, exploring the impact of reducing the treatment effect duration for atezolizumab. Note, however, that without also adjusting the time on treatment curve for atezolizumab, these scenarios imply that a significant proportion of patients continue to take atezolizumab for some time following loss of efficacy. As this may lack clinical plausibility, the ERG has provided a further set of scenarios in Tables A3 and A4, which assume that atezolizumab treatment is stopped from the point of loss of efficacy.

All the analyses are conducted using the confidential PAS discount for atezolizumab and the list price for pembrolizumab. The results including the confidential PAS price for pembrolizumab are provided in a further cPAS appendix.

Table A1 Company post technical engagement revised base case with updated GP and occupational therapist costs for the progressive disease state

Parameter	Value	Atezo Mono			Pembro mono			Atezo Mono vs. Pembro Mono						
		Life Years	QALYS	Costs	Life Years	QALYS	Costs	Inc. QALYs	Inc. Costs	ICER	Inc. NMB WTP £30K	Inc. NMB WTP £20K	Inc. NHB WTP £30K	Inc. NHB WTP £20K
Company post-technical engagement base case		[redacted]						-0.07	-42,263	572,939	40,050	40,788	1.34	2.04
Company post-technical engagement base case	New GP and OT costs in PD state	[redacted]						-0.07	-41,644	564,549	39,431	40,169	1.31	2.01
Company post-technical engagement with gamma extrapolation of pembro ToT	New GP and OT costs in PD state	[redacted]						-0.07	-42,723	579,166	40,510	41,247	1.35	2.06
Atezolizumab 1,680mg every 4 weeks (Q4W) versus Pembrolizumab 400mg every 6 weeks dosing (Q6W)														
Company post-technical engagement base case	New GP and OT costs in PD state	[redacted]						-0.07	-43,343	587,581	41,130	41,868	1.37	2.09
Company post-technical engagement with gamma extrapolation of pembro ToT	New GP and OT costs in PD state	[redacted]						-0.07	-44,383	601,677	42,170	42,908	1.41	2.15

ICER, incremental cost-effectiveness ratio; **LYs**, life years; **QALYs**, quality-adjusted life years; **TTD**, time to treatment discontinuation.

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.;

NHB, net health benefit calculated as: *incremental gain in QALYs – (incremental cost / opportunity cost threshold).* A positive NHB implies that overall population health would be increased as a result of the new intervention

Table A2 - Alternative ERG base case with updated utility parameters (ITT WT for progression free and progressive disease states) and revised GP and occupational therapist visits in the progressive disease state.

Parameter	Value	Atezo Mono			Pembro mono			Atezo Mono vs. Pembro Mono						
		Life Years	QALYS	Costs	Life Years	QALYS	Costs	Inc. QALYs	Inc. Costs	ICER	Inc. NMB WTP £30K	Inc. NMB WTP £20K	Inc. NHB WTP £30K	Inc. NHB WTP £20K
ERG original base		[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	-0.084	-43,715	521,544	41,200	42,038	1.4	2.1
ERG base alternative case with ITT-WT utilities		[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	-0.07	-43,715	592,614	41,502	42,239	1.38	2.11
ERG original base	New GP and OT costs in PD state	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	-0.084	-43,096	514,159	40,581	41,419	1.35	2.07
ERG base alternative case with ITT-WT utilities	New GP and OT costs in PD state	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	-0.074	-43,096	584,224	40,883	41,620	1.36	2.08
Atezolizumab 1,680mg every 4 weeks (Q4W) versus Pembrolizumab 400mg every 6 weeks dosing (Q6W)														
ERG base alternative base case with ITT-WT utilities		[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	-0.07	-45,239	613,271	43,026	43,763	1.43	2.19
ERG base alternative case with ITT-WT utilities	New GP and OT costs in PD state	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	-0.07	-44,620	604,880	42,407	43,144	1.41	2.16

ICER, incremental cost-effectiveness ratio; **LYs**, life years; **QALYs**, quality-adjusted life years; **TTD**, time to treatment discontinuation.

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.;

NHB, net health benefit calculated as: *incremental gain in QALYs – (incremental cost / opportunity cost threshold).* A positive NHB implies that overall population health would be increased as a result of the new intervention

Table A3. Exploration of the duration of treatment effect with reference to the alternative ERG base case with utilities based on the ITT WT population) and revised GP and occupational therapist visits in the progressive disease state (atezolizumab versus pembrolizumab) – alternative to Table 33 of the ERG report

Parameter	Value	Atezo Mono			Pembro mono			Atezo Mono vs. Pembro Mono						
		Life Years	QALYS	Costs	Life Years	QALYS	Costs	Inc. QALYs	Inc. Costs	ICER	Inc. NMB WTP £30K	Inc. NMB WTP £20K	Inc. NHB WTP £30K	Inc. NHB WTP £20K
ERG base		[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	-0.07	-43,096	584,224	40,883	41,620	1.36	2.08
Pembro treatment effect duration	6 years	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	-0.12	-43,297	359,506	39,684	40,888	1.32	2.04
	7 years	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	-0.16	-43,451	278,140	38,765	40,327	1.29	2.02
	8 years	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	-0.18	-43,574	236,148	38,038	39,883	1.27	1.99
Atezolizumab treatment effect duration	8 years	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	-0.13	-43,321	342,967	39,532	40,795	1.32	2.04
	7 years	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	-0.14	-43,393	304,115	39,113	40,540	1.30	2.03
	6 years	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	-0.16	-43,487	265,408	38,571	40,210	1.29	2.01
	5 years	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	-0.19	-43,611	227,110	37,850	39,771	1.26	1.99
Atezolizumab treatment effect duration, with treatment stopped from point of efficacy loss	8 years	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	-0.13	-47,097	372,860	43,307	44,571	1.44	2.23
	7 years	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	-0.14	-48,186	337,701	43,905	45,332	1.46	2.27
	6 years	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	-0.16	-49,679	303,200	44,764	46,402	1.49	2.32
	5 years	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	-0.19	-51,546	268,429	45,785	47,705	1.53	2.39
Atezolizumab and pembrolizumab treatment effect durations	Atezo 8; pembro 6	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	-0.17	-43,524	251,801	38,338	40,067	1.28	2.00
	Atezo 8; pembro 7	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	-0.21	-43,679	209,368	37,420	39,507	1.25	1.98
	Atezo 8; pembro 8	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	-0.24	-43,802	184,878	36,694	39,063	1.22	1.95

ICER, incremental cost-effectiveness ratio; LYs, life years; QALYs, quality-adjusted life years

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.;

NHB, net health benefit calculated as: *incremental gain in QALYs – (incremental cost / opportunity cost threshold).* A positive NHB implies that overall population health would be increased as a result of the new intervention

Table A4. Exploration of the duration of treatment effect with reference to the alternative ERG base case with utilities based on the ITT WT population) and revised GP and occupational therapist visits in the progressive disease state (atezolizumab versus pembrolizumab) – alternative to Table 33 of the ERG report (Atezolizumab 1,680mg every 4 weeks (Q4W) versus Pembrolizumab 400mg every 6 weeks dosing (Q6W))

Parameter	Value	Atezo Mono			Pembro mono			Atezo Mono vs. Pembro Mono						
		Life Years	QALYS	Costs	Life Years	QALYS	Costs	Inc. QALYs	Inc. Costs	ICER	Inc. NMB WTP £30K	Inc. NMB WTP £20K	Inc. NHB WTP £30K	Inc. NHB WTP £20K
ERG base		[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	-0.07	-44,620	604,880	42,407	43,144	1.41	2.16
Pembro treatment effect duration	6 years	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	-0.12	-44,821	372,158	41,208	42,412	1.37	2.12
	7 years	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	-0.16	-44,975	287,894	40,288	41,851	1.34	2.09
	8 years	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	-0.18	-45,098	244,406	39,562	41,407	1.32	2.07
Atezolizumab treatment effect duration	8 years	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	-0.13	-44,845	355,030	41,055	42,318	1.37	2.12
	7 years	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	-0.14	-44,917	314,794	40,636	42,063	1.35	2.10
	6 years	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	-0.16	-45,011	274,708	40,095	41,734	1.34	2.09
	5 years	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	-0.19	-45,135	235,045	39,374	41,294	1.31	2.06
Atezolizumab treatment effect duration, with treatment stopped from point of efficacy loss	8 years	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	-0.13	-48,667	385,288	44,877	46,140	1.50	2.31
	7 years	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	-0.14	-49,791	348,955	45,511	46,938	1.52	2.35
	6 years	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	-0.16	-51,250	312,788	46,334	47,973	1.54	2.40
	5 years	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	-0.19	-53,170	276,889	47,409	49,330	1.58	2.47
Atezolizumab and pembrolizumab treatment effect durations	Atezo 8; pembro 6	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	-0.17	-45,048	260,616	39,862	41,591	1.33	2.08
	Atezo 8; pembro 7	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	-0.21	-45,203	216,672	38,944	41,030	1.30	2.05
	Atezo 8; pembro 8	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	-0.24	-45,325	191,310	38,218	40,587	1.27	2.03

ICER, incremental cost-effectiveness ratio; LYs, life years; QALYs, quality-adjusted life years

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.;

NHB, net health benefit calculated as: *incremental gain in QALYs – (incremental cost / opportunity cost threshold).* A positive NHB implies that overall population health would be increased as a result of the new intervention