# Chair's presentation

# Atezolizumab for treating locally advanced or metastatic non-small-cell lung cancer after chemotherapy

2nd Appraisal Committee meeting

Committee C

Lead team: Gail Coster, Paul Tappenden, Judith Wardle

ERG: LRiG

NICE technical team: Jessica Maloney, Fay McCracken

Company: Roche

13 September 2017

# ACD: preliminary recommendation

- Atezolizumab is **not recommended**, within its CHMP opinion, for treating locally advanced or metastatic non-small-cell lung cancer in adults after chemotherapy (and targeted treatment if they have an epidermal growth factor receptor [EGFR] or anaplastic lymphoma kinase [ALK]-positive tumour).

*Note: The committee are aware of the conclusions and decisions so far for the other related appraisals (pembrolizumab and nivolumab), in their preparation for this topic meeting.*

# Atezolizumab, Tecentriq, Roche

| | |
|---|---|
| **Anticipated marketing authorisation** | Treatment of adult patients with locally advanced or metastatic non-small cell lung cancer (NSCLC) after prior chemotherapy. *Patients with EGFR activating mutations or ALK-positive tumour mutations should also have received targeted therapy before atezolizumab.* |
| **Administration & dose** | 1,200 mg, every three weeks as intravenous infusion, fixed dose one vial per administration<br>Treat until loss of clinical benefit or unmanageable toxicity<br>Based on the OAK trial, the average time on therapy per patient (mean) is 7.78 months, equivalent to 11.3 cycles. |
| **Mechanism of action** | IgG1 monoclonal antibody, binds directly and selectively to PD-L1 preventing it from binding to PD-1 and B7.1. |
| **Cost** | • List price: £3807.69 per 20mL vial.<br>• PAS: Updated simple discount submitted to DoH for agreement. |
| **Cost of a course of treatment** | • The average cost per treatment course is £42,913.66 at list price. |

# Clinical evidence

| | OAK (n=1,225*) | POPLAR (n=287) |
|---|---|---|
| Design | Randomised, open label, phase III study | Randomised, open label, phase II study |
| Intervention | Atezolizumab, 1,200 mg every three weeks (n=425) | Atezolizumab, 1,200 mg every three weeks (n=144) |
| Comparator | Docetaxel, 75 mg/m$^2$ every three weeks (n=425) | Docetaxel, 75 mg/m$^2$ every three weeks (n=143) |
| Population<br>Recruited regardless of PD-L1 expression | • Locally advanced or metastatic NSCLC ≥18 years old<br>• ECOG PS 0 or 1<br>• Measurable disease by RECIST v1.1<br>• Adequate haematological and end-organ function<br>• Last dose of prior therapy administered ≥21 days prior to randomisation<br>• Patients with advanced lung cancer and EGFR mutation must have experienced disease progression with an EGFR TKI (e.g. erlotinib, getfitinib) | |
| Outcomes | Primary: Overall survival<br>Secondary: Progression free survival, objective response rate, duration of response, safety and tolerability, EQ-5D-3L, EORTC Quality-of-Life Questionnaire Core 30 (QLQ-C30) and its Lung Cancer Module (LC13) | Primary: Overall survival<br>Secondary: Progression free survival, objective response rate, duration of response, safety and tolerability, EORTC Quality-of-Life Questionnaire Core 30 (QLQ-C30) and its Lung Cancer Module (LC13) |

*pre-specified analysis of first 850 patients provided sufficient power to test the co-primary endpoints

# Committee's conclusions (I)

| Issue | Committee's conclusion |
|---|---|
| **PD-L1 expression** | Atezolizumab more effective than docetaxel regardless of PD-L1 expression. Disappointed company did not present all relevant PD-L1 subgroup results. |
| **Comparators** | Would like comparison in PD-L1 subgroup of atezolizumab with pembrolizumab. |
| **OS vs nintedanib + docetaxel uncertain** | OS for atezolizumab compared with nintedanib plus docetaxel is highly uncertain, wide variety of factors affecting the results (model choice, included studies).<br>• ERG assumed no survival gain as ERG preferred estimate of OS not statistically significant (3.33; -0.16, 6.74).<br>• Company mean OS estimate 3.7 months<br>• ERG additional analysis used the ERGs preferred assumptions for OS and applied the company's preferred estimate for comparative effectiveness (OS for atezolizumab 2.86 months compared with nintedanib)<br>Committee concluded that OS estimate is likely to lie between these two analyses (0 and 2.86 months) |
| **Errors in economic model** | Committee accepted the corrections made by the ERG to the company's economic model.<br>1. Inaccurate application of the discount rate<br>2. Failure to apply an age-related utility decrement<br>3. Inappropriate half-cycle correction to modelling of time on treatment |
| **Trial populations are not equivalent** | Company base case compared atezolizumab (whole population) with nintedanib plus docetaxel (whole population), this was wider than the marketing authorisation for nintedanib plus docetaxel (adenocarcinoma histology). The committee would prefer comparison in adenocarcinoma population. |

# Committee's conclusions (II)

| Issue | Committee's conclusion |
|---|---|
| **Cure rate model & rate** | Mixed cure model not appropriate as not sufficiently justified by the company and the long-term effect of immunotherapy on NSCLC is largely unknown. Cure rate not sufficiently supported by evidence. |
| **Extrapolation of overall survival** | Company's log-logistic model produces implausibly long survival tail. Prefer ERG extrapolation:<br>• KM data for atezolizumab up to week 83 followed by extrapolation using exponential model as more appropriate visual fit and more clinically plausible |
| **Lifetime treatment effect** | Lifetime treatment effect for atezolizumab is implausible, not presented with evidence to agree on the length of treatment effect after stopping treatment. |
| **ICERs** | • £170,497 per QALY gained compared with docetaxel (list prices).<br>• £100,000 to £150,000 per QALY gained compared with nintendanib plus docetaxel (list prices, the PAS ICER is confidential). |
| **End of life criteria** | Compared with docetaxel:<br>• meets EoL criteria.<br>Compared with nintedanib plus docetaxel:<br>• 3 month OS extension not met, considerable uncertainty in fractional polynomial method used by the company.<br>• Based on committee preferred assumptions estimated OS gain for atezolizumab compared with nin+doc is between 0 and 2.86 months. |

# ACD cost-effectiveness summary: Company and ERG analyses vs docetaxel (with previous atezolizumab PAS)

| Company base case | Inc. cost | Inc. QALY | ICER | Change |
|---|---|---|---|---|
| Deterministic | [redacted] | 0.75 | [redacted] | - |
| Probabilistic | [redacted] | 0.74 | [redacted] | - |
| **ERG scenario** | | | | |
| C1) Discounting algorithms | [redacted] | 0.747 | [redacted] | [redacted] |
| C2) Age-related utility decrement | [redacted] | 0.717 | [redacted] | [redacted] |
| C3) TTD half-cycle correction | [redacted] | 0.746 | [redacted] | [redacted] |
| ERG corrected company base case (C1-C3) | [redacted] | 0.718 | [redacted] | [redacted] |
| R1) ERG preferred OS for atezolizumab and docetaxel (KM data up to 19 months, followed by exponential extrapolation with HR 1 applied for docetaxel) | [redacted] | 0.312 | [redacted] | [redacted] |
| R2) R1 + atezolizumab treatment duration set to 5 years (to simulate 3 years) | [redacted] | 0.302 | [redacted] | [redacted] |

Source: company PAS template table 6, company submission table 4, ERG confidential appendix 1,

*Note: the company has submitted an updated PAS for atezolizumab*

# Cost-effectiveness summary: Company and ERG analyses vs nintedanib plus docetaxel (list prices)

| Company base case | Inc. cost | Inc. QALY | ICER | Change |
|---|---|---|---|---|
| Deterministic | £36,209 | 0.65 | £56,076 | - |
| Probabilistic | £34,357 | 0.63 | £57,777 | |
| **ERG scenario** | | | | |
| C1) Discounting algorithms | £36,896 | 0.659 | £55,959 | -£117 |
| C2) Age-related utility decrement | £36,209 | 0.618 | £58,608 | +£2,532 |
| C3) TTD half-cycle correction | £37,470 | 0.647 | £57,949 | +£1,873 |
| ERG corrected company base case (C1-C3) | £38,168 | 0.632 | £60,366 | +£4,290 |
| R3) ERG preferred OS for atezolizumab and assumed equal for nintedanib+docetaxel | £32,105 | 0.027 | £1,170,260 | +£1,114,185 |
| R4) R3 + treatment duration effect for atezolizumab and nintedanib treatment duration set to 5 years (to simulate 3 years) | £32,105 | 0.027 | £1,170,793 | +£1,114,718 |
| R5) ERG preferred OS for atezolizumab, FP ITC for nintedanib+docetaxel OS and treatment duration effect for both set to 5 years | £34,458 | 0.185 | £186,259 | +£130,183 |
| R6) ERG preferred OS for atezolizumab, LUME-Lung 1 HR for nintedanib+docetaxel OS and treatment duration effect for both set to 5 years | £33,276 | 0.148 | £225,159 | +£169,083 |
| Source: ERG addendum table 1 p5, company submission table 83 p199 & table 93 p206 | | | | |

*Note: there is a PAS for atezolizumab and nintedanib, PAS price comparisons will be presented in part 2.*

# ACD consultation responses

- Consultee comments from:
  - Roche
  - Clinical expert
  - RCP
- No web comments or commentator comments
- Company new evidence
  - Revised PAS
  - Updated data cut (not used in updated economic model):
    - OAK: data on patients without events (%) and median duration of response (months) in the secondary population
    - POPLAR: 2 year and 3 year overall survival to validate OS extrapolation
  - Cost-minimisation analysis atezolizumab (all-comers) compared with pembrolizumab (PD-L1 positive)

# Consultation comments – PD-L1 subgroups (I)

**Roche**

- ‘Atezolizumab targets the ligand PD-L1’… ‘pembrolizumab targets the protein, PD-1.’… ‘They target the same immune checkpoint’…but there are ‘differences in terms of other co-inhibitory interactions that they blockade.’
- ‘The marketing authorisation is narrower for pembrolizumab’… ‘a comparison of PD-L1 expressing patients is not appropriate due to the differing diagnostic tests’
- In the pembrolizumab study ‘only people whose tumours expressed PD-L1 (based on a TPS of ≥1%) were eligible for randomisation’

# Consultation comments - PD-L1 subgroups (II)

The company did not provide clinical and cost-effectiveness analyses for populations who are PD-L1 positive, or PD-L1 negative for all relevant comparators because:

- ACD states there is correlation between PD-L1 expression and response but "PD-L1 is not a perfect biomarker and therapies such as atezolizumab have shown benefit in people with PD-L1-positive and negative tumours".
- OS benefit is the same for lowest expressers (tumour cell [TC] and immune cells [IC] both <1%) and those with higher levels of expression.
- In OAK 25% reduction in risk of death (HR 0.75) for 379 patients (with TC/IC expression<1% ) 26% reduction (HR 0.74) in the 463 patients with higher levels of expression.
- Atezolizumab does not require PD-L1 test because benefits all patients, so treatment is not delayed for testing and there is reduction in NHS resource use.

# OAK - overall survival by PD-L1 expression

Cost-effectiveness results by PD-L1 expression were requested by NICE.

| Population | n (%) | Median OS (months) | | HR (95% CI) |
|---|---|---|---|---|
| | | Atezolizumab | Docetaxel | |
| ITT | 850 (100) | 13.8 | 9.6 | **0.73 (0.62, 0.87)** |
| TC3 or IC3 | 137 (16) | 20.5 | 8.9 | 0.41 (0.27, 0.64) |
| TC2/3 or IC2/3 | 265 (31) | 16.3 | 10.8 | 0.67 (0.49, 0.90) |
| TC1/2/3 or IC1/2/3 | 463 (54) | 15.7 | 10.3 | **0.74 (0.58, 0.93)** |
| TC0 and IC0 | 379 (45) | 12.6 | 8.9 | **0.75 (0.59, 0.96)** |

Company did not present these results in their submission. Presented in ERGR, published data.

Company presented these results in their submission

**ERG comments:**

- ERG presented OS data by PD-L1 expression from OAK trial published in January 2017 in their report, some results were not presented by the company
- Analyses by level of PD-L1 expression are specified in the protocols for OAK and POPLAR, full results for both trials should be provided by the company
- Scope states that biological subgroups should be presented if data is available

# Consultation comments – pembrolizumab as a comparator

**Roche**

- Rationale for pembrolizumab exclusion not fully captured in ACD
  - Pembrolizumab is not standard of care in NSCLC patients whose tumours express PD-L1 because of PD-L1 test implementation challenges, but changing as a result of the recommendation.
  - 'comparison of PD-L1 expressing patients is not appropriate due to the differing diagnostic tests'… 'the patient populations identified with these two different assays are not equivalent':
    - Atezolizumab: Ventana (SP142), based on TC and IC, PD-L1 expressers defined as: expression on 1% or more for TC or IC
    - Pembrolizumab: Dako 22C3 based on TC only, PD-L1 expressers defined as ≥1% PD-L1 staining
- NMA shows pembrolizumab (PD-L1 ≥1% TPS) and atezolizumab (all-comers) are equivalent in efficacy
- Roche provided cost minimisation analysis… 'this is a conservative approach: by comparing non-equivalent populations, there is a risk the relative clinical benefits of pembrolizumab are overestimated'

# Consultation comments - comparators

**Roche**

- ‘real-world significance of [nintedanib] as a comparator is very limited’
- ‘Roche has heard from several expert lung clinicians that this regimen is only used in a very small minority of second-line adenocarcinoma patients’
- feedback from leading clinical oncologist from large NSCLC centre: 7 patients have been treated since December 2015 with nintedanib
- ‘docetaxel and pembrolizumab comparators should carry more weight for decision making purposes’

**Clinical expert & RCP**

- ‘number of patients who actually receive this combination treatment [nintedanib plus docetaxel] is small.’
- ‘In the Greater Manchester and Cheshire Cancer Network (population 3.4 million), pharmacy data suggests 13 patients received docetaxel plus nintedanib in the past 20 months.’ (nationwide figures not yet available)

# Comments – clinical data on long term survival

**Clinical expert & RCP**

- little data on long term survival of NSCLC patients receiving immunotherapy, some evidence presented at conferences demonstrates a potentially significant improvement in 3 and 5 year overall survival.
- ERG model underestimates the long-term survival benefit

| Pembrolizumab KEYNOTE-001 | Nivolumab CA209-003 | ERG model |
|---|---|---|
| n= 449, median follow up 34.5 months. **3 year OS 19%** (29.7% in those with PDL-1 expression >50). | **18% 3 year OS and 16% 5 year OS** in patients who received nivolumab. (small patient numbers). | Approx. **3 year OS 14%** and **5 year OS 4%.** |

**ERG comments**

- Promising results but this should not be used as the justification of any projection of life-time survival (model time horizon is 25-years)
- Evidence is only available for max 5 years
- Pembrolizumab KEYNOTE-001
  - Phase I, randomised, parallel assignment, open label, for pembrolizumab only
  - Unclear if baseline characteristics are similar to patients in OAK and POPLAR
- Nivolumab CA209-003
  - Phase I dose-escalation cohort expansion trial for nivolumab only
  - Heavily pre-treated patients (1 to 5 prior regimens)
  - Results are for patients that received 3 different doses (1, 3, or 10 mg/kg every 2 weeks in 8-week cycles for up to 96 weeks); the recommended dose of nivolumab is 3mg/kg nivolumab every 2 weeks
  - OS was an exploratory objective

Abbreviations: AACR, American association for cancer research; ASCO, American Society of Clinical Oncology

# Consultation comments – ITC vs. nintedanib plus docetaxel

**Roche**

- 'the reduced network is acceptable, but should be analysed under fixed effects to obtain any meaningful insights.'… 'if the committee have a preference for the random effects, the extended network should be used.'
- Literature shows 'it is not appropriate to utilise random effects on a small, reduced network'
  - Because 'between-studies variance will be poorly identified and likely include values that are implausibly high'

# Consultation comments – duration of treatment effect

**Roche**

- 'Duration of treatment effect is an area of uncertainty for new immunotherapies'
- There is a 'lack of evidence for a single clinically plausible scenario'
- Disagree with ERG preferred 3 year treatment benefit cap, it is 'arbitrary and clinically inappropriate'
- 'Roche have provided a range of scenarios exploring different treatment effect durations; however, questions of clinical plausibility remain'
- 'atezolizumab is cost effective in all duration of treatment effect scenarios'

**ERG comments**

- No additional information presented in response to ACD on how clinical plausibility of 10% 5-year OS rate was obtained from clinicians
- Clinical opinion of what may be plausible (as opposed to 'likely') for a treatment that is in its infancy in terms of long-term outcomes is not robust, even if the process for gathering this information was robust
- ERG prefer to limit the duration of treatment effect of atezolizumab to 3 years (in line with TA428 pembrolizumab), to produce consistency between submissions for immunotherapy treatments in patients with NSCLC

# Consultation comments – overall survival extrapolation

**Roche**

- ERG and committee preference is ‘inappropriate, unjustified and unrepresentative of data available for both docetaxel and atezolizumab survival’ and pembrolizumab and nivolumab (act on same immune checkpoint)
- Log-logistic model is a robust choice, ‘accurately reflects the long term survival tails that are being witnessed with immunotherapies’
  - most appropriate parametric distribution
  - best statistical fit based on AIC and BIC,
  - best visual fit - validated with clinical experts at an advisory board
- ‘The ERG have not provided any evidence to support their statement that “the log-logistic distribution [is] not robust”’
- ‘Clinical experts also highlighted “immunotherapies might be able to create a long-term durable response for a proportion of patients with lung cancer”.’
- Committee preferred extrapolation is inappropriate
  - PH assumption OAK not met
  - Not validated by additional published data or by clinical experts
  - Underestimates survival of patients

*Note: company did not provide graphs with updated curve fits in response to ACD*

# ERG comments – OS extrapolation

- Log-logistic distribution produces a long survival tail, therefore needs to be justified
- Information presented in the CS and in the company response to the ACD, does not sufficiently justify the predicted atezolizumab 5-year survival rate or the long tail predicted by the log-logistic extrapolation.
- ERG's preferred extrapolation relies on the OAK trial data and not on any speculation about plausible long-term survival rates
- ERG report shows evidence that cumulative hazards had become linear for atezolizumab and docetaxel arms in the OAK trial after week 56. So an exponential extrapolation could be applied from week 56 for both treatment arms
- Some separation in OS between atezolizumab and docetaxel appeared so different exponential curves were fitted

# Consultation comments – cure model & cure fraction

**Roche**

*Mixed cure model*

- a proportion of patients experience 'long term, sustained response to immunotherapies' and the mixed-cure model accounts for this
- Mixed cure is appropriate for immunotherapies but 'Roche appreciates the committee's preference not to proceed with this methodology.'

*Cure rate*

- 'data from the OAK trial has been analysed further, exploring the proportion of patients with durable, sustained, complete responses, which further supports a 2% cure fraction'
- 'the true long term effect of immunotherapy on NSCLC is largely unknown, beyond the 5-year OS data published by BMS at AACR in April this year which showed a 5-year OS of 16%'
- 'Roche appreciates the uncertainty of the 2% cure fraction, and the committee's preference not to proceed with this.'

# Consultation comments – end of life

**Roche**

- 'the point estimate mean overall survival benefit of atezolizumab is greater than 3 months versus nintedanib plus docetaxel in the adenocarcinoma population.'
- 'demonstrates the end of life criteria for atezolizumab versus nintedanib + docetaxel is met.'
- Mean OS of atezolizumab compared with nintedanib plus docetaxel is greater than 3 months…'8.94 months mean OS difference as predicted by the economic model'

**ERG comments**

*Comparison with docetaxel:*

- ERGs remodelled OS suggests atezolizumab generates a mean survival gain of 4.7 months vs. docetaxel. For whole trial population, suggests life expectancy is extended by more than 3 months.

*Comparison with docetaxel+nintedanib:*

- Size of survival gain uncertain
- No information presented by the company in response to ACD has changed the ERGs end of life assessment
- Compared with nintedanib plus docetaxel the size of the survival gain is uncertain. ITC network provided by company during clarification, atezolizumab (total population) nintedanib plus docetaxel (adenocarcinoma histology) shows difference in OS is not statistically significant 3.33 months (95% CI −0.16 to 6.74)
- Therefore atezolizumab does not offer an extension to life of at least 3 months compared with nintedanib.

# Company new evidence

Company provided 3 year data from poplar & 3 and 5 year data for nivolumab and pembrolizumab to support overall survival assumptions

| Data source | Treatment | 2 year OS | 3 year OS | 5 year OS |
|---|---|---|---|---|
| New base case OS: KM+log logistic | Atez | 30% | 19% | 10% |
| New scenario: KM+Gamma | Ates | 30% | 17% | 6% |
| Original company preferred OS: 2% mixed cure methodology | Atez | 32% | 21% | 12% |
| Original ERG and committee preferred OS: KM+exponential | Atez | 29% | 16% | 4% |
| POPLAR | Atez | [redacted] | [redacted] | - |
| CA209-003 | Nivolumab | 24% | 18% | 16% |
| KEYNOTE-001* | Pemb | 30% | 19% | - |
| KEYNOTE-010** | Pemb | 30% | - | - |
| Checkmate-017 (squamous) | Nivolumab | 23% | - | - |
| Checkmate-057 (non-squamous) | Nivolumab | 29% | - | - |

*Includes unknown PD-L1 status and TPS <1%

**PD-L1 expressers (TPS ≥1%) only

**ERG comments**: data from KEYNOTE-001 (pembrolizumab) and CA209-003 (nivolumab) should not be used to inform long term OS for atezolizumab because:

- Nivolumab not a relevant comparator
- Single arm trials (no comparator)
- Pembrolizumab trial data based on different population to company model
- Data presented on covers 20% of time horizon of company model (5 years out of 25)

Primary analysis showed median or atezolizumab was 16.3 months, this new data demonstrates responses are stillduration of response f ongoing.

## OAK, duration of response in the secondary population

| | Atezolizumab [redacted] | Docetaxel [redacted] |
|---|---|---|
| Patients without event, n (%) | [redacted] | [redacted] |
| Median duration of response, months (95% CI) | [redacted] | [redacted] |

Note: not adjusted for treatment switching

# Company new evidence - updated ITC

**Survival differences for new restricted network: atezolizumab (ITT), docetaxel, nintedanib+docetaxel (adenocarcinoma), and pembrolizumab (PD-L1+)**

| Network | Expected survival difference in months (95% Credible interval)* Outcome | Atez vs docetaxel | Atezolizumab vs pembrolizumab | Atez vs docetaxel & nintedanib |
|---|---|---|---|---|
| New restricted | OS | 5.90 (3.57 to 8.31) | -0.18 (-5.58 to 4.60) | 3.33 (-0.15 to 6.81) |
| | PFS | 0.78 (0.08 to 1.51) | 0.04 (-1.28 to 1.21) | -0.09 (-1.43 to 1.14) |
| New restricted (adjusted for crossover) | OS | 7.06 (4.65 to 9.62) | 1.38 (-4.33 to 6.01) | 4.67 (1.03 to 8.13) |
| | PFS | NR | NR | NR |
| | *Results came from the 'best fitting' Weibull FE FP model. Source: company response appendix 1 p14 | | | |

**ERG comments:**

- Non-equivalent populations are compared, results should be interpreted with caution.
- ERG acknowledges random effects (RE) models can be difficult to fit to small networks
- However, FE and RE results presented in ACM1 suggest statistical heterogeneity and that this impacts on the precision and therefore reliability of the ITC estimates
- ERG is unsure if the RPSFT method is valid for the additional ITC
- a range of factors influence the results from the company's ITC (choice of comparators and population selected, type of fractional polynomial [FP] model chosen and the use of FE or RE), difficult to determine 'best' model to use

# Company updated model

- Company new base-case
  - Updated PAS
  - Lifetime treatment effect
  - KM + log-logistic curve - underestimates OS compared with nivolumab data, considered conservative estimate
    - validated for clinical plausibility by mapping against the age adjusted background mortality curve
  - Corrected for ERG identified errors
- Company alternative scenarios
  - Adjusted for treatment switching in OAK trial
  - Treatment effects
    - Waning effect on treatment effect of atez after 5 years (based on melanoma) (up to time horizon 25 years) linearly decreasing effect of treatment (interpret with caution)
    - Treatment effect 5, 10, 15 and 20 years
  - Overall survival extrapolation
    - Kaplain Meier + gamma curve (2nd best statistical fit with small tail of long-term survivors)

# ERG comments on company updated model (I)

- Errors identified by ERG
  - incorrect application of discounting
    - Accepted by company
  - absence of age-dependent utility decrements
    - Company highlighted error with ERG formula, (apply to atezoluzumab when utilities are based on progression status, but model uses TTD) so company's correction does not impact the ICERs
  - incorrect use of a half-cycle correction to TTD data.
    - Company highlighted that this leads to stopping treatment with nintedanib after 6 cycles (same as docetaxel). Docetaxel is limited to 6 cycles in clinical practice however nintedanib treatment is normally continued until disease progression (and this is what occurs in the ERG corrected model).
- Waning of treatment effect
  - Likelihood, effect and mechanism of waning is unknown
  - ERG prefer to limit the duration of treatment effect of atezolizumab to 3 years (in line with TA428 pembrolizumab), to produce consistency between submissions for immunotherapy treatments in patients with NSCLC

# ERG comments on company updated model (II)

- Treatment switching:
  - Original CS stated that “crossover was considered to only make a marginal impact, hence was excluded from the economic model”. However, company has undertaken an analysis of treatment switching and included the results in an updated economic model
  - ERG unable to comment on whether the methods used to adjust OS have been applied correctly without access to patient level data. However it is unlikely that adjusting for crossover materially impacts on projected OS curves for docetaxel (as only a small percentage of patients cross over for a small period of time)
  - OS for docetaxel was 1.17 years (original model) compared to 1.188 (response to ACD), any adjustment for crossover has had a minor effect
  - the ERG has not amended the preferred extrapolation for treatment switching
  - the ERG preferred extrapolation, the predicted OS extrapolation for docetaxel was already more pessimistic (docetaxel, mean life expectancy=1.3 years) than the updated company extrapolation.

# Updated cost effectiveness results: Company and ERG analyses **vs docetaxel** (with updated atezolizumab PAS)

| Company base case | Inc. cost | Inc. QALY | ICER | Change |
|---|---|---|---|---|
| Deterministic | [redacted] | 0.6 | [redacted] | - |
| Probabilistic | [redacted] | 0.6 | [redacted] | - |
| **ERG scenario** | | | | |
| ERG corrected company base case (C1-C3) | [redacted] | 0.718 | [redacted] | |
| New company model submitted in response to the ACD | [redacted] | 0.598 | [redacted] | [redacted] |
| R2) ERG corrected original base case with ERG preferred OS for atezolizumab and docetaxel, and atezolizumab treatment duration effect set to 3 years | [redacted] | 0.302 | [redacted] | [redacted] |
| Source: Company ACD comments p40 | | | | |

Updated cost effectiveness results: Company and ERG analyses **vs nintedanib plus docetaxel** (with updated atezolizumab PAS, nintedanib list price)

| Company base case | Inc. cost | Inc. QALY | ICER | Change |
|---|---|---|---|---|
| Deterministic | [redacted] | 0.39 | [redacted] | - |
| Probabilistic | [redacted] | 0.37 | [redacted] | |
| **ERG scenario** | | | | |
| R4) ERG corrected original base case with ERG preferred OS for atezolizumab and assumed equal to OS for nintedanib+docetaxel, and treatment duration effect for both set to 3 years | [redacted] | 0.027 | [redacted] | [redacted] |
| R5) ERG preferred OS for atezolizumab, FP ITC for nintedanib+docetaxel OS and treatment duration effect for both set to 5 years | [redacted] | 0.175 | [redacted] | [redacted] |
| R6) ERG preferred OS for atezolizumab, LUME-Lung 1 HR for nintedanib+docetaxel OS and treatment duration effect for both set to 5 years | [redacted] | 0.148 | [redacted] | [redacted] |

Source: Company ACD comments p40



Note: there is a PAS for nintedanib, results including atezolizumab and nintedanib PAS will be presented in part 2 of the meeting.

# Updated company scenario analyses

| | Scenario | ICER vs docetaxel (updated atezolizumab PAS) | ICER vs nintedanib plus docetaxel (updated atez PAS, list price nintedanib) |
|---|---|---|---|
| Not adjusted for cross-over | Base case (lifetime treatment effect) | [redacted] | [redacted] |
| | Waning treatment effect (5 to 25 years) | [redacted] | [redacted] |
| | Treatment effect 5 years | [redacted] | [redacted] |
| | Treatment effect 10 years | [redacted] | [redacted] |
| | Treatment effect 15 years | [redacted] | [redacted] |
| | Treatment effect 20 years | [redacted] | [redacted] |
| Adjusted for cross-over | Lifetime | [redacted] | [redacted] |
| | Waning effect: 5-25 years | [redacted] | [redacted] |
| | 5 years | [redacted] | [redacted] |
| | 10 years | [redacted] | [redacted] |
| | 15 years | [redacted] | [redacted] |
| | 20 years | [redacted] | [redacted] |



Note: there is a PAS for nintedanib, results including atezolizumab and nintedanib PAS will be presented in part 2 of the meeting.

# Updated results: cost minimisation analysis vs pembrolizumab

- Cost minimisation analysis provided on the basis that atezolizumab and pembrolizumab are equivalent clinically.
- Company considers this a conservative approach because populations are non-equivalent there is a risk that pembrolizumab benefits are overestimated
- Original cost utility analysis model adapted to incorporate pembrolizumab costs, and remove quality of life data
- TTD data for pembrolizumab unavailable so PFS curves used and a scenario is incorporated where TTD for pembrolizumab is considered equivalent to atezolizumab.
- Acquisition cost:
  - Pembrolizumab and atezolizumab both have a PAS in place
  - Atezolizumab 1 vial per administration, pembrolizumab 3 vials per administration. No vial sharing for either.
  - Scenario analysis using MSD estimate (for pembrolizumab appraisal) where the average number of vials required per patient per cycle was 3.39

# Company cost minimisation analysis vs. pembrolizumab

- Administration:
  - Same for both products: IV infusion every three weeks
- Adverse events cost:
  - No adverse events with an incidence of ≥2% were identified in either treatment arm; these costs were excluded from the analysis.
- PD-L1 test:
  - Cost of PD-L1 testing is included for pembrolizumab only
  - Cost per eligible patient calculated by proportion of patients who would be eligible for treatment. The total cost per eligible patient was estimated at £337.51
- Stopping rule:
  - Pembrolizumab has a two year clinical stopping rule so all acquisition and administration costs are stopped after two years.

**ERG comments**:

- cost-minimisation results presented in the company response to the ACD of limited value to decision makers.
- analysis is not robust as the populations of the trials included in the NMA are not the same and the confidence intervals around the OS hazard ratio between the two treatments are wide.
- Even if trials are comparable, the different MOAs cast doubt over whether efficacy remains equivalent over remaining 23 year model time horizon

## CMA Base case results (atez PAS price, pembrolizumab list price)

| | | Atezolizumab | Pembrolizumab | Increment | % abs inc |
|---|---|---|---|---|---|
| **Mean costs in PFS/On treatment** | Treatment cost | [redacted] | £37,367 | [redacted] | [redacted] |
| | Diagnostic cost | £0 | £338 | -£338 | [redacted] |
| | Drug administration | £2,426 | £1,884 | £542 | [redacted] |
| | Adverse events | £0 | £0 | £0 | [redacted] |
| | Supportive care | £9,919 | £8,226 | £1,693 | [redacted] |
| **Total costs in PFS/On treatment** | | [redacted] | £47,815 | [redacted] | [redacted] |
| **Mean costs in PD/Off treatment** | Supportive care | £9,022 | £9,924 | -£903 | [redacted] |
| | Subsequent therapy cost | £3,289 | £3,308 | -£20 | [redacted] |
| **Total costs in PD/Off treatment** | | £12,310 | £13,233 | -£923 | [redacted] |
| **Total costs** | | [redacted] | £61,048 | [redacted] | 100% |

## Scenario analyses (atez PAS price, pembrolizumab list price)

| Scenario | Total cost atez | Total cost pemb | Inc. | % abs inc. |
|---|---|---|---|---|
| MSD dosing assumption for pemb (3.39 vials per patient per cycle) | [redacted] | £65,861 | [redacted] | 100% |
| TTD for pembrolizumab is considered equivalent to atezolizumab | [redacted] | £66,919 | [redacted] | 100% |



Note: there is a PAS for atezolizumab and pembrolizumab, results including both PAS' will be presented in part 2 of the meeting.

# Company's new modelling

| | Adjustment | Match committee's preference? | ERG comments |
|---|---|---|---|
| **Comparators** | Cost minimisation analysis for pembrolizumab | Partially – comparison provided for all-comers (atez) vs PD-L1 positive (pembrolizumab) requested CEA | - |
| **PD-L1 subgroup** | No PD-L1 analysis by subgroup provided | Not provided | - |
| **Extrapolation** | KM data and extrapolation using log-logistic model | Partially | Prefer KM and extrapolation using exponential |
| **Model corrections** | As per ERG corrections<br>Modified ERG approach for C2 and C3 | Yes | Company made some slight adjustments to corrections, do not impact greatly on ICER |
| **Cure model** | Cure model not implemented | Yes | - |
| **Treatment effect** | Base case uses lifetime treatment effect. Scenarios presented: waning effect and 5, 10, 15 & 20 years | No evidence presented on which to agree clinically plausible scenario | Prefer 3 year continued effect after stopping treatment |
| **Network meta analysis** | Reduced network using relevant comparators, fixed effects model | Partially – preferred random effects model | Difficult to identify 'best' model, statistical heterogeneity between model choices impacts on precision and reliability of results |

# Key issues for consideration

- What is the most plausible method for overall survival extrapolation?
- Duration of treatment effect
  - Is it appropriate to apply a waning treatment effect to atezolziumab?
  - What is the most plausible duration of treatment effect after stopping atezolizumab. Is there a need for a stopping rule?
- What is the risk of making a recommendation for the all-comers population considering all of the relevant comparators (docetaxel, nintedanib plus docetaxel and pembrolizumab) and:
  - the clinical subgroup data by PD-L1 status
  - the absence of cost-effectiveness subgroup analyses by PD-L1 status?
- Does atezolizumab have similar or improved clinical efficacy to pembrolizumab based on the ITC? Is the evidence robust? Are the cost minimisation analyses provided for all-comers (atezolizumab) vs PD-L1 positive (pembrolizumab) suitable for decision making?
- What is the most plausible ICER with revised proposed PAS for nivolumab vs docetaxel?
- What is the most plausible ICER with revised proposed PAS for nivolumab vs nintedanib?
- Is the end of life criterion of 3 month life extension met for atezolizumab compared with nintedanib plus docetaxel?