NICE National Institute for Health and Care Excellence

Slides for public.
AIC and CIC information redacted

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

Chair's presentation

2nd appraisal meeting - Committee D

Chair: Lindsay Smith

Lead team: Giles Monnickendam, Malcolm Oswald, Martin Bradley

NICE Technical team: Ziqi Zhou, Sally Doss, Jasdeep Hayre

Company: Roche

Evidence Review Group (ERG): Peninsula Technology Assessment Group (PenTAG)

7th July 2022

Recap of the 1st committee meeting

- The appraisal committee was unable to develop recommendations for atezolizumab for adjuvant treatment of resected non-small-cell lung cancer due to:
  - uncertainties about the modelling approach and projected outcomes for post disease-free modelling in the company's model
  - concerns that the QALY gains, and potentially the cost-effectiveness, of treatments in these health states may be underestimated
- NICE paused this appraisal pending further analyses being completed
- Company submitted additional analyses which has been critiqued by the ERG

Reason for pausing the appraisal

Uncertainties about the modelling approach and projected outcomes for post disease-free modelling in the company's model (key issue)

Company economic modelling was not acceptable

- Uncertainties to what extent disease-free survival (DFS) improves overall survival
- Data limitation when using a log-logistic or Weibull distribution to model disease-free survival
- Uncertainty about the company's cure assumption and some inappropriate adjustments to the disease-free survival extrapolation.
- Inappropriate approach to the treatment pathway
- Some inappropriate costs in the company's analysis

The committee requested further analyses to be made available

NICE recommended that the company:

- Conduct a **primary analysis** building on the ERG's alternative and optimistic base case analysis
- Conduct a **sensitivity analysis** with further exploration of the cure assumptions and consideration of alternative extrapolations
- Address several **additional considerations** relating to issues identified in ACM1

Committee requests after ACM1 (1)

Issue	Committee request	Incorporated by company?
Modelling approach	An updated analysis to include assumptions in the ERG's optimistic and alternative preferred analyses	**Partially:** • Provided updated analysis but did not include every assumption in the ERG preferred analyses
Treatment pathway	An updated analysis to include immunotherapy retreatment following metastatic disease recurrence following atezolizumab as adjuvant treatment	**Yes**
Modelling of post DFS health states	Adjusting the modelling of the post DFS health states to force projections to fit different IMpower010 OS KM projections, across different scenarios	**Yes**
	Additional cost-effectiveness analyses that better fit expected outcomes in previous NICE appraisals	**No:** • Original approach kept
Cure assumptions	Additional relevant evidence for cure proportion assumption and cure timing assumption	**Yes**

Committee requests after ACM1 (2)

Issue	Committee request	Incorporated by company?
Extrapolation of DFS data	Present sensitivity analyses and commentary on the use of alternative extrapolations and the impact on cost-effectiveness	**Yes**
Source of transitions	Provide justification of the external sources used for transitions in the model and supplement with additional literature searches	**Partially** • Did not extend additional search to cover evidence for all post-DFS transition risks
Immature data from IMPOWER010	Provide additional trial data, if available	**Partially** • Provided updated overall survival trial data but did not provide a corresponding interim analysis of DFS data
Adjustments to the DFS extrapolation	Provide updated Kaplan-Meier (KM) data if available and include in the economic model	**Partially** • Did not include KM steps

Key issues to be resolved

Key issues	Impact
Issue 1: Limitations in modelling approach	
• Does the company's updated modelling approach reduce the uncertainty in the clinical and cost-effectiveness analysis?	
Issue 2: Uncertainty in post disease-free survival	
• How appropriate are the company's additional modelling assumptions for post disease-free survival ?	
Issue 3: Uncertainty in the long-term disease-free survival benefit	
• How appropriate are the company's additional modelling assumptions for disease-free survival?	
Issue 4: Immature data from IMPOWER010	
• Does the additional evidence reduce the uncertainty in the clinical and cost-effectiveness analysis?	

Key:  **High impact**  **Unknown impact**  **Small impact**

Atezolizumab (Tecentriq, Roche)

Description of technology	IgG1 monoclonal antibody, binds directly and selectively to PD-L1 preventing it from binding to PD-1 and B7.1
Marketing authorisation (UK license granted January 2022)	Adjuvant treatment following complete resection for adult patients with Stage II to IIIA (7th edition of the UICC/AJCC-staging system) non-small cell lung cancer (NSCLC) whose tumours have PD-L1 expression on ≥ 50% of tumour cells (TC) and whose disease has not progressed following platinum-based adjuvant chemotherapy.
Dosage and administration	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. Section 4.2 of Summary of Product Characteristics (SPC) states recommended duration of treatment of 1 year unless disease recurrence or unacceptable toxicity.
List price	£3,807.69 per 20 ml vial (1,200 mg); £2,665.38 per 14 ml vial (840mg) *Confidential simple discount patient access scheme (PAS) has been approved*

Issue 1: Limitations in modelling approach – missing immunotherapy retreatment

ACM1: committee suggested scenario where people could receive retreatment after 3 months. Analysis shows impact of allowing retreatment at 6 and 12 months after treatment discontinuation

Company: scenario analyses shows impact of retreatment at 3, 6 and 12 months after treatment discontinuation

Scenario assumptions (3 month retreatment scenario only):

- 50% of people who had metastatic recurrence between months 3-6 after treatment discontinuation were retreated
- Not all people would receive immunotherapy retreatment, possibly due to previous discontinuation as a result of an immune-related adverse events
- 100% of people who had metastatic recurrence 6 months after treatment discontinuation were retreated

ERG comments

- Key strength: Attempted to capture timing of retreatment to inform its likelihood. Applied a 50% chance of eligibility for retreatment for those entering the 1st metastatic recurrence state between cycle 14 and 17, before assuming all are eligible from cycle 18 onwards
- Limitations: Assumes all discontinuations occur at 11 months to capture time from discontinuation. But, in PD-L1 ≥50% TC stage II–IIIA group, there were discontinuations at most treatment cycles, and by cycle 16 (week 48, approx. 11 months) 75.2% of those randomised to atezolizumab remained on-treatment
- Results: The company's scenario reduces the predicted ICERs versus the ERG's approach

Issue 2: Uncertainty in post disease-free survival

ACM1: committee suggested analyses for post DFS modelling to ensure the outcomes of the cost-effectiveness model align with previous NICE technology appraisals in metastatic NSCLC (e.g., TA531, TA705, TA584 and TA683)

Company approach involved 3 main steps:

1. Adjusting the transition probabilities
2. Comparing metastatic health state QALY gains with previous NICE appraisals
3. Converting the model to a metastatic model

(Each of these are discussed over the next few slides in further detail)

Abbreviations: DFS – disease free survival; NSCLC – non-small cell lung cancer; QALY – quality-adjusted life years

Adjusting the transition probabilities

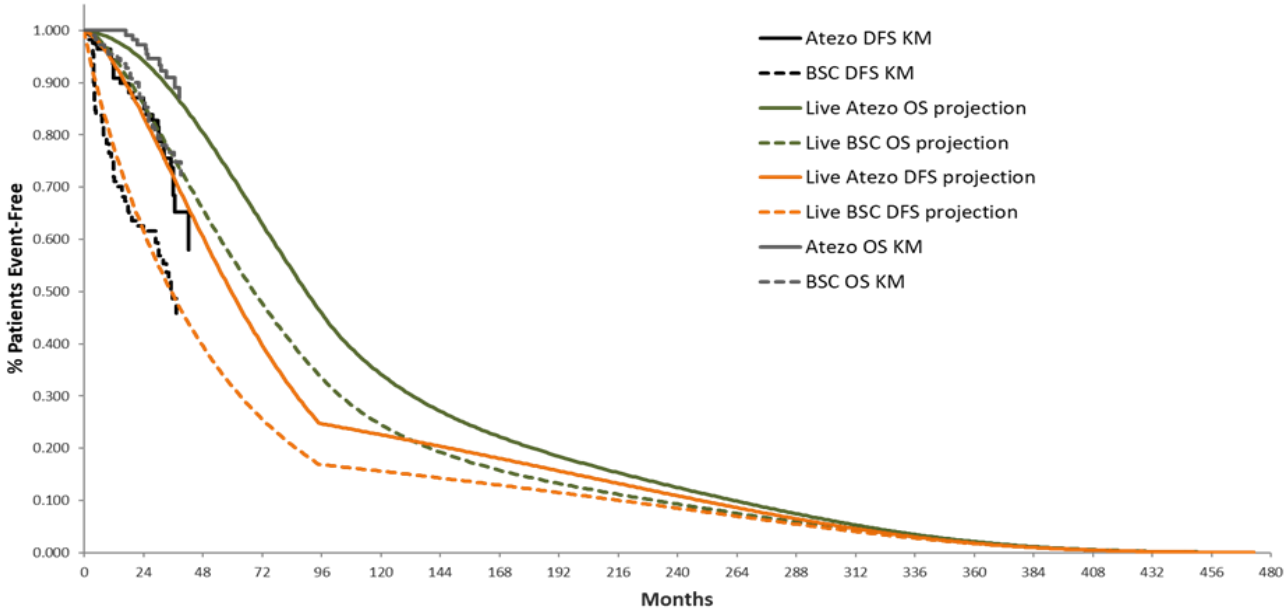
Company:

- Used an adjustment factor input to ensure a better fit of the modelled OS data to the IMpower010 II-IIIA PD-L1 expression on ≥ 50% of tumour cells (TC) observed OS data
- The application of the adjustment factor to the post DFS health state transition probabilities leads to
  - ➢ An increase in OS and QALYs in the post DFS health states for both the atezolizumab and BSC arms
  - ➢ An increase in the costs as people are on immunotherapy treatment for longer

ERG comments:

- Forcing the post DFS transitions to meet one arm's KM OS curve did not produce a good visual fit to the other arm's KM OS curve
- None of these scenarios are a preferable alternative to the company's existing approach

Figure: lifetime DFS and OS projections from scenario using company's adjustments to post-DFS transitions to hit IMpower010 BSC OS KM at 36 months with ERG's alternative assumptions



Abbreviations: OS - overall survival; QALY - quality-adjusted life years; DFS – disease free survival; BSC – best supportive care; KM - Kaplan-Meier.

Comparing metastatic health state QALY gains with previous NICE appraisals

Company:

- QALY gains for BSC arm of the ERG model were compared with the QALY gains of the immunotherapy arms of the NICE appraisals (e.g., TA531, TA705, TA584 and TA683)
- QALY gains in the atezolizumab arm were not used because all people in atezolizumab arm of the ERG model proceed to using metastatic chemotherapy
- Results are within, not below, health benefit predictions of immunotherapy 1st metastatic recurrent treatments in previous appraisals
- Higher post-metastatic QALY projections in BSC arm of post DFS transition probability adjusted analyses produce a higher post-metastatic QALY projection than unadjusted analyses

Source	QALY gains
Previous NICE submissions	[redacted]
Total metastatic health state with adjusting the transition probabilities	[redacted]
The metastatic health state with alterations	[redacted]

ERG comments:

- ERG does not find company's argument convincing due to the limitations of these scenarios

Abbreviations: QALY – quality-adjusted life years; BSC – best supportive care

Converting the model to a metastatic model

Company:

- Provided a further scenario → allow patients to proceed to 1L metastatic health state after cycle 1 and compared the outcomes with previous metastatic NSCLC NICE-submitted models
- Adjustment factors that ensures the transition probabilities equal a value that result in the modelled OS to equal the KM OS at 36 months for the BSC were used
- The cost-effectiveness model is unlikely to underestimate QALYs in the metastatic health state

ERG comments:

- People in the relevant (Stage II-IIIA) IMpower010 sample are expected to be younger than those in the 1st metastasis setting

Abbreviations: NSCLC – non-small cell lung cancer; OS – overall survival; KM OS– Kaplan-Meier overall survival; BSC – best supportive care

Issue 3: Uncertainty in the long-term disease-free survival benefit

ACM1: Committee requested additional relevant evidence for cure proportion and cure timing

Company:

- Updated literature: Updated literature search which identified 2 new sources (Shin et al. 2021 & Maeda et al. 2010a). Both have reported 5-year recurrence-free probability after complete resection by stage II and III, however they have limitations in applicability to UK clinical practice
- Cure timepoints: 5 years for BSC and 6 years for atezolizumab (5 years in the active monitoring group plus a 1-year atezolizumab treatment period). 7 and 8 year cure assumptions for atezolizumab also provided

ERG comments

- Updated literature reported recurrence-free probability by disease stage, allowing isolation of stage 2 and 3 probability estimates
- Unless the post-10-year recurrence-free probability is zero, the lifetime recurrence-free probability estimates conditional upon survival to 5 years will be higher, and the true “cure” proportion will be lower
- Study selection process was not possible to verify as no PRISMA flow diagram and not addressing generalisability

Issue 3: Uncertainty in the long-term disease-free survival benefit

ACM1: committee asked for analyses and commentary on alternative extrapolations of DFS

Company: provided justification for the DFS extrapolation

Proportional hazard assumption: the hazards of a DFS event are proportional over time across the atezolizumab and BSC arms

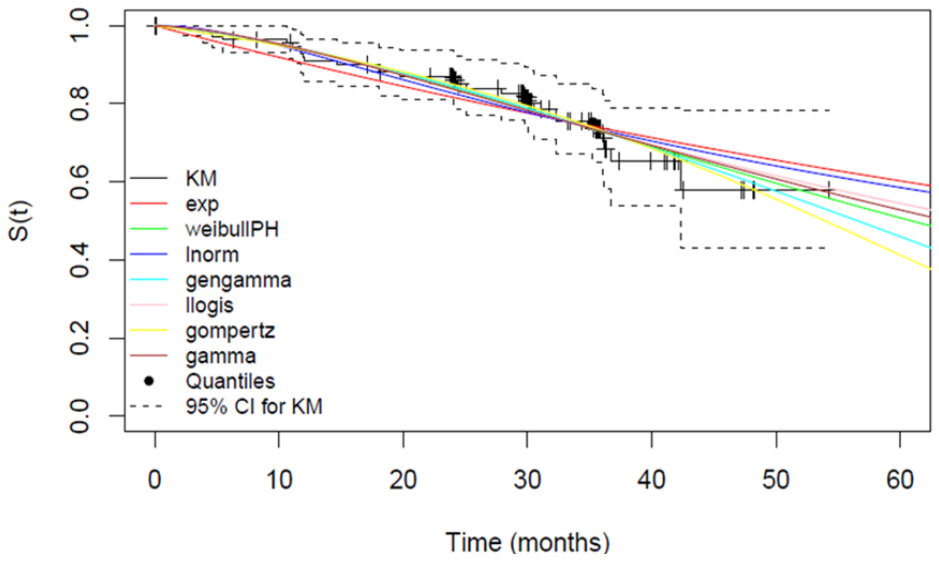
- Parametric distributions were fitted separately for the intervention and control arm
- 7 distributions - Exponential, Weibull, Log-Logistic, Log-Normal, Gompertz, Generalised Gamma and Gamma

- **Adjusting the DFS curves**
  - Cure: The proportion of people who are not at risk of a DFS event increases from year 3 to a maximum of 85.6% at year 6
  - Mortality: The model adjusted the probability of death with a standardised mortality ratio of 1.25 to account for excess mortality
  - Treatment effect: The model assumes treatment effect of atezolizumab ceases at year 5 or the same year at which the proportion of cured patients reaches its maximum
- **Literature and expert clinical opinion:** a 5-year DFS of ~40% and a 5-year OS of ~ 55%.
- **Company base case extrapolation:** a 5-year OS estimate for the BSC arm of XXX% (close to the clinical opinion of 50%). XXX% 5-year DFS in the BSC arm (within the clinically plausible DFS ranges). Model aligns with the available published data and UK clinical expert validation

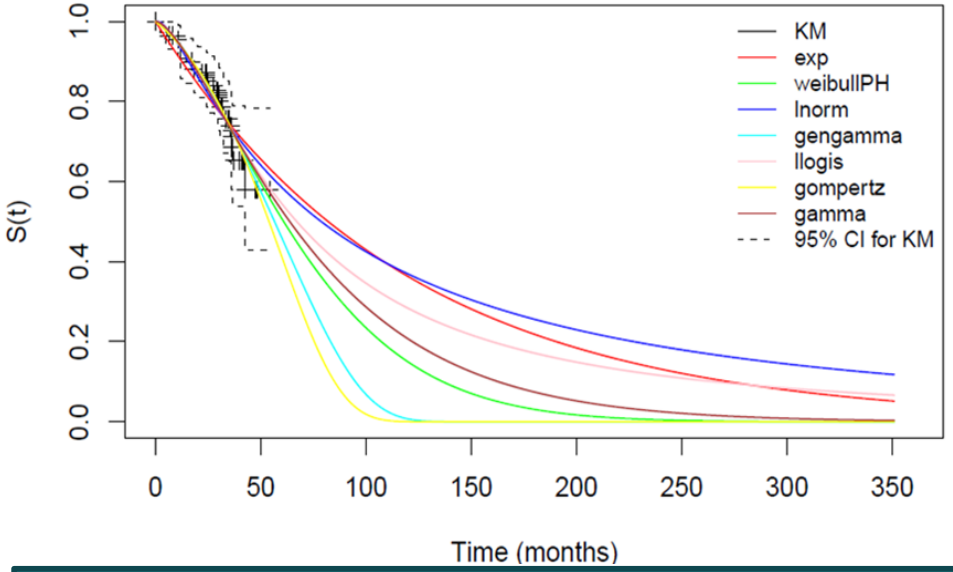
Abbreviations: DFS – disease free survival; OS – overall survival; BSC – best supportive care

Issue 3: Uncertainty in the long-term disease-free survival benefit

- **Overall survival:** the proportion of people that the model estimated to be alive at 5, 10, 20 and 30 years for both the atezolizumab and BSC arms when each of the distributions were used to extrapolate DFS.
- **Statistical fit**: assessed using the AIC and BIC, but noted there was no clearly best-fitting distribution statistically
- **Visual fit**



Fit of estimated DFS to Kaplan-Meier plot across parametric models (IMpower010, DFS, Stage II–IIIA, PD-L1 ≥50%, atezolizumab arm, 21 Jan 2021 data-cut

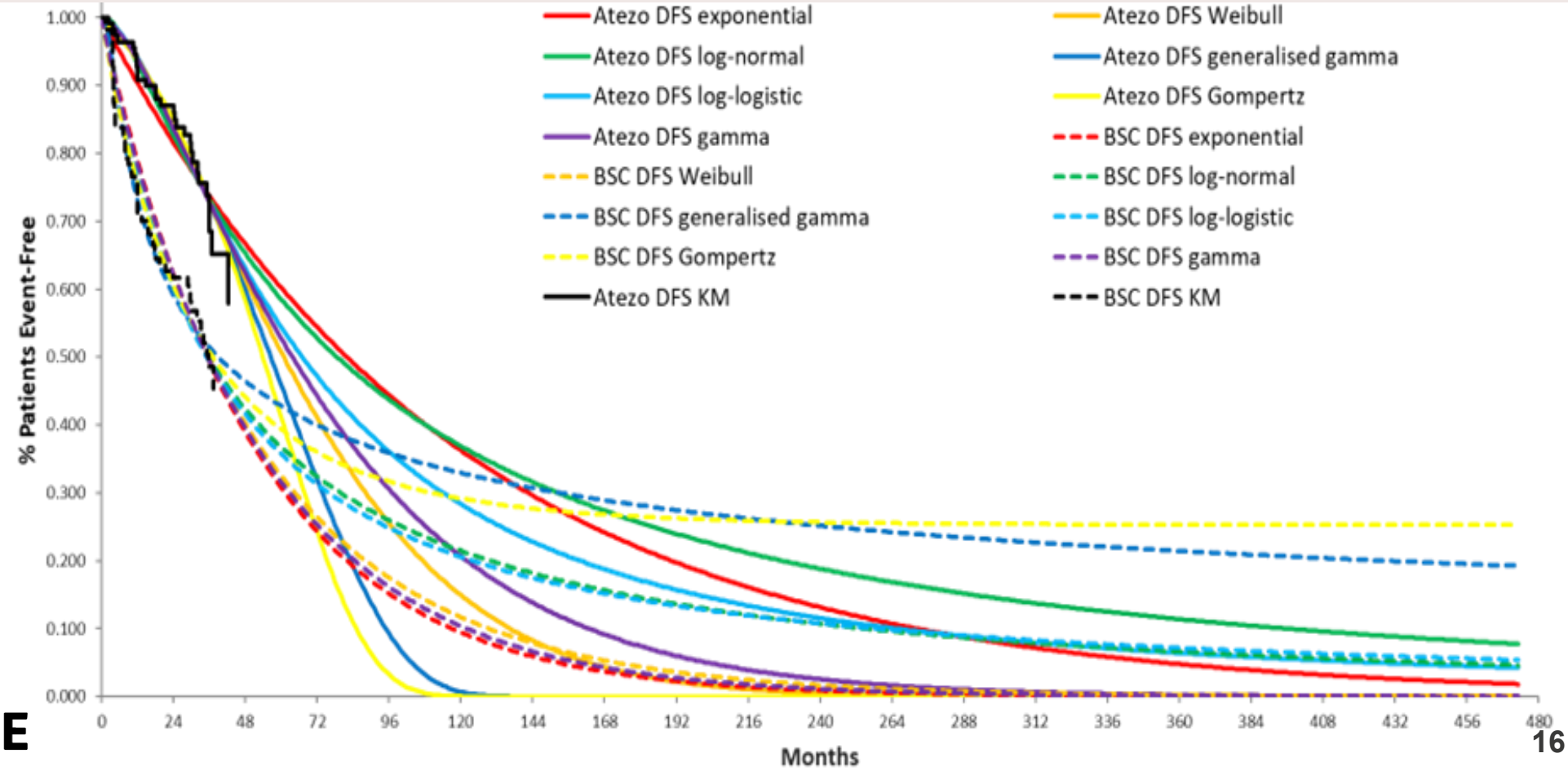


Extrapolation of DFS across Parametric Models (IMpower010, DFS, Stage II–IIIA, PD-L1 ≥50%, atezolizumab arm, 21 Jan 2021 data-cut)

Abbreviations: DFS – disease free survival; BSC- best supportive care; AIC - Akaike Information Criterion; BIC - Bayesian Information Criteria

Issue 3 – ERG comments

- The most pessimistic projection for atezolizumab are those assuming Gompertz or generalised gamma models → atezolizumab offers a lifetime QALY loss relative to BSC at a higher cost
- Exponential, gamma or log-normal models → results are more favourable for atezolizumab
- The variability in lifetime projections of DFS across different parametric model fits → the sensitivity of results to different underling parametric model



Parametric model fits to IMpower010 DFS KM data (PD-L1 ≥50% TC Stage II–IIIA subgroup)

Issue 4: Immature data from IMPOWER010

As part of the cost-effectiveness analyses, the committee asked the company to update its analysis

- **Further justification or additional literature searches for the transitions in the model?**
- **Additional trial data?**
- **Updated pivotal trial Kaplan-Meier data?**

Company

The company presented additional evidence

- Justification of external resources for transitions in the model
- Searched for additional evidence on event risk in the locoregional recurrence state only
- Updated overall survival trial data of IMpower010

ERG

- Relevant papers are highly likely to be missed in the search for external resources due to difficulty in determining search strategy in PubMed
- Not clear of the reason of no extension of the addition search to cover evidence for all post DFS transition risks
- The company did not provide a corresponding interim analysis of DFS data of IMpower010, nor explain the rationale for the recent database lock

Updated overall survival from IMpower010

The updated OS results demonstrate a [redacted] in the PD-L1≥50% Stage II-IIIA NSCLC population.

Kaplan-Meier curve of interim OS in the PD-L1≥50% Stage II-IIIA population, clinical data cut-off: [redacted] (Data on File)

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	Atezolizumab	BSC
	n=115	n=114
Patients with OS event	[redacted]	[redacted]
Median OS, months	[redacted]	[redacted]
HR (95% CI)	[redacted]	
p-value	[redacted]	

Abbreviations: OS – overall survival; BSC – best supportive care; NSCLC – non-small cell lung cancer; NE: not evaluable

Updated overall survival from IMpower010

Company:

- Incorporated the latest OS data into the post-ACM1 company base case model
- Provided a summary - the updated IMpower010 DFS Stage II–IIIA PD-L1+ OS data (data cut-off date: [redacted]) and the DFS KM data (data cut-off date: 21st Jan 2021)
- Included the respective unadjusted log-normal model fit to each KM curve, and the post-ACM1 company base case projection for each endpoint

ERG comments:
The company provided the updated OS KM data as datapoints within the economic model, but **no KM steps included** as committee requested

Abbreviations: OS – overall survival; DFS – disease free survival; KM OS– Kaplan-Meier overall survival

Cost-effectiveness results: overview

Revised company analysis did not include all the scenarios in ERG-preferred analyses from ACM 1

Revised company analysis	ERG-preferred analyses	
Revised ERG-corrected company	**ERG optimistic**	**ERG alternative**
Including retreatment 12 months after treatment discontinuation	Remove "ramping up" and treatment waning adjustments	Same assumptions as optimistic analysis except: • Assume Weibull distribution for DFS (where Log-logistic distribution in optimistic) • Cure assumption of 8 years (where 5 years in optimistic) ERG also provide an exploratory analysis with retreatment with immunotherapy permitted in atezolizumab arm
Using Maeda et al 2010a for recurrence-free probability beyond 5 years after complete resection in stage II people	AE and disutility for all treatments	
The trial data to inform recurrence type is pooled across arms	Assume atezolizumab batch remakes	
All people assumed to incur terminal care costs arms	Atezolizumab administration burden	
Removal of double administration costing for combination treatments	Treatment pathway update	
Using the log-normal extrapolation with cure adjustments for DFS modelling	Revised costings	

Scenarios in the company updated analysis

Scenarios in the company updated analysis not requested by the committee

ERG preferred scenarios but not in the company updated analysis

Slide summarising the results that will be shown in Part 2

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Abbreviations: DFS – disease free survival; AE – adverse events

Cancer Drugs Fund

Committee decision-making criteria:

Impower010 trial is currently ongoing. Company state that data cuts are event driven and difficult to predict timings

Proceed down if answer to each question is yes

Starting point: drug not recommended for routine use due to **clinical uncertainty**

1. Is the model structurally robust for decision making? (omitting the clinical uncertainty)

2. Does the drug have plausible potential to be cost-effective at the offered price, taking into account end of life criteria?

3. Could further data collection reduce uncertainty?

4. Will ongoing studies provide useful data?

and

5. Is CDF data collection via SACT relevant and feasible?

Consider recommending entry into CDF (invite company to submit CDF proposal)

Define the nature and level of clinical uncertainty. Indicate the research question, analyses required, and number of patients in NHS in England needed to collect data.

Key issues to be resolved

Key issues	Impact
Issue 1: Limitations in modelling approach	
Does the company's updated modelling approach reduce the uncertainty in the clinical and cost-effectiveness analysis?	
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How appropriate are the company's additional modelling assumptions for post disease-free survival?	
Issue 3: Uncertainty in the long-term disease-free survival benefit	
How appropriate are the company's additional modelling assumptions for disease-free survival ?	
Issue 4: Immature data from IMPOWER010	
Does the additional evidence reduce the uncertainty in the clinical and cost-effectiveness analysis?	

Question for Committee:

- **Has the additional analysis submitted by the company sufficiently resolved the uncertainties raised in ACM1?**
- **Can atezolizumab be recommended for routine commissioning or through the Cancer Drug Fund?**

Key:  **High impact**  **Unknown impact**  **Small impact**