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 [ID3852]

# Lead team presentation

1st appraisal meeting - Committee D

Chair: Lindsay Smith

Lead team: Giles Monnickendam, Malcolm Oswald, Martin Bradley

NICE Technical team: Alan Moore, Sally Doss, Jasdeep Hayre

Company: Roche

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

5th May 2022

# Key issues

| Key issues from ERG report | Impact |
|---|---|
| **Issue 1: Immature data from IMpower010** |  |
| • Does the immaturity of the data from IMpower010 add to uncertainty in the clinical and cost-effectiveness analysis? | |
| **Issue 2: Modelling Disease-Free Survival** |  |
| • How appropriate are the company's modelling assumptions for Disease-Free Survival? | |
| **Issue 3: Modelling post Disease-Free Survival outcomes** |  |
| • How appropriate are the company's modelling assumptions for post Disease-Free Survival? | |
| **Issue 4: Treatment pathway** |  |
| • Does the company's model capture the relevant treatment pathway?<br>• Should immunotherapy retreatment in the atezolizumab be modelled? | |
| **Issue 5: Costs** |  |
| • Has the company's analysis included the appropriate costs? | |

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

# Background:

## Resected non-small-cell lung cancer

- In the UK, lung cancer is the third most common type of cancer, with approximately 47,800 new cases every year
- Lung cancers are classified into two different categories: non-small cell lung cancer (NSCLC) and small-cell lung cancer (SCLC). ~ 88% of all lung cancer cases are diagnosed as NSCLC
- Approximately half of all NSCLC patients are diagnosed with early Stage I–III disease
- For early NSCLC, surgery (lobectomy) is a treatment option with curative intent, and can be complemented by neoadjuvant or adjuvant chemotherapy – adjuvant chemotherapy is more commonly used
- Disease can reoccur after surgery - within about 5 years of surgery in 45% of patients with stage 1b, 62% with stage 2, and 76% with stage 3 disease

NICE Source: Company submission and NICE technology appraisal TA761: (Osimertinib for adjuvant treatment of EGFR mutation-positive non-small-cell lung cancer after complete tumour resection)

# Clinical perspective

**Submission received from British Thoracic Oncology Group (BTOG)**

## Unmet need

- Outcomes post surgical resection remain poor. Better adjuvant treatments needed

## Current treatment

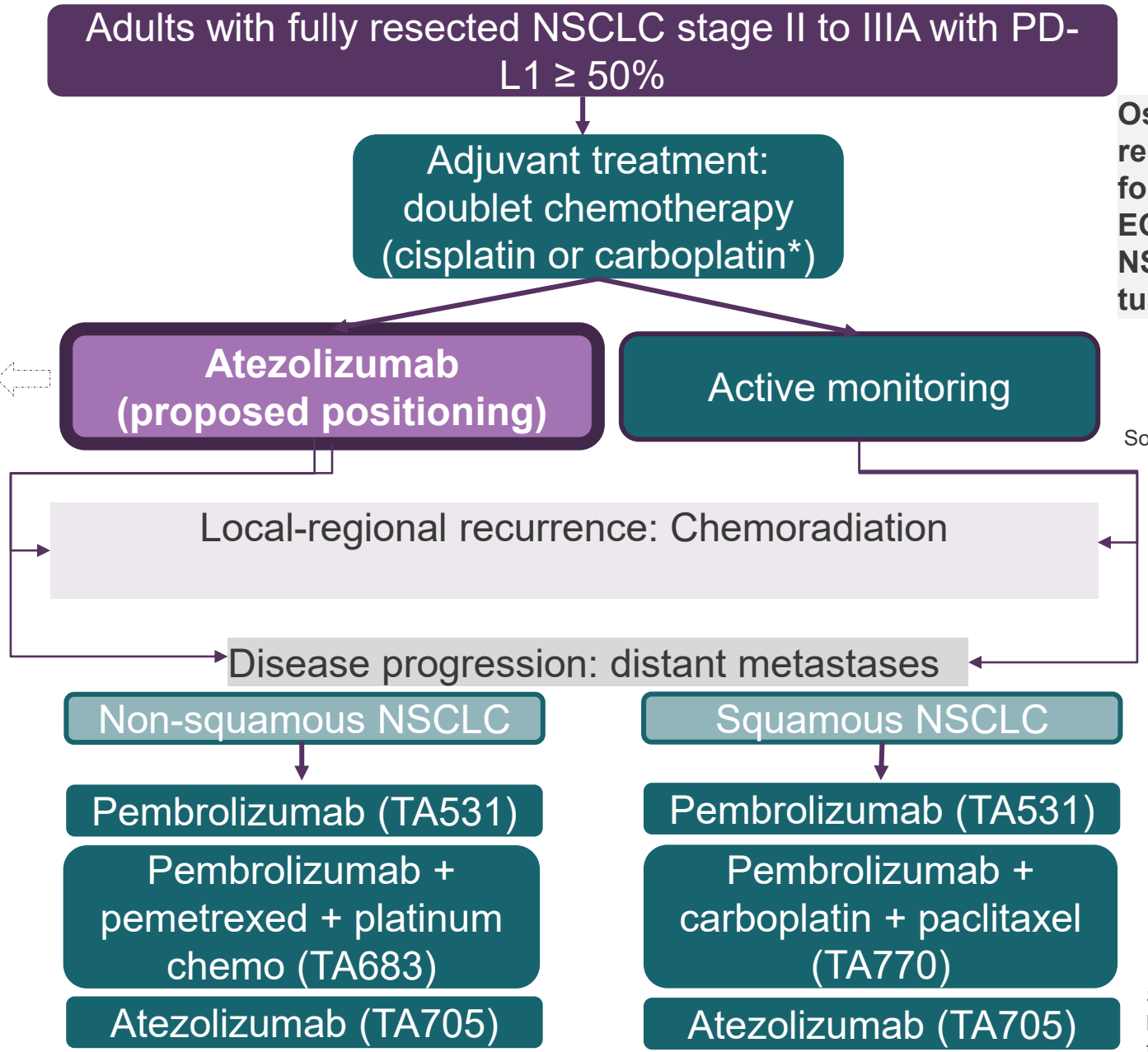
- Adjuvant chemotherapy: 4 cycles of platinum-based treatment post surgery
- Aim to increase disease-free survival and chance of cure - but minimal benefit

## Atezolizumab

- Would be used as an adjunct to the current adjuvant chemotherapy
- More resources up front:
  - Extra chair time
  - More frequent monitoring (e.g. for toxicity) and imaging
- But fewer patients will recur with advanced metastatic disease, reducing resources
- IMpower010 trial and appraisal offers a huge step forward in clinical outcomes for patients

# Treatment pathway

- **Project Orbis** initiative (innovative and clinical significance).
- 'Innovation Passport' through **MHRA's ILAP.**




**Osimertinib recently recommended in the CDF for adjuvant treatment of EGFR mutation-positive NSCLC after complete tumour resection [TA761]**

Source: Company submission figure 1

Source: NICE technical team, based on NICE NSCLC technology appraisals



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Abbreviations: CDF: Cancer Drugs Fund, NSCLC: non-small cell lung cancer, MHRA: Medicines and Healthcare products Regulatory Agency, ILAP: Innovative Licensing

# 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:<br>• 840 mg administered intravenously every two weeks, or<br>• 1,200 mg administered intravenously every three weeks, or<br>• 1,680 mg administered intravenously every four weeks.<br><br>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)<br><br>*Confidential simple discount patient access scheme (PAS) has been approved* |

# Background

| | |
|---|---|
| **Comparators** | • Established clinical management without atezolizumab (that is, active monitoring) |
| **Subgroups** | • EGFR/ALK status |
| **Clinical trial** | IMpower010: Phase III, open label, RCT comparing atezolizumab (up to ~1 year of treatment) to best supportive care (active monitoring) |
| **Key results** | Intention to treat population (PD-L1 ≥ 1%)<br>Disease-free survival:<br>Atezolizumab, NE v BSC, 35.3 months; HR = 0.66 (95% CI, 0.50-0.88)<br>Overall survival* HR: 0.77 (95% CI: 0.51, 1.17)<br><br>PD-L1 ≥50% subgroup (MA licence, Stage IIA to IIIA)<br>Disease-free survival:<br>Atezolizumab, NE vs BSC, 35.7 months; HR = 0.43 (95% CI, 0.27, 0.68)<br>Overall survival* HR: 0.37 (95% CI, 0.18, 0.74) |

NICE *OS data highly immature and based on small number of events. Median OS not reached in either arm



Abbreviations: RCT; Randomised control trial, HR: Hazard ratio, NE: not estimable

# Evidence from IMpower010

**IMpower010**

**Phase III, open label, randomised controlled trial**

**Patients enrolled**
- Adults with completely resected stage IB(≥4 cm)-IIIA NSCLC^.
- ECOG 0-1
- Lobectomy or pneumonectomy

Cisplatin + pemetrexed, gemcitabine, docetaxel or vinorelbine 1-4 cycles (n=1280)

**Atezolizumab monotherapy (n=507*)**

1200mg 1x every 3 weeks up to maximum of ~1 year (16 cycles)

**Randomisation 1:1**

**Best supportive care (active monitoring) (n=498*)**

*PD-L1≥50% and stage II to IIIA: Atezolizumab n=115, Best supportive care n=114

IMpower010 is ongoing.
A data cut from January 2021 informs this appraisal

**Outcomes**

**Primary**
- Disease-free survival ★

**Secondary (Selected)**
- Overall survival

**Quality of life data**
- No quality of life data was collected

*license is restricted to PD-L1≥ 50% and stages II to IIIA

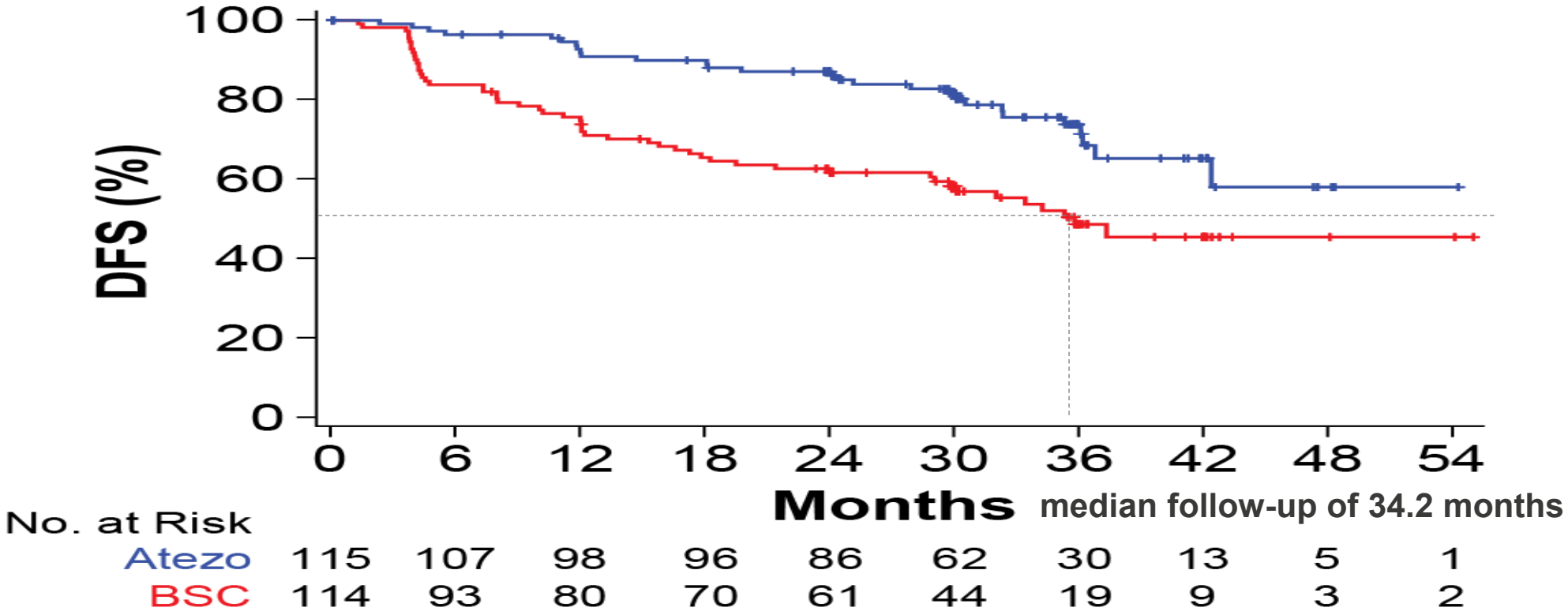
★ Used in model

^per the Union Internationale Contre le Cancer staging system (UICC)/American Joint Committee on Cancer staging system (AJCC) staging system, 7th edition; Detterbeck et al. 2009

Abbreviations: NSCLC: Non small cell lung cancer

# Results from IMpower010

## Kaplan-Meier curve of disease-free survival, PD-L1 ≥50% and Stage II to IIIA population




| | Atezolizumab (n=115) vs. BSC (n=114) | Hazard ratio (95% CI) | P-value |
|---|---|---|---|
| Median DFS (months) | NE vs 35.7 | 0.43 (0.27, 0.68) | 0.0002 |
| Median OS (months)* | NE | 0.37 (0.18, 0.74) | NR |

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*exploratory analysis: company note OS data should be interpreted with caution due to low number of events – median OS could not be calculated in either arm.

Abbreviations: CI; Confidence interval, NE; Not estimable, Not reported

# Results from IMpower010: Overall Survival

Company's model relies on DFS outcomes from IMpower010 as Median OS is not mature and was not reached in either arm

**Kaplan-Meier plot of Overall Survival (PD-L1 ≥50% Stage II–IIIA population)**

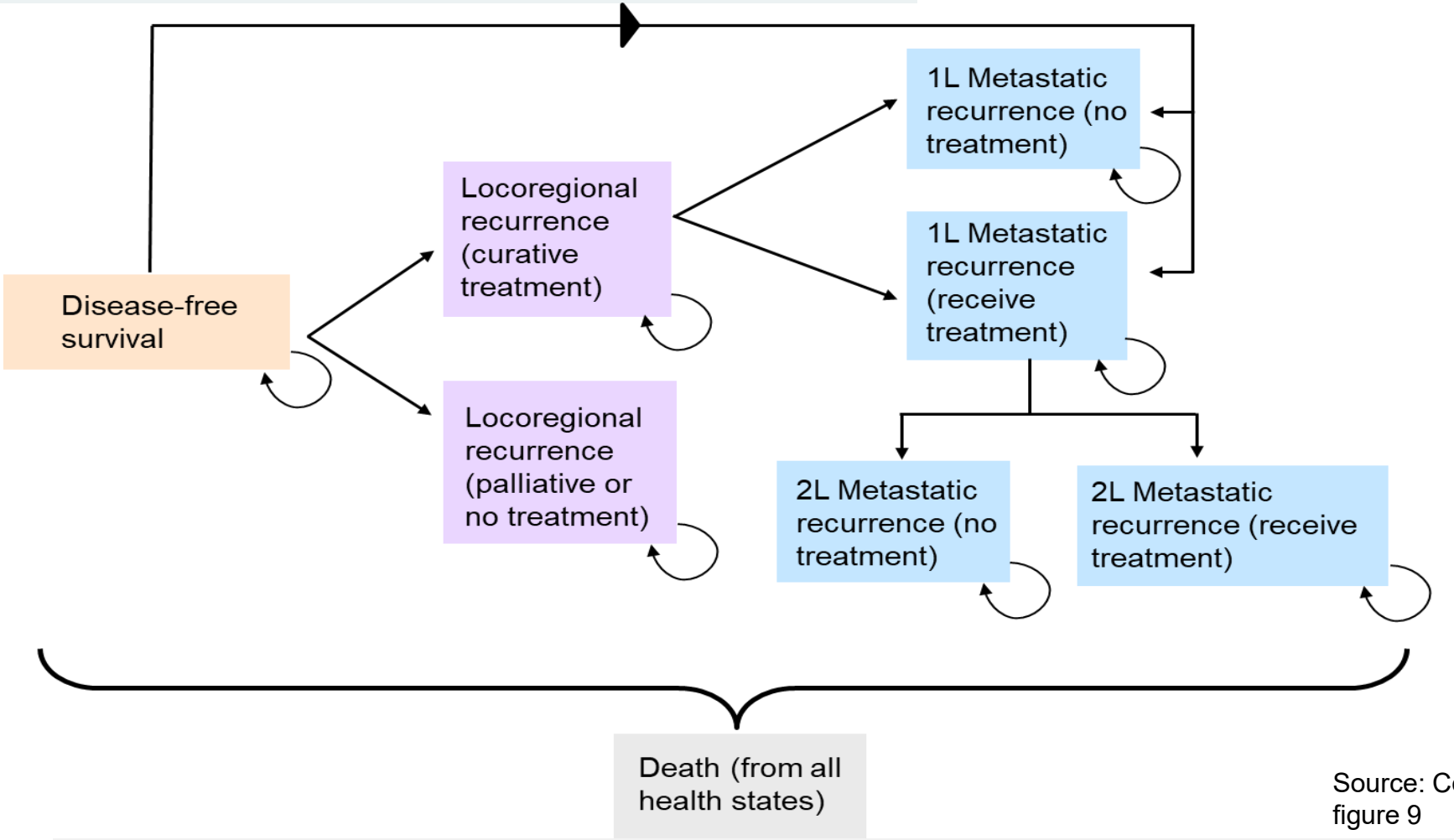
**NICE (data cut: January 2021, median follow-up of 34.2 months)**



Abbreviations: DFS: disease-free survival, OS: overall survival

# Model structure

**Company model:** Markov model with 8 health states




Source: Company submission, figure 9

**ERG comments on model structure**:
Same health states used in TA761 (Osimertinib adjuvant treatment for EGFR+ NSCLC). TA761 model allows locoregional + distant metastasis event risks to vary with time, using tunnel states. Therefore, the submitted model for this appraisal relies on stronger assumptions of time invariant transitions post DFS.



Abbreviations: DFS: disease free survival

# Model transition rates and assumptions

| Transitions | Source |
|---|---|
| DFS to LR, 1LM and death | IMpower010 |
| LR (curative treatment) to 1LM and death | Nakamichi et al (PFS and OS Stages I-III NSCLC, treated with chemoradiotherapy/radiotherapy, n=74) |
| LR (palliative or no treatment) to death | Kruser et al (OS with locoregional recurrence after radiotherapy for Stages I–IV, n=37) |
| 1LM (receive treatment) to 2LM and death | IMpower150 (trial of atezolizumab for 1st line metastatic non-squamous NSCLC, n=356) |
| 1LM (no treatment) to death | Wong et al (using National Cancer database [U.S]) |
| 2LM (receive treatment) to death | OAK study (used in TA520: Atezolizumab 2nd line metastatic NSCLC, n=850) |
| 2LM (no treatment) to death | Wong et al (using National Cancer database [U.S]) |
| **Assumptions** | **Description** |
| Retreatment assumption | No retreatment with immunotherapy assumed for the atezolizumab arm based on clinical expert input |
| Cure assumption | Company cite Sonoda et al 2020 study to inform assumption that 91.5% in DFS after 5 years are assumed cured. Company validate this source with clinician experts |

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Abbreviations: DFS; disease-free survival, LR; locoregional recurrence , 1LM; 1st line metastases, 2LM; 2nd line metastases, NSCLC; non-small cell lung cancer, PFS; progression-free survival, OS; overall survival

# Issue 4: Treatment Pathway

Model assumptions about subsequent treatments received in each model arm impact on the cost-effectiveness of atezolizumab.

## Company's approach to modelling the treatment pathway

- Company assume that no further lines of immunotherapy would be given following disease progression with adjuvant atezolizumab treatment – based on clinical expert opinion
- Base subsequent treatment choices in the model on clinical expert opinion

## Subsequent treatment assumptions in company model

| Model state | Assumptions |
|---|---|
| Locoregional recurrence | **Both arms:**<br>Curative treatment: 80% (chemoradiotherapy or radiotherapy)<br>Palliative treatment: 20% |
| 1st line metastatic | **Atezolizumab:** 100% pemetrexed + carboplatin<br>**BSC:** 28% pembrolizumab + pemetrexed, 23% pemetrexed + cisplatin, 33% pembrolizumab, 16% pembrolizumab + carboplatin |
| 2nd line metastatic | **Both arms:** [redacted] Nintedanib + docetaxel, [redacted] Pemetrexed + carboplatin, [redacted] docetaxel, [redacted] Gemcitabine and carboplatin |

# Issue 4: Treatment Pathway (2)

## ERG comments

- ERG believe company's approach to modelling post DFS treatments does not capture complexity of the treatment pathway
- ERG use NHS-algorithm to inform treatment availability and uptake assumptions:
  - 1st metastatic treatment: Assume 80% fit for treatment are immunotherapy suitable
    - 70% of which assumed to have stable disease and receive atezolizumab or pembrolizumab (equal uptake) as opposed to receiving pembrolizumab combination treatment
  - Also assume 75% have non-squamous disease, 90% of platinum chemotherapy is carboplatin and 90% of doublet chemotherapy is gemcitabine + platinum
- ERG clinical expert agreed with company's position that retreatment following metastatic disease progression after adjuvant atezolizumab would not occur in NHS practice.
  - ERG provide exploratory analysis in which the same assumptions of metastatic treatment are applied the atezolizumab arm (retreatment with immunotherapy)
  - This analysis increased incremental QALYs in the atezolizumab arm by [redacted]. The ERG states this highlights their concerns that the company's model underestimates benefits of metastatic treatment

◉ Does the company's analysis capture the treatment pathway appropriately? Should immunotherapy retreatment in the atezolizumab arm be modelled?

# Issue 1: Immature data from IMpower010

IMpower010 is an ongoing trial comparing atezolizumab with best supportive care (active monitoring). Median overall survival has not been reached in either arm in latest data cut

**IMpower010 data PD-L1 ≥50%**
**(data cut: January 2021, median follow-up of 34.2 months)**

## ERG comments

**Available data:**

- Overall survival is gold standard outcome for oncology: OS data immature
- DFS trial data for IMpower010 for PD-L1 ≥ 50% also immature, due to the smaller sample size compared to full trial population (median DFS not reached in atezolizumab arm)
- Small number of patients at the tails of KM curves
- No data from IMpower010 to inform cure assumption

**Impact:**

- Issue cannot be resolved with current available data and increases uncertainty in cost-effectiveness estimates
- Provision of more data (IMpower010 is ongoing) could help to reduce uncertainty

◉ Does the immature data from IMpower010 increase uncertainty in the cost-effectiveness results?

# Issue 2: Modelling Disease-Free Survival

Disease-Free Survival (DFS) was a primary outcome measure in IMpower010 and impacts significantly on cost-effectiveness estimates. Overall survival data are not mature enough. The company's analysis makes several adjustments to DFS data

Company note that while there is no robust evidence on the correlation between DFS and OS, clinical experts agreed DFS was a reliable surrogate for OS and Mauguen et al. 2013 (study of adjuvant chemotherapies) findings supported this

## Company's approach to modelling DFS

- Fitted parametric curves to the IMpower010 patient-level data:
  - Selected log-logistic curve after considering standard parametric models
- Literature identified on longer term survival and cure proportions
- "Ramping up" adjustment:
  - Implemented 3 years before the assumed cure point in the model to adjust for a unrealistic "kink" in the DFS curve
- Treatment effect duration adjustment:
  - Model assumes the same probability in both arms of an event occurring at 5 years (based on previous NICE NSCLC appraisals)
- Validated cure assumption survival outputs with identified literature and UK clinical expert opinion



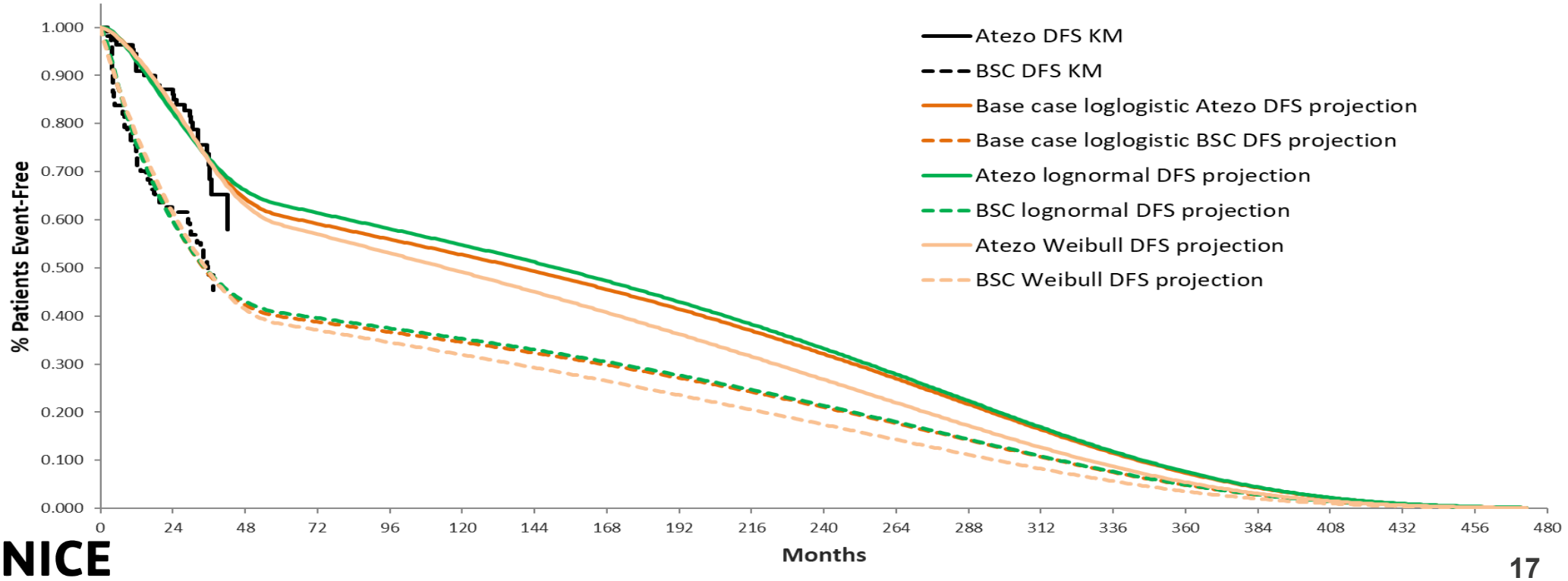
Abbreviations: DFS: disease-free survival, OS: overall survival

# Issue 2: Modelling Disease-Free Survival (2)

## Fitting parametric curves

- Company select a log-logistic model to fit to DFS data but noted there was no clearly best fitting model (AIC/BIC values similar). Log-logistic selected on validity of estimated outcomes
  - ERG noted lognormal and Weibull distributions could also be appropriate
- Company identified Pignon et al which estimated 5-year DFS and OS of 40% and 55% respectively. ERG note estimates are optimistic given that 38% had stage IA or IB NSCLC

**Company base case DFS projections alongside alternative projections based on other standard parametric models considered plausible by ERG (Graphs include a 5-year cure assumption, "ramping up" and treatment effect assumptions as in company's base-case)**





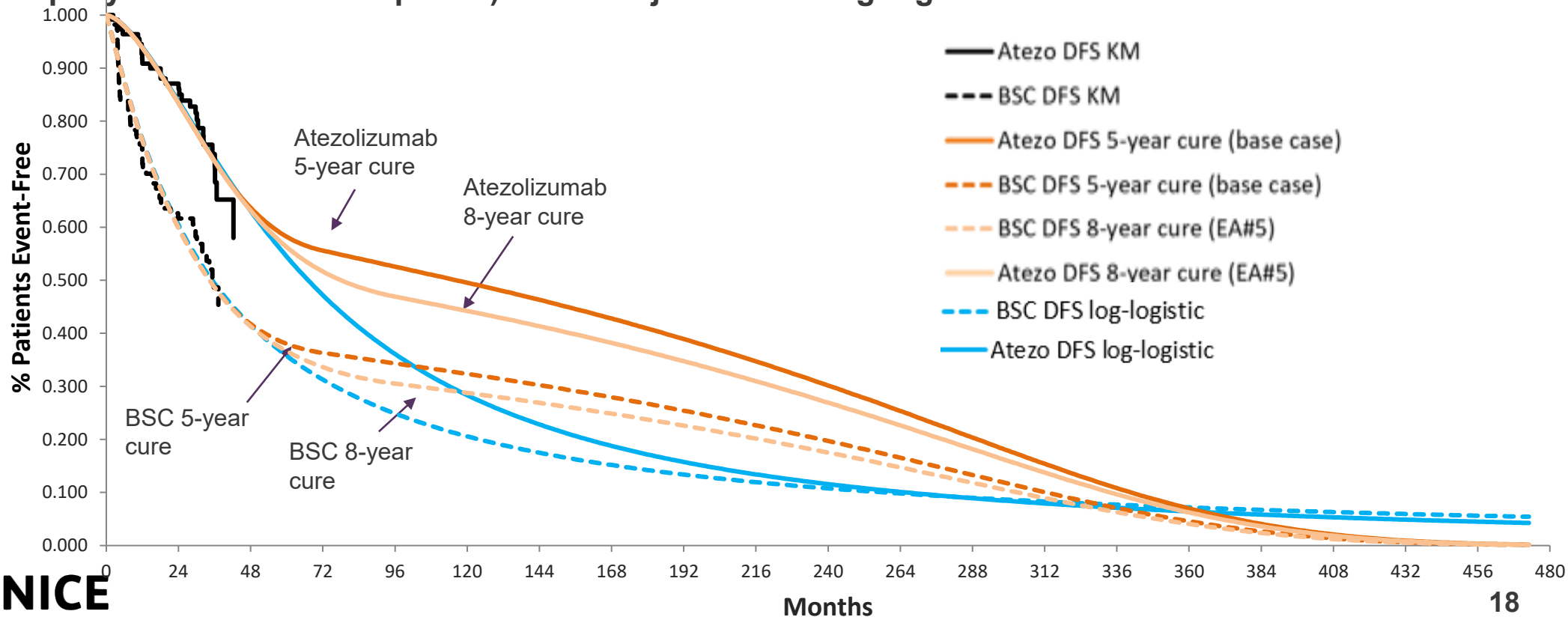

Abbreviations: DFS: disease-free survival, AIC: Akaike Information Criterion, BIC: Bayesian Information Criterion

# Issue 2: Modelling Disease-Free Survival (3)

## Cure assumption

- Company cite Sonoda et al 2019 to assume 91.5% of patients cured after 5 years in DFS
  - ERG noted source used data from 1 Japanese hospital between 1990-2006, with 53% of patients with stage IA disease. Express concern at appropriateness of source to inform cure assumption
- ERG provide alternative 8-year cure assumption scenario, based on TA761 (Osimertinib for EGFR mutation-positive NSCLC after resection) and uncertainty of the company's base case

**8-year cure DFS projections alongside company base case five-year DFS projections (includes company base case assumptions) and unadjusted DFS log-logistic curves**



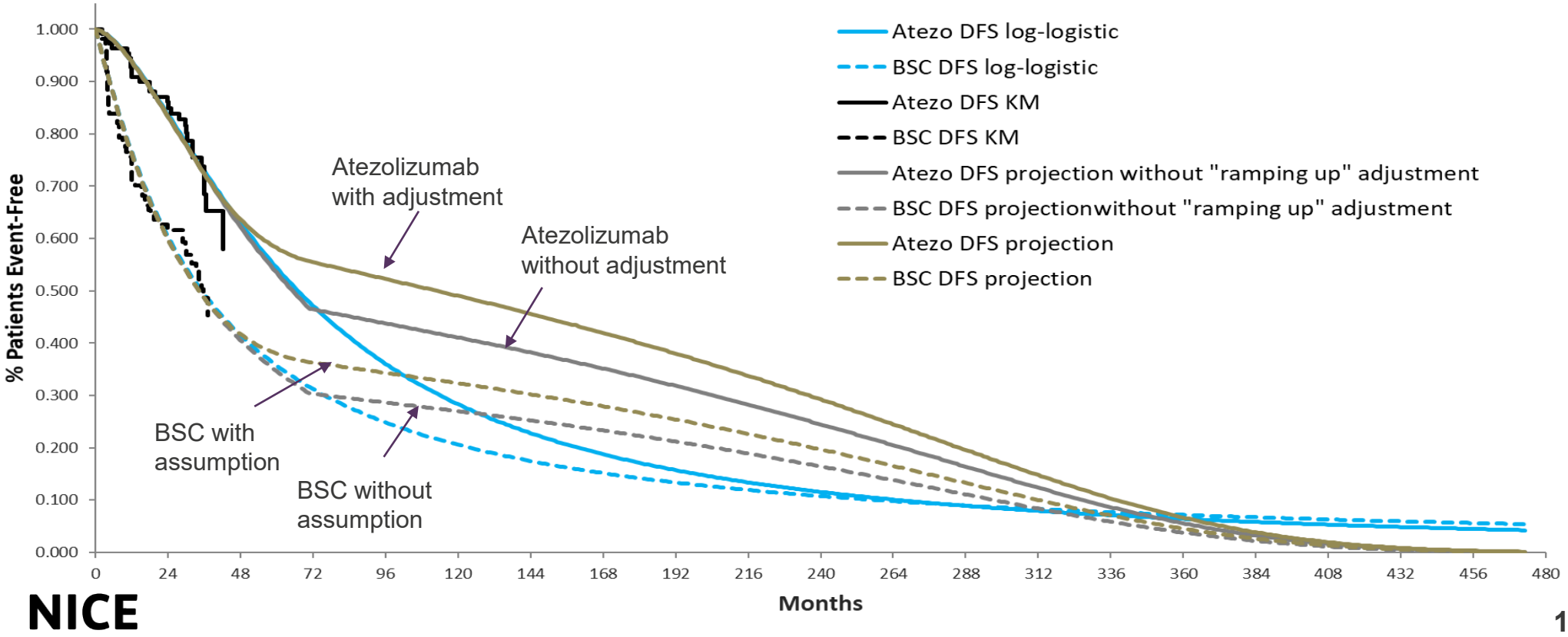

Abbreviations: DFS: disease-free survival

# Issue 2: Modelling Disease-Free Survival (4)

## "Ramping up" adjustment

- Company linearly increased % of DFS cohort assumed cured from 0% at 3 years to 91.5% at 6 years to adjust for what they consider an unrealistic" kink" in the DFS curves caused by cure assumptions
- ERG believes there is no justification for this adjustment and notes that this assumption impacts longer term outcomes beyond these timepoints

**Cure assumption-adjusted log-logistic DFS projections alongside unadjusted log-logistic DFS extrapolations (assuming a 5-year cure assumption)**






Abbreviations: DFS: disease-free survival

# Issue 3: Modelling post DFS outcomes

Modelling of outcomes after disease-free survival is more reliant on sources other than data from IMpower010

## Company approach

- Use of external sources to model most post DFS state transitions found by a focused literature review as data from IMpower010 not available for all transitions
  - Assume either exponential models to these sources or use median outcomes
- Use clinical expert opinion to estimate % who receive treatment in each post DFS state
- Assumes a different % of DFS events being locoregional recurrence or 1st metastatic recurrence for the atezolizumab arm ([redacted] and [redacted] respectively) compared to the BSC arm ([redacted] and [redacted]) on data from post-hoc analysis of IMpower010



Abbreviations: DFS: disease-free survival,

# Issue 3: Modelling post DFS outcomes (2)

## ERG comments

- ERG concerned company's approach may underestimate QALY benefits of post-adjuvant immunotherapies (a DFS QALY benefit of adjuvant immunotherapy = **** discounted QALYs); more than 11 times greater than the post-DFS QALY benefit of immunotherapy (comparator arm; **** discounted QALYs)
- ERG not confident that the company have used the most appropriate post-DFS transition sources. Company partially report a search strategy, with no PRIMSA diagram or explicit inclusion criteria for study selection
- No exploration of appropriateness of exponential model for fitting to external data, and no other models fitted – ERG analysis suggests exponential models only suitable for limited number of sources
- ERG feel there is insufficient evidence from IMpower010 to assume different rates of DFS event type by treatment arm
- ERG clinical expert expressed uncertainty if adjuvant atezolizumab offered survival benefit but noted that DFS outcomes were encouraging
- ERG note that Mauguen et al. 2013 (study of adjuvant chemotherapies) source identified by the company also stated "*extrapolation to targeted treatments, however, is not automatically warranted*"



Abbreviations: DFS: disease-free survival, QALY; Quality-adjusted life year

# Issue 3: Modelling post DFS outcomes (3)

Modelled OS projections are impacted by modelling of DFS and post-DFS health states. ERG notes company analysis estimates a significant DFS and OS benefit for atezolizumab, based on short trial data. ERG also note OS is underestimated in both arms compared to KM data

**Company base case OS projections, alongside OS KM plots and for the IMpower010 PD-L1 ≥50% TC Stage II–IIIA population**

**Outcomes (company base case)**

| (% alive) | 12 months | 36 months |
|---|---|---|
| ATZ OS KM | XXX | XXX |
| ATZ OS curve | XXX | XXX |
| BSC OS KM | XXX | XXX |
| BSC OS curve | XXX | XXX |

Abbreviations:
ATZ: atezolizumab
BSC: best supportive care
OS: overall survival
KM: Kaplan-Meier

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◉ How appropriate are the company's modelling assumptions for post Disease-Free Survival?

# Issue 5: Costs

The company make some costing assumptions which the ERG believe bias the analysis in favour of atezolizumab

## Company costing approach

- Assume no treatment discontinuation within metastatic recurrence states (do include a 2-year stopping rule for pembrolizumab)
- Assume only some patients will incur a terminal care cost: when cause of death is disease-related (51% in atezolizumab arm and 65% in BSC arm)
- NHS and patient burden associated with adjuvant atezolizumab administration:
  - No additional resource above administration costs assumed for implementing atezolizumab in the adjuvant setting
- Administration cost of doublet IV therapy is twice that of IV monotherapy
- Assume no atezolizumab batch remakes in practice

## ERG comments

- ERG believe the company's cost assumptions in general favour the atezolizumab arm
- Carry out scenario analysis:
  - those with metastatic disease are assumed to spend 50% of time before next recurrence or death receiving treatment (in absence of data)
  - All patients assumed to incur terminal care costs
  - Inclusion of adjuvant atezolizumab resource burden
  - Costs for clinical review and blood test
  - Removal of double administration costing for combination treatments
  - A pharmacy-data informed batch-remake rate for adjuvant atezolizumab (1.012 vials assumed per patient)

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◉ Has the company's analysis included the appropriate costs?

# Uncertainty

A summary of various uncertainties in the evidence base and company submission

| Uncertainty | Description |
|---|---|
| **Data** | • IMpower010 is ongoing. Limited data from this trial informs analysis<br>• Median DFS has not been reached in the atezolizumab arm<br>• Median OS has not been reached in either arm (very limited OS events have occurred) |
| **Cure assumption** | • Company cite Sonoda et al to assume 91.5% of people are cured in DFS state at 5 years<br>• ERG note Sonoda et al study is based on a single hospital (Japan, 1990-2006) and includes 53% with NSCLC stage IA<br>• ERG provide alternative scenario – cure assumed at 8 years in DFS |
| **Model structure and outcomes** | • Model does not allow time variant transitions between many health states - TA761 used tunnel states to allow transitions to vary over time<br>• Many transitions are limited to exponential or median values from sources with heterogeneous populations<br>• Company's model appears to underestimate the cost-effectiveness of metastatic disease health states |
| **Retreatment with immunotherapy** | • Company assume no retreatment with immunotherapy following disease progression with adjuvant atezolizumab<br>• ERG provide scenario with retreatment. TA761 modelled retreatment |



Abbreviations: DFS: disease-free survival, OS: overall survival

# Equality considerations, innovation and end of life criteria

## Innovation

Comments from submissions

Company: Atezolizumab is a step change in management of early NSCLC. no other adjuvant treatment options are available other than osimertinib for patients with EGFR+ early NSCLC, however EGFR+ patients are only a small subset of NSCLC patients

British Thoracic Oncology Group: adjuvant treatment to date has added very minimal benefit. Atezolizumab would be a significant improvement to current treatment

## Equality issues

- No equality issues were raised by consultees or commentators

## End of life criteria

- The company do not make a case for meeting NICE's end of life criteria

◉ Is atezolizumab considered innovative? Are there any potential equality issues?

# 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.



◉ Is atezolizumab a suitable candidate for the Cancer Drugs Fund?

# Cost-effectiveness analysis

Summary of key cost-effectiveness scenarios that will be considered in part 2

## Company analysis

| Company base case (key parameters) |
|---|
| Use log-logistic distribution to model DFS |
| Assume 91.5% cured at 5 years in DFS (Sonoda et al 2020) |
| Assume no re-treatment with immunotherapy after metastatic disease progression in atezolizumab arm |
| Treatment effect duration of 5 years |
| "Ramping up" adjustment from year 3 due to kink in DFS curve with cure assumption |

## ERG scenarios

| ERG optimistic analysis |
|---|
| Remove "ramping up" and treatment waning adjustments |
| DFS event type not affected by treatment arm |
| AE and disutility for all treatments |
| Assume atezolizumab batch remakes |
| Atezolizumab administration burden |
| Terminal costs (all patients) |
| Treatment pathway update |
| Revised costings |

| ERG alternative analysis |
|---|
| Same assumptions as optimistic analysis except:<br>• Assume Weibull distribution for DFS<br>• Cure assumption of 8 years<br><br>ERG also provide an exploratory analysis with retreatment with immunotherapy permitted in atezolizumab arm |

All ICERs are reported in PART 2 slides because they include confidential PAS discounts

# Key issues

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| • Does the immaturity of the data from IMpower010 add to uncertainty in the clinical and cost-effectiveness analysis? | |
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