**NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE**

**SINGLE TECHNOLOGY APPRAISAL**

# Atezolizumab for treating non-small-cell lung cancer after platinum-based chemotherapy [ID970]

The following documents are made available to the consultees and commentators:

1. **Response to consultee, commentator and public comments on the Appraisal Consultation Document (ACD)**

2. **Consultee and commentator comments on the Appraisal Consultation Document 2** from:
   - Roche (company)
   - National Cancer Research Institute – Associations of Cancer Physicians – Royal College of Physicians – Royal College of Radiologists - *joint response endorsed by Dr Yvonne Summers – clinical expert*

   *'No comment' response from Department of Health*

3. **Comments on the Appraisal Consultation Document from experts:** Dr Yvonne Summers – Clinical Expert, nominated by Royal College of Physicians

4. **Comments on the Appraisal Consultation Document 2 received through the NICE website**

5. **Appendix of new evidence** – submitted by Roche

6. **New evidence requested by NICE** – submitted by Roche

7. **Evidence Review Group critique of company comments and new evidence** – prepared by Liverpool Reviews & Implementation Group (LRiG)

*Any information supplied to NICE which has been marked as confidential, has been redacted. All personal information has also been redacted.*

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

### Single Technology Appraisal

## Response to consultee, commentator and public comments on the Appraisal Consultation Document (ACD)

**Type of stakeholder:**

**Consultees –** Organisations that accept an invitation to participate in the appraisal including the companies, national professional organisations, national patient organisations, the Department of Health and the Welsh Government and relevant NHS organisations in England. Consultees can make a submission and participate in the consultation on the appraisal consultation document (ACD; if produced). All non-company consultees can nominate clinical experts and/or patient experts to verbally present their personal views to the Appraisal Committee. Company consultees can also nominate clinical experts. Representatives from NHS England and clinical commissioning groups invited to participate in the appraisal may also attend the Appraisal Committee as NHS commissioning experts. All consultees have the opportunity to consider an appeal against the final recommendations, or report any factual errors, within the final appraisal determination (FAD).

**Clinical and patient experts and NHS commissioning experts** – The Chair of the Appraisal Committee and the NICE project team select clinical experts and patient experts from nominations by consultees and commentators. They attend the Appraisal Committee meeting as individuals to answer questions to help clarify issues about the submitted evidence and to provide their views and experiences of the technology and/or condition. Before they attend the meeting, all experts must either submit a written statement (using a template) or indicate they agree with the submission made by their nominating organisation..

**Commentators –** Commentators can participate in the consultation on the ACD (if produced), but NICE does not ask them to make any submission for the appraisal. Non-company commentator organisations can nominate clinical experts and patient experts to verbally present their personal views to the Appraisal Committee. Commentator organisations representing relevant comparator technology companies can also nominate clinical experts. These organisations receive the FAD and have opportunity to report any factual errors. These organisations include comparator technology companies, Healthcare Improvement Scotland any relevant National Collaborating Centre (a group commissioned by NICE to develop clinical guidelines), other related research groups where appropriate (for example, the Medical Research Council and National Cancer Research Institute); other groups such as the NHS Confederation, the NHS Commercial Medicines Unit, the Scottish Medicines Consortium, the Medicines and Healthcare Products Regulatory Agency, the Department of Health, Social Services and Public Safety for Northern Ireland).

**Public –** Members of the public have the opportunity to comment on the ACD when it is posted on the Institute's web site 5 days after it is sent to consultees and commentators. These comments are usually presented to the appraisal committee in full, but NICE reserves the right to summarise and edit comments received during consultations, or not to publish them at all, where in the reasonable opinion of NICE, the comments are voluminous, publication would be unlawful or publication would be otherwise inappropriate.

**Please note:** Comments received in the course of consultations carried out by NICE 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 submissions that NICE has received, and are not endorsed by NICE, its officers or advisory committees.

| Comment number | Type of stakeholder | Organisation name | Stakeholder comment<br>Please insert each new comment in a new row | NICE Response<br>Please respond to each comment |
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| 1 | Company | Roche Products Ltd; hereinafter "Roche" | Roche remain disappointed with the second provisional negative recommendation.<br><br>Based on our reading of the ACD, the key concerns underpinning the draft negative recommendation are around the following points:<br>• The true long term survival of current chemotherapy and future immunotherapies<br>• Implementation of a 2 year stopping rule<br>• Uncertainty in the indirect treatment analysis (ITC) resulting in:<br>o the comparison to pembrolizumab being excluded, and<br>o end of life criteria questioned versus nintedanib + docetaxel<br>• Lack of subgroup analysis<br><br>In addition, there are some further inferences that we feel should be highlighted:<br>• Dismissal of clinical expert opinion regarding:<br>o overall survival estimates of atezolizumab and docetaxel, and<br>o nintedanib + docetaxel as a relevant comparator<br>• Uncertainty regarding the duration of treatment effect<br>• Use of cross-over adjustment to demonstrate the true relative efficacy of atezolizumab<br><br>Our full response is provided below and addresses in turn each of the above mentioned key points underpinning the draft negative recommendation and additional analyses to support a reversal of this preliminary negative recommendation. | Comment noted. At the third appraisal committee meeting all these points were addressed. The committee also recalled the clinical expert to the meeting to address the uncertainties highlighted in the consultation comments. |
| 2 | Company | Roche | **Overall survival predictions**<br><br>The ACD states:<br><br>*"The committee concluded that the log-logistic curve produced implausibly optimistic long-term survival outcomes at 5 years (10% alive). The ERG's preferred method was to use Kaplan–Meier data up to 19 months and then extrapolate using an exponential curve, which was the best fit visually for the trial data after 19 months. The committee considered that this also produced optimistic long-term survival outcomes at 5 years (4% alive) but that these were* | Comment noted. At the third appraisal committee meeting, the committee discussed the overall survival predictions. The committee accepted that overall survival at 5 years is likely to be similar to that predicted for other |

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| | | | *clinically plausible."*<br><br>Roche acknowledge that extrapolation of overall survival (OS) poses an ongoing challenge in the evaluation of immunotherapies. Roche carefully considered NICE's guide to methods in developing a response, and would like to draw attention to the advice on survival extrapolation in Section 5.7.7: "[When evaluating external validity] it is important to consider the clinical and biological plausibility of the inferred outcome, as well as coherence with external data sources such as historical data sets or other relevant clinical trials" (National Institute for Health and Care Excellence, 2013).<br><br>Availability of evidence from other relevant clinical trials can be utilised to minimise the uncertainty associated with immunotherapies, and natural history data are available and can be utilised for patients treated with standard chemotherapy. Roche would like to emphasise to the committee that the use of a Kaplan-Meier plus exponential distribution results in a corresponding docetaxel survival estimate of a maximum 1.2% of patients alive at 5 years, and 4% of patients alive at 5 years for atezolizumab.<br><br>This assumption cannot be deemed as externally valid, as it results in lower values than any of the estimates from:<br>• The evidence base available describing outcomes for locally advanced and metastatic NSCLC patients on docetaxel:<br>o Docetaxel estimates from recent RCT data (3 year OS: 6-10%)<br>o Available natural history data sources (NLCA, SEER and FlatIron) (5 year OS: 3-7%)<br>• The evidence base available describing outcomes for locally advanced and metastatic NSCLC patients on immunotherapy:<br>o Atezolizumab RCT data from POPLAR (3 year OS: 19%)<br>o Other relevant immunotherapy trial data from the KEYNOTE and CheckMate NSCLC studies (5 year OS: 16%)<br>• Expert opinion from lung cancer clinical experts (10%)<br><br>In addition, these estimates are inconsistent with:<br>• The committee's briefing document for this appraisal, which suggests a 10% OS in locally advanced / metastatic patients at 5 years (slide 3, (Excellence, 2017))<br>• The committee-accepted assumptions in the appraisal of pembrolizumab (National Institute for Health and Care Excellence, 2016)<br>• The mechanism of action (MOA) for checkpoint inhibitor immunotherapies | immunotherapies. The committee therefore concluded that the Kaplan–Meier data with a log-logistic curve was appropriate for decision-making purposes. Section 3.12 of the FAD has been updated to reflect this. |

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| | | | **External validity of survival modelling**<br><br>***Expert clinical opinion and MOA***<br>As previously highlighted to the Committee, Roche sought the advice of 10 lung cancer experts on the validity of survival extrapolation. Clinical experts, who are best positioned to validate statistical modelling based on their vast experience in the area, have consistently agreed across this and the previous appraisal for pembrolizumab that the survival estimates following the Kaplan-Meier plus log-logistic approach are clinically plausible, appropriate and representative of the anticipated benefit of immunotherapies in this disease area.<br><br>In addition to clinical plausibility, clinical experts also agreed with the pharmacodynamic plausibility of this assumption. The mechanism of action of the PD-1 and PD-L1 checkpoint inhibitors, including atezolizumab, is very different from that of chemotherapy, which results in very different efficacy and safety outcomes. One key example of this is the duration of response: the latest data from the OAK trial shows that the median duration of response is now 23.9 months compared to 6.3 months with docetaxel. This is consistent with the phase II POPLAR data, where atezolizumab duration of response is currently at 22.3 months (range: 2.9 – 38.7+), and still increasing with follow up, versus 7.2 months (range: 1.5 to 15.4) for docetaxel. Such data demonstrates that checkpoint inhibitor immunotherapy cannot be treated in the same way as chemotherapy with respect to extrapolation of outcomes. This is now widely understood and accepted. Long term survival benefits of immunotherapy have already been observed in melanoma, and is now also being translated into and witnessed in NSCLC. As such, a KM+exponential extrapolation of survival, traditionally appropriate for chemotherapy, is not sufficient in capturing the long term benefits of atezolizumab: as witnessed by the ERG's extrapolation under-predicting survival even at 3 years in comparison with POPLAR.<br><br>***Relevant clinical trial evidence for atezolizumab and other immunotherapies***<br>Although the economic model utilises the Phase III OAK study, Roche are concerned that additional RCT evidence for atezolizumab have been disregarded by the committee. It would also appear that evidence from other relevant immunotherapy trials has been disregarded, despite input from clinical experts confirming that the medicines result in similar outcomes from a clinical and biological perspective.<br><br>In our previous response to ACD, academic in confidence survival figures from the phase II POPLAR trial were provided demonstrating the ERG-preferred extrapolation underestimated the value of atezolizumab. In addition, long term survival estimates from other anti-PD-1 immunotherapies (deemed by the lung cancer clinical community as generalizable to atezolizumab in terms of mode of action, efficacy, safety and long term outcomes) were | |

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| | | | provided. The POPLAR data highlight 1-, 2- and 3-year survival which is consistent with the previous immunotherapy studies, reflecting the similarity in the core mode of action of atezolizumab with pembrolizumab and nivolumab (see Appendix 1 for an updated summary). These data represent the best available evidence for external validation of survival modelling methods, yet appear to have been disregarded in favour of non-clinical opinion of visual fit of the preferred distribution, at an arbitrary time point. As well as undervaluing the potential outcomes achievable with atezolizumab, we believe that this also significantly undervalues the outcomes currently achieved with routine care within the NHS, across the time horizon.<br><br>***Natural history datasets***<br>The Committee will be aware that Roche evaluated the validity of survival extrapolation methods alongside external natural history data sources from the National Lung Cancer Audit (Beckett P et al., 2013). Two analyses are available from point of diagnosis: Stage IV metastatic patients and Stage IIIB/IV patients who are eligible for chemotherapy, which more closely aligns with the population under consideration for treatment with atezolizumab. Survival at 5 years for the Stage IV group was **3%,** while survival in the IIIB/IV cohort was **7%.**<br><br>The longitudinal National Cancer Institute's SEER (Surveillance, Epidemiology and End Results) dataset provides corroborative evidence: a 2014 analysis for patients with distant metastases (Stage IV) showed a five-year overall survival of 5.2%; an estimate for "regional" disease is published but is likely to include earlier stage patients (32.3%) (EJ; Cronin KA (eds),, 2014).<br><br>In order to provide accurate estimates for the population under review, i.e. previously-treated patients receiving docetaxel for Stage IIIB/IV NSCLC, Roche conducted an analysis using an additional evidence source: the United States Flatiron Database, which contains electronic health record information of over 2 million cancer patients. Eligible patients treated with docetaxel between January 1st 2011 and March 31st 2017 were included. (Full details of the database and methods used are described in Appendix 2). Results were consistent with the NLCA and SEER published estimates: **3.7%** of pre-treated patients survived for 5 years (including 15% of patients with subsequent immunotherapies, thus some confounding). This data aligns more closely with Roche's preferred method of survival extrapolation and are underestimated by the Committee-preferred method.<br><br>**Inconsistency with previous Committee assumptions and decisions**<br><br>***Committee briefing document***<br>We would like to highlight to the committee that the use of these survival extrapolations in fact | |

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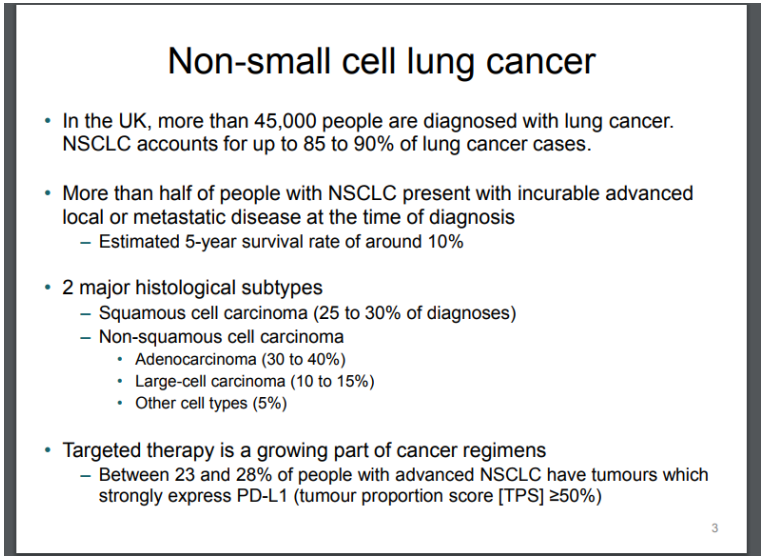
| | | | also contradict NICE's internal estimates of long term survival, as depicted in slide 3 of the briefing document. This has been included below for reference.<br><br>  <br><br><br>***Precedent in the appraisal of pembrolizumab***<br>As mentioned in the final appraisal determination for pembrolizumab, after incorporating the March 2016 data cut, 9.6% of patients in the pembrolizumab arm were anticipated to be alive at 5 years. This value already included a 'waning of treatment effect' and had been deemed reasonable from consultation comments from clinical experts. Whilst the committee could not agree on a single clinically plausible scenario, any treatment waning scenario earlier than from year 10 onwards which reduced this 5 year OS estimate was not cost effective (see Table 4 of company response to ACD dated 24th October 2016 – also included in Appendix 3). As such, only under assumptions whereby 5 year OS estimates for pembrolizumab were approximately 10% (rounding up), was this product deemed a cost effective option and therefore recommended for use. Where atezolizumab has demonstrated at least non-inferiority to this comparator, precedence and a consistent approach would confirm that the Roche extrapolation is a suitable analysis for decision making. Artificially manipulating the survival projection downwards by choosing a survival extrapolation that goes against the available evidence is not reasonable and not best practice. | |

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| | | | In conclusion, Roche would like to highlight that none of the available evidence results in survival estimates as low as 1.2% for docetaxel patients, nor suggest that immunotherapy overall survival is likely to be as low as 4%. It is important to reiterate that the estimate of 5-year overall survival deemed clinically plausible by clinical experts with decades of experience in the field and by the Committee when evaluating pembrolizumab in the same indication, is significantly higher than that currently used in this appraisal. Roche strongly believe that the available evidence summarised above provides extensive validation of the estimates derived from the Kaplan-Meier plus log-logistic survival distribution. | |
| 3 | Company | Roche | **Implementation of a 2-year stopping rule**<br><br>The ACD states:<br><br>*"The committee heard from the company that there was an ongoing study investigating the effect of a 1-year maximum treatment length, the interim results of which showed that patients who discontinued therapy after 1 year had statistically significantly worse progression-free survival than those who continued therapy until they no longer benefited clinically … The committee heard from the Cancer Drugs Fund clinical lead that the long-term consequences of stopping treatment are unknown, but clinical experience of immunotherapies in other indications suggests that significant treatment-related toxicities may occur while the disease is still responding. There is growing concern among clinicians about the use of immunotherapies beyond 2 years … The Cancer Drugs Fund clinical lead clarified that a 2-year stopping rule is acceptable to both patients and clinicians, and would be implementable. Having determined this, the committee concluded that it would have liked to have seen a 2-year stopping rule applied in the economic model"*.<br><br>Roche acknowledges that such a stopping rule could improve the cost effectiveness of atezolizumab. However, such a rule makes a marginal difference in the ICER, as demonstrated in Appendix 4.<br><br>Roche believes that a recommendation based on an arbitrary stopping rule is unreasonable in light of evidence submitted and will not be acceptable to patients and clinicians, given the new evidence now available.<br><br>Results from CheckMate 153, a randomised trial exploring the impact of continuous versus 1-year fixed duration of an immunotherapy in patients with advanced NSCLC, were presented at the ESMO congress in September 2017. These data demonstrated that patients who stopped treatment had a statistically significant higher risk of progressing (HR: 0.42 [95% CI: 0.25, 0.71]), and a numerically higher risk of dying (HR: 0.63 [95% CI: 0.33, 1.20]) (Spigel D, 2017) | Comment noted. At the third appraisal committee meeting, the committee discussed the company's evidence for not applying a 2-year stopping rule. The committee was aware that there is growing concern among clinicians about the use of immunotherapies beyond 2 years and that other immunotherapy treatments for previously treated NSCLC (pembrolizumab and nivolumab) include 2-year stopping rules. The committee concluded that it prefers a 2-year stopping rule applied in the economic model. Section 3.13 of the FAD has been updated to reflect this. |

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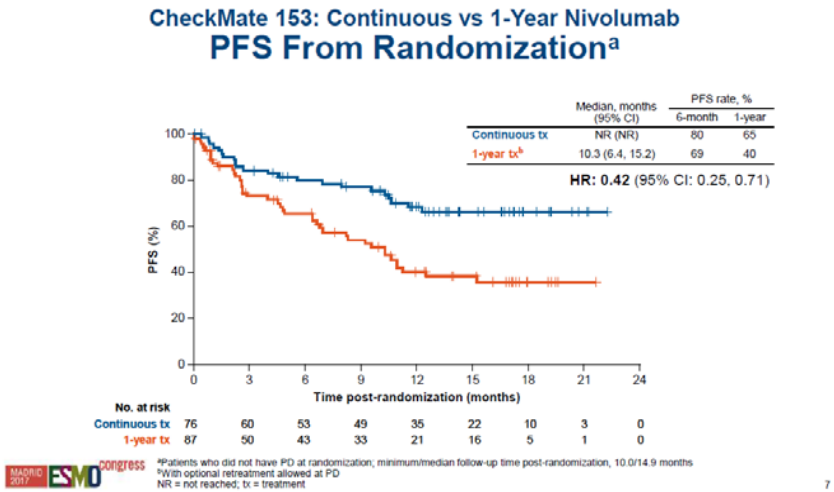
| | | | (see Appendix 4, and diagram below). Since this data were published, there has been growing concerns among the clinical community regarding a stopping rule that has shown a detrimental effect on patients.<br><br>  <br><br><br>Previous NICE recommendations on stopping rules for other immunotherapies were made before this evidence became available, thus was considered a reasonable approach. However, now the CheckMate evidence is available, Roche are concerned NICE is disregarding available new information and the hierarchy of evidence to impose such a stopping rule. Regarding potential future “significant treatment-related toxicities”, Roche would like to highlight atezolizumab’s stopping rules already account for these, as listed in the SmPC: “until loss of clinical benefit or **unmanageable toxicity**.” Discontinuation should be dealt with case by case by clinicians who are best positioned to decide when to discontinue treatment and if toxicities outweigh the benefits.<br>Roche have ensured the Patient Access Scheme (PAS) provided to the NHS accounts for the long term budget concerns.<br><br>To conclude, a stopping rule is not in the best interests of patients, the NHS and is unreasonable in light of published RCT evidence. | |
| 4 | Company | Roche | **Indirect treatment analysis**<br><br>The ACD states: | Comment noted. The committee agreed to use the company’s updated |

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| | | | "*The ERG noted that the heterogeneity was such that atezolizumab may not increase overall survival compared with nintedanib plus docetaxel. The analysis estimated a difference in overall survival for atezolizumab (whole population) compared with nintedanib plus docetaxel (in people with adenocarcinoma) of 3.33 months (95% CI -0.15 to 6.81) … The indirect treatment comparison estimated a difference in overall survival for atezolizumab (whole population) compared with pembrolizumab (PD-L1 expression ≥1%) of –0.18 months (95% CI –5.58 to 4.60) … The committee agreed to use the company's updated network, but noted the uncertainty associated with all the indirect analyses. It could not conclude with any certainty that atezolizumab is clinically equivalent to pembrolizumab."*<br><br>As such, the committee preferred assumptions were to disregard the comparison with pembrolizumab, and conclude atezolizumab does not provide >3 months extension to life over nintedanib + doctetaxel, and therefore the end of life criteria were not met.<br><br>As highlighted in our response to the first ACD, we recognise there is uncertainty in the network driven by the inconsistent populations and thus a potential overestimation of benefit of nintedanib + docetaxel. Nevertheless, as highlighted by clinical experts, real world usage of nintedanib + docetaxel is minimal, thus should not be considered an appropriate comparator: docetaxel and pembrolizumab are the appropriate comparators for decision making purposes in this appraisal.<br><br>With regard to the comparison to pembrolizumab, Roche are disappointed the committee did not consider this comparison further and remain confident it demonstrates atezolizumab as at least non-inferior to pembrolizumab and likely cost saving to the NHS. Nevertheless, Roche are reassured by the statement in the ACD: "*The committee concluded that a comparison in people with PD-L1-positive NSCLC as defined by the tests would be appropriate, given that there was likely overlap in the patients identified*", demonstrating NICE would be willing to utilise an indirect comparison in the equivalent populations, even if it is anticipated to have limited difference given the efficacy across subgroups for atezolizumab. | network, but noted that there is uncertainty associated with all the indirect analyses. The committee concluded that the data suggests atezolizumab is clinically equivalent to pembrolizumab. Section 3.9 of the FAD has been updated to reflect this. |
| 5 | Company | Roche | **Subgroup analysis**<br><br>The ACD states:<br><br>*"The marketing authorisation for atezolizumab is for adults with locally advanced or metastatic NSCLC after chemotherapy, and after chemotherapy and targeted treatment in people with EGFR- or ALK-positive tumours; it does not specify treatment based on PD-L1 expression … Comments from consultation stated that it was inappropriate to make a recommendation based* | Comments noted. The committee accepted the company's economic models for the subgroup analyses by PD-L1 expression.<br><br>The committee agreed that |

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| | | | *on PD-L1 expression because PD-L1 is not a perfect biomarker and atezolizumab has shown benefit regardless of PD-L1 expression. Nevertheless, although PD-L1 is not a perfect biomarker, the committee considered it to be a reasonable guide as to those who may benefit from targeted treatment. Consequently, it was disappointed that the company did not present clinical and cost-effectiveness results for all of the relevant PD-L1 subgroups (including TC3 or IC3 and TC2/3 or IC 2/3)"*<br><br>As also highlighted in the ACD: "*any cost-effectiveness estimates by PD-L1 subgroup would be even more uncertain than the estimates for the whole population because atezolizumab has shown benefit in people with both PD-L1-positive and PD-L1-negative tumours."*<br><br>Roche recognises the benefit of atezolizumab increases as the level of PD-L1 expression increases. However, similarly, it is unethical to restrict access only to these patients, when atezolizumab has demonstrated a statistically significant and clinically meaningful improvement in OS for the low and negative PD-L1 expressors, of a similar order to that delivered by immunotherapies already approved for PDL-1 positive patients. The low and negative PD-L1 expressors are the population with the greatest unmet need in current practice. Roche encourage the committee to consider any clinical rationale for not providing access for these patients, especially in consideration of NICE's commitment to advancing equality of opportunity.<br><br>In this response to ACD, Roche has provided full clinical results of all subgroups of interest for the committee to consider (please see Appendix 5). As these data show, atezolizumab has demonstrated statistically significant results, irrespective of PD-L1 expression. In addition, the confidence intervals for each subgroup overlap, demonstrating each subgroup could be considered as equally benefitting from treatment.<br><br>In addition, Roche has also provided economic results for the following subgroups:<br>• PD-L1 positive (TC/IC 1/2/3)<br>• PD-L1 low, negative or unidentifiable expression (TC/IC 0)<br>• All-comers, as based on our marketing authorisation<br><br>Roche appreciates the committee's eagerness to see cost-effectiveness in the high expressors (TC/IC 3); however the OAK primary data cut was not statistically powered for the TC/IC 3 subgroup, and as a result the patient numbers are small, and confidence intervals (CI) large. Based on the OAK data, patients with high expression may benefit more from treatment with atezolizumab, compared to low expressors, but the additional benefit is uncertain, and could overlap with the benefit seen in other groups (see CI of all subgroups below) (Barlesi F et al., 2016). | results of the OAK trial show atezolizumab is more effective than docetaxel regardless of PD-L1 expression however the trial did not include pembrolizumab (the appropriate comparator for the majority of patients recruited). The committee concluded that the full trial population is not suitable for decision making. This has been updated in section 3.6 of the FAD.<br><br>The committee heard from Cancer Drugs Fund clinical lead and the clinical expert at the third committee meeting that nintedanib plus docetaxel (in the adenocarcinoma population only) is considered a relevant treatments in people whose disease does not express PD-L1. Comments received during the first and second consultation stated that nintedanib plus docetaxel is only used for a small number of people in clinical practice, which the committee accepted. See section 3.2 of the FAD. |

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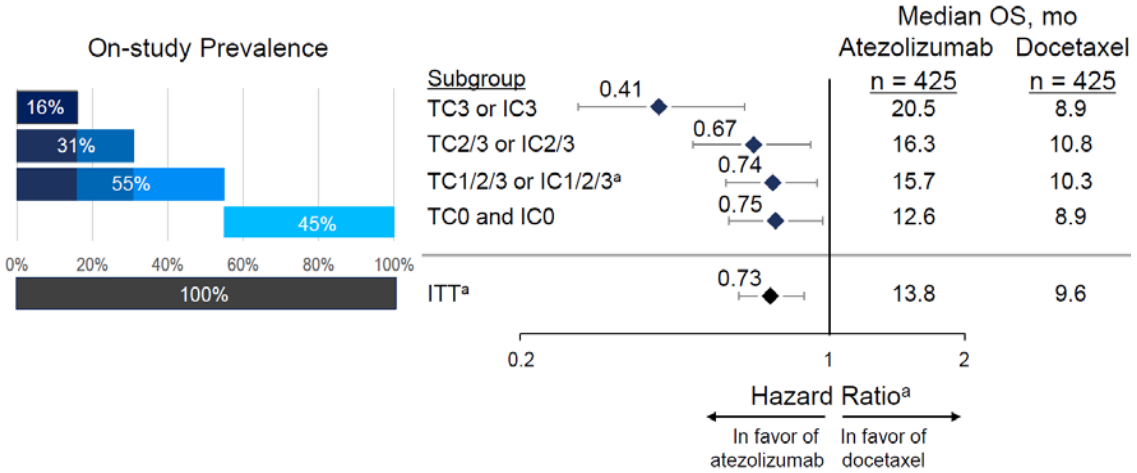
| | | |  <br>We would also highlight that the TC/IC 3 and TC/IC 1/2/3 results are in line with other immunotherapies, as demonstrated in the ITCs provided (Appendix 6). Other immunotherapies have been recommended for funding in a wider population (TC/IC 1/2/3, >1% TPS) despite similar efficacy gains in the highest expressors (Herbst et al., 2016, National Institute for Health and Care Excellence, 2016). The ITC provided in these high expressors, we hope, will encourage NICE to focus on the more complete and appropriately powered subgroups and ITT, including where the unmet need currently is: the patients with no or low PD-L1 expression who currently have no access to immunotherapy, yet who receive essentially the same benefit from atezolizumab as those with higher levels of PD-L1 that currently have access to immunotherapies.<br><br>As discussed above, due to the limited real world usage of nintedanib+docetaxel, Roche do not believe it is an appropriate comparator in the ITT population. Thus is further emphasised in the subgroup analyses due to heterogeneity in the study populations. As discussed by the committee in the appraisal of pembrolizumab (National Institute for Health and Care Excellence, 2016), the LUME-LUNG 1 trial did not assess PD-L1 expression. Therefore, the committee concluded that the trial populations were too different, thus an indirect treatment comparison was not appropriate for decision-making. The same is true for the appraisal of atezolizumab. Therefore, this comparison is not provided for either the PD-L1 positive or negative subgroups.<br><br>***PD-L1 positive (TC/IC 1/2/3)***<br>For the PD-L1 positive (TC/IC 1/2/3) patients, there are two appropriate comparators: docetaxel, | |

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| | | | and pembrolizumab (>1% TPS). As such, an ITC was conducted (see Appendix 6). As NICE were hesitant to accept "equivalence" or "non-inferiority" statements in the previous analysis, a CEA has been conducted for both comparators.<br>As agreed with NICE, results of this analysis will be provided by 3rd November (Appendix 9).<br><br>***PD-L1 low and negative (TC/IC 0)***<br>Regarding the low and negative expressors, for whom pembrolizumab is not an appropriate comparator, a cost effectiveness analysis versus docetaxel is provided. As docetaxel is the only comparator, and was also the comparator in the OAK trial, only the OAK data is utilised.<br>See Appendix 7 for full results of this analysis.<br><br>***All-comer population***<br>We reiterate, the all-comer population should be deemed as the appropriate population to base decision making on. Therefore, results utilising the all-comer population are presented in Appendix 8. In addition, a comparison of all populations will be provided by 3rd November in Appendix 10.<br><br>Atezolizumab is the only immunotherapy to have demonstrated statistically significant benefit, irrespective of PDL1 expression. Patients who identify as PD-L1 positive, even at the lowest level of expression (>1% TPS, TC/IC 1/2/3) currently have immunotherapy treatment options available to them (pembrolizumab and nivolumab). Conversely, except for a small proportion of squamous patients, patients with low positivity or negative expression have no immunotherapy option available and thus are a population with clear unmet need, which atezolizumab is able to meet. | |
| 6 | Company | Roche | **Consideration of clinical expert opinion**<br><br>The clinical expert community (BTOG-NCRI-ACP-RCP-RCR) have actively contributed to this appraisal, either through consulting with Roche to validate the economic model inputs, attendance at the committee meetings or in responding to the ACDs.<br><br>As experts in this field, they have provided their view on the value of immunotherapies and the treatment pathway as it stands currently. Most importantly, they have also examined and scrutinised the predicted survival resulting from both the ERG's and Roche's extrapolation.<br><br>The process guide states "the processes are designed to produce robust guidance for the NHS with appropriate contribution from stakeholders". We ask the Committee to demonstrate the value clinical experts contribute to the NICE process, by considering their point of view also in this appraisal, particularly on OS extrapolation, where clinical experts are best positioned to | Comments noted. The committee have fully considered all comments made by clinical experts, consultees, commentators and the public at both the ACD 1 and ACD 2 consultation. All comments have been considered by the committee in accordance with section 6 of the NICE guide to the methods of technology appraisal. |

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| | | | validate statistical modelling based on their vast experience in the area. In a situation where limited follow-up results in uncertainty over long-term outcomes it is important that the interpretation of extrapolation is informed by the experience of clinical experts both with lung cancer and immunotherapy experience | At the third appraisal committee meeting the committee recalled the clinical expert to discuss the clinical issues raised at the second appraisal consultation. The committee discussed the overall survival predictions and accepted that overall survival at 5 years is likely to be similar to that predicted for other immunotherapies. See response to section 3.12 of the FAD. |
| 7 | Company | Roche | **Duration of treatment effect**<br><br>The ACD states:<br><br>*"The company explained that atezolizumab's mechanism of action suggests that its effects on tumours would continue after treatment stopped. The committee considered this assumption to be biologically plausible, but it was concerned about the lack of evidence to support this. The committee considered that the treatment effect was unlikely to last more than 5 years after treatment had stopped. It concluded that although it was biologically plausible for treatment effects to continue after stopping treatment, the length of any continued effect was uncertain."*<br><br>Roche appreciates the uncertainty regarding the long term duration of treatment effect for immunotherapies and it acknowledges that the Committee routinely takes decisions in situations of uncertainty. As demonstrated in the results accompanying Roche's response to the first ACD, atezolizumab is cost effective in all duration-of-treatment effect scenarios.<br><br>However, we would like to highlight that such a cap on duration-of-treatment effect is in contrast to a potential 2 year stopping rule. We would encourage NICE to take a pragmatic approach by allowing patients to fully benefit from immunotherapies and not implementing a stopping rule. If a stance is taken on capping duration of treatment effect, it is perverse to then encourage patients to discontinue treatment at 2 years and, vice versa, if treatment benefit is not capped | Comment noted. The committee considered the company's comments however it reiterated its conclusion from the second ACD that the treatment effect was unlikely to last more than 5 years after treatment had stopped. And that although it was biologically plausible for treatment effects to continue after stopping treatment, the length of any continued effect was uncertain. See section 3.12 of the FAD. |

| Comment number | Type of stakeholder | Organisation name | Stakeholder comment<br>Please insert each new comment in a new row | NICE Response<br>Please respond to each comment |
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| | | | an increased impact on overall survival is to be expected on the long term, compared to chemotherapy. | |
| 8 | Company | Roche | **Use of cross-over adjustment**<br><br>The ACD states:<br><br>*"In response to consultation, the company provided analyses that adjusted for this subsequent treatment. These analyses used the rank-preserving structural failure time method, which the ERG stated was not suitable for adjusting for subsequent therapies (it is normally used to adjust for treatment crossover). Therefore the committee agreed that it would use the estimates from the unadjusted trial data."*<br><br>In Roche's response to the previous ACD, full cost effectiveness results adjusting for treatment switching in the OAK trial were provided. As detailed in the original submission, 5% of patients randomized to atezolizumab and 17% of patients in the docetaxel arm went on to receive subsequent cancer immunotherapies. By not adjusting for treatment switching, Roche were taking a conservative estimate of the OS benefit of atezolizumab, and thus the cost effectiveness. This is in contrast with the approach taken by other appraisals, including pembrolizumab. Thus, the analysis was presented for transparency and clarity purposes for the committee.<br><br>The rank-preserving structural failure time (RPSFT) method was used and previously accepted by the NICE committee as an appropriate method in the appraisal of pembrolizumab (National Institute for Health and Care Excellence, 2016). In the pembrolizumab clinical trial, similarly to OAK, cross-over was not permitted, but patients switched to other immunotherapies. Given the subsequent therapies received were "similar" to pembrolizumab, it was deemed the RPSFT method could be used for adjusting for subsequent therapies – not just treatment crossover, as it is normally used for. In this precedent, the RPSFT method was endorsed for treatment switching by the Committee. A consistent approach would confirm that this is a suitable analysis for decision making. | Comment noted. The committee was aware that in NICE technology appraisal guidance on pembrolizumab the preferred method for adjusting for the effects of crossover was the 2-stage adjustment method not the rank-preserving structural failure time. Therefore the committee agreed that it would use the estimates from the unadjusted trial data. Section 3.5 of the FAD has been updated. |
| 10 | Clinical expert | The Christie Hospital NHS Trust & University Hospital South Manchester | In response to the negative ACD2 for Atezolizumab in NSCLC, I would make the following comment.<br>With regard to the committee's comments on overall survival with atezolizumab, the committee has heard from a number of experts that there is little to distinguish between the PD-1/PD-L1 inhibitors in terms of safety and efficac; this view appears to have been accepted in the absence of head to head data. However, in reviewing the estimates of longer term survival used for modelling, it has chosen to disregard the previously discussed 3 and 5 year survival data for pembrolizumab and nivolumab (see previous response) and accept the ERGs proposed 4% 5 | Comment noted. At the third appraisal committee meeting, the committee discussed the overall survival predictions. The committee accepted that overall survival at 5 years is likely to be similar to that |

| Comment number | Type of stakeholder | Organisation name | Stakeholder comment<br>Please insert each new comment in a new row | NICE Response<br>Please respond to each comment |
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| | | | year survival which is not based on any data from NSCLC patients treated with immunotherapy. We would take the view that the committee's accepted view on longer term survival is unduly pessimistic and not supported by the available data. | predicted for other immunotherapies. The committee therefore concluded that the Kaplan–Meier data with a log-logistic curve was appropriate for decision-making purposes. Section 3.12 of the FAD has been updated to reflect this. |
| 13 | NHS Professional | Web comment | Survival from advanced NSCLC continues to be very poor with many patients in my clinics declining docetaxel chemotherapy due to its toxicity. Atezolizumab action against the PD-L1 axis is mechanistically different from pembrolizumab and nivolumab and has been shown in the OAK and POPLAR trials to have greater efficacy than docetaxel in an unselected population.<br><br>The proportion of patients with high levels of PD-L1 expression on immune cells and tumour cells in these clinical trials was only 16% and so is not relevant to the vast majority of patients suffering from this disease. The proportion of patients suitable for nintedanib and docetaxel in my clinics is small and is not a useful comparator.<br><br>Approval of atezolizumab for advanced NSCLC, especially squamous cell carcinoma patients who have previously received chemotherapy would provide people with a chance to extend their survival using a treatment with a more favourable side effect profile. I urge the committee to approve this indication for atezolizumab. | Comments noted. The committee agreed that results of the OAK trial show atezolizumab is more effective than docetaxel regardless of PD-L1 expression however the trial did not include the appropriate comparator for the majority of patients recruited. The committee concluded that the full trial population is not suitable for decision making. See section 3.6 of the FAD. |
| 14 | NHS Professional | Web comment | As a physician with long experience in the management of patients with lung cancer, I am disappointed that if the negative decision of NICE expressed in the ACD on the use of Atezolizumab in advanced NSCLC (issued October 2017) is upheld, NHS patients will be denied access to a very effective agent. As the committee recognises, patients with advanced NSCLC have both a very poor prognosis and a high symptom burden. The current “standard” second-line treatment for this group of patients is Docetaxel and the other comparator regimen of docetaxel plus nintedanib is, in my experience very little used, so I would question the decision to use this as a comparator regimen.<br><br>I believe that single agent docetaxel is in many ways a very poor comparator regime in this context, from the point of views both of patient experience and in terms of it mod of action. Docetaxel is a very unpleasant drug, especially in this group of patients who are often very unwell and, in my experience, tolerate that drug poorly. The response rates to single agent | Comments noted. The committee heard from Cancer Drugs Fund clinical lead and the clinical expert at the third committee meeting that nintedanib plus docetaxel (in the adenocarcinoma population only) is considered a relevant treatments in people whose disease does not express PD-L1. Comments received during |

| Comment number | Type of stakeholder | Organisation name | Stakeholder comment<br>Please insert each new comment in a new row | NICE Response<br>Please respond to each comment |
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| | | | docetaxel are poor and I can think of very few patients in my clinical experience who I would judge to have benefited significantly from it; the side effect burden in this patients group is very high.<br><br>The statement in the ACD that: "..a small proportion of patients who decline docetaxel or cannot tolerate it" is, in my view highly misleading and does not reflect clinical practice or experience.<br><br>Also the biological action of both docetaxel and nintedanib are completely different from immunotherapies (as they are form each other, of course) and I believe it is incorrect, from a biological mechanistic standpoint, to use the same exponential curve method to assess the likelihood of longer term survival with the chemotherapy agent, docetaxel and the immunotherapies in general and atezolizumab in particular. The major advance we are seeing with atezolizumab and some of the other immunotherapies is what looks highly likely to be a significant proportion of very long term survivors in a group of patients who have universally had a dire prognosis and a certain death sentence with previous therapeutic options. Clearly we do not have hard evidence of the proportion of such patients likely to be alive after therapies such as atezolizumab, but from my detailed knowledge of the survival patterns of lung cancer patients and what I have seen of the data from relevant trials, I firmly believe the idea of a 10% 5 year survival rate to be entirely plausible; indeed even a 5% survival rate (deemed "plausible" by the committee) in this group of patients with stages IIIB/IV NSCLC who have relapsed after first line therapy should be seen as a major advance!<br><br>With regards the issue of PD-L1 status, whilst it is very likely that response rates are higher in patients with greater levels of PD-L1 positivity, this correlates less well with long term survival benefit. In addition, in the group of patients for whom we have very little effective second line therapies, namely those with relapsed Squamous Cell Carcinoma, I consider immunotherapy with agents such as atezolizumab to be a very major advance, with very reasonable response rates even in PD-L1 negative patients, so that any arbitrary threshold would deny such patients the chance for significant benefit.<br><br>I would ask the committee to take these clinically-based comments into account when considering their final decision. | the first and second consultation stated that nintedanib plus docetaxel is only used for a small number of people in clinical practice, which the committee accepted. See section 3.2 of the FAD.<br><br>At the third appraisal committee meeting, the committee discussed the overall survival predictions. The committee accepted that overall survival at 5 years is likely to be similar to that predicted for other immunotherapies. The committee therefore concluded that the Kaplan–Meier data with a log-logistic curve was appropriate for decision-making purposes. Section 3.12 of the FAD has been updated to reflect this. |

No comment received from: Department of Health

NICE National Institute for Health and Care Excellence

# Atezolizumab for treating non-small-cell lung cancer after platinum-based chemotherapy [ID970]

Consultation on the appraisal consultation document – deadline for comments **5pm on Wednesday 1 November 2017 via NICE Docs.**

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| **Organisation name – Stakeholder or respondent** (if you are responding as an individual rather than a registered stakeholder please leave blank): | **Roche Products Ltd**; hereinafter "Roche" |
| **Disclosure** Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry. | **N/A** |
| **Name of commentator person completing form:** | [redacted] |

| Comment number | Comments<br><br>Insert each comment in a new row.<br>Do not paste other tables into this table, because your comments could get lost – type directly into this table. |
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| | Roche remain disappointed with the second provisional negative recommendation.<br><br>Based on our reading of the ACD, the key concerns underpinning the draft negative recommendation are around the following points:<br>• The true long term survival of current chemotherapy and future immunotherapies<br>• Implementation of a 2 year stopping rule<br>• Uncertainty in the indirect treatment analysis (ITC) resulting in:<br>o the comparison to pembrolizumab being excluded, and<br>o end of life criteria questioned versus nintedanib + docetaxel<br>• Lack of subgroup analysis<br><br>In addition, there are some further inferences that we feel should be highlighted:<br>• Dismissal of clinical expert opinion regarding: |

# Atezolizumab for treating non-small-cell lung cancer after platinum-based chemotherapy [ID970]

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| | ○ overall survival estimates of atezolizumab and docetaxel, and<br>○ nintedanib + docetaxel as a relevant comparator<br>• Uncertainty regarding the duration of treatment effect<br>• Use of cross-over adjustment to demonstrate the true relative efficacy of atezolizumab<br><br>Our full response is provided below and addresses in turn each of the above mentioned key points underpinning the draft negative recommendation and additional analyses to support a reversal of this preliminary negative recommendation. |
| 1 | **Overall survival predictions**<br><br>The ACD states:<br><br>*"The committee concluded that the log-logistic curve produced implausibly optimistic long-term survival outcomes at 5 years (10% alive). The ERG's preferred method was to use Kaplan–Meier data up to 19 months and then extrapolate using an exponential curve, which was the best fit visually for the trial data after 19 months. The committee considered that this also produced optimistic long-term survival outcomes at 5 years (4% alive) but that these were clinically plausible."*<br><br>Roche acknowledge that extrapolation of overall survival (OS) poses an ongoing challenge in the evaluation of immunotherapies. Roche carefully considered NICE's guide to methods in developing a response, and would like to draw attention to the advice on survival extrapolation in Section 5.7.7: "[When evaluating external validity] it is important to consider the clinical and biological plausibility of the inferred outcome, as well as coherence with external data sources such as historical data sets or other relevant clinical trials" (National Institute for Health and Care Excellence, 2013).<br><br>Availability of evidence from other relevant clinical trials can be utilised to minimise the uncertainty associated with immunotherapies, and natural history data are available and can be utilised for patients treated with standard chemotherapy. Roche would like to emphasise to the committee that the use of a Kaplan-Meier plus exponential distribution results in a corresponding docetaxel survival estimate of a maximum 1.2% of patients alive at 5 years, and 4% of patients alive at 5 years for atezolizumab.<br><br>This assumption cannot be deemed as externally valid, as it results in lower values than any of the estimates from:<br>• The evidence base available describing outcomes for locally advanced and metastatic NSCLC |

patients on docetaxel:

- Docetaxel estimates from recent RCT data (3 year OS: 6-10%)
- Available natural history data sources (NLCA, SEER and FlatIron) (5 year OS: 3-7%)

- The evidence base available describing outcomes for locally advanced and metastatic NSCLC patients on immunotherapy:
  - Atezolizumab RCT data from POPLAR (3 year OS: 19%)
  - Other relevant immunotherapy trial data from the KEYNOTE and CheckMate NSCLC studies (5 year OS: 16%)
- Expert opinion from lung cancer clinical experts (10%)

In addition, these estimates are inconsistent with:

- The committee's briefing document for this appraisal, which suggests a 10% OS in locally advanced / metastatic patients at 5 years (slide 3, (Excellence, 2017))
- The committee-accepted assumptions in the appraisal of pembrolizumab (National Institute for Health and Care Excellence, 2016)
- The mechanism of action (MOA) for checkpoint inhibitor immunotherapies

**External validity of survival modelling**

***Expert clinical opinion and MOA***

As previously highlighted to the Committee, Roche sought the advice of 10 lung cancer experts on the validity of survival extrapolation. Clinical experts, who are best positioned to validate statistical modelling based on their vast experience in the area, have consistently agreed across this and the previous appraisal for pembrolizumab that the survival estimates following the Kaplan-Meier plus log-logistic approach are clinically plausible, appropriate and representative of the anticipated benefit of immunotherapies in this disease area.

In addition to clinical plausibility, clinical experts also agreed with the pharmacodynamic plausibility of this assumption. The mechanism of action of the PD-1 and PD-L1 checkpoint inhibitors, including atezolizumab, is very different from that of chemotherapy, which results in very different efficacy and safety outcomes. One key example of this is the duration of response: the latest data from the OAK trial shows that the median duration of response is now 23.9 months compared to 6.3 months with docetaxel. This is consistent with the phase II POPLAR data, where atezolizumab duration of response is currently at 22.3 months (range: 2.9 – 38.7+), and still increasing with follow up, versus 7.2 months (range: 1.5 to 15.4) for docetaxel. Such data demonstrates that checkpoint inhibitor

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| | immunotherapy cannot be treated in the same way as chemotherapy with respect to extrapolation of outcomes. This is now widely understood and accepted. Long term survival benefits of immunotherapy have already been observed in melanoma, and is now also being translated into and witnessed in NSCLC. As such, a KM+exponential extrapolation of survival, traditionally appropriate for chemotherapy, is not sufficient in capturing the long term benefits of atezolizumab: as witnessed by the ERG's extrapolation under-predicting survival even at 3 years in comparison with POPLAR.<br><br>***Relevant clinical trial evidence for atezolizumab and other immunotherapies***<br>Although the economic model utilises the Phase III OAK study, Roche are concerned that additional RCT evidence for atezolizumab have been disregarded by the committee. It would also appear that evidence from other relevant immunotherapy trials has been disregarded, despite input from clinical experts confirming that the medicines result in similar outcomes from a clinical and biological perspective.<br><br>In our previous response to ACD, academic in confidence survival figures from the phase II POPLAR trial were provided demonstrating the ERG-preferred extrapolation underestimated the value of atezolizumab. In addition, long term survival estimates from other anti-PD-1 immunotherapies (deemed by the lung cancer clinical community as generalizable to atezolizumab in terms of mode of action, efficacy, safety and long term outcomes) were provided. The POPLAR data highlight 1-, 2- and 3-year survival which is consistent with the previous immunotherapy studies, reflecting the similarity in the core mode of action of atezolizumab with pembrolizumab and nivolumab (see Appendix 1 for an updated summary). These data represent the best available evidence for external validation of survival modelling methods, yet appear to have been disregarded in favour of non-clinical opinion of visual fit of the preferred distribution, at an arbitrary time point. As well as undervaluing the potential outcomes achievable with atezolizumab, we believe that this also significantly undervalues the outcomes currently achieved with routine care within the NHS, across the time horizon.<br><br>***Natural history datasets***<br>The Committee will be aware that Roche evaluated the validity of survival extrapolation methods alongside external natural history data sources from the National Lung Cancer Audit (Beckett P et al., 2013). Two analyses are available from point of diagnosis: Stage IV metastatic patients and Stage IIIB/IV patients who are eligible for chemotherapy, which more closely aligns with the population under consideration for treatment with atezolizumab. Survival at 5 years for the Stage IV group was **3%,** while survival in the IIIB/IV cohort was **7%.** |

# Atezolizumab for treating non-small-cell lung cancer after platinum-based chemotherapy [ID970]

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| | The longitudinal National Cancer Institute's SEER (Surveillance, Epidemiology and End Results) dataset provides corroborative evidence: a 2014 analysis for patients with distant metastases (Stage IV) showed a five-year overall survival of 5.2%; an estimate for "regional" disease is published but is likely to include earlier stage patients (32.3%) (EJ; Cronin KA (eds),, 2014).<br><br>In order to provide accurate estimates for the population under review, i.e. previously-treated patients receiving docetaxel for Stage IIIB/IV NSCLC, Roche conducted an analysis using an additional evidence source: the United States Flatiron Database, which contains electronic health record information of over 2 million cancer patients. Eligible patients treated with docetaxel between January 1st 2011 and March 31st 2017 were included. (Full details of the database and methods used are described in Appendix 2). Results were consistent with the NLCA and SEER published estimates: **3.7%** of pre-treated patients survived for 5 years (including 15% of patients with subsequent immunotherapies, thus some confounding). This data aligns more closely with Roche's preferred method of survival extrapolation and are underestimated by the Committee-preferred method.<br><br>**Inconsistency with previous Committee assumptions and decisions**<br><br>***Committee briefing document***<br>We would like to highlight to the committee that the use of these survival extrapolations in fact also contradict NICE's internal estimates of long term survival, as depicted in slide 3 of the briefing document. This has been included below for reference. |

# Atezolizumab for treating non-small-cell lung cancer after platinum-based chemotherapy [ID970]

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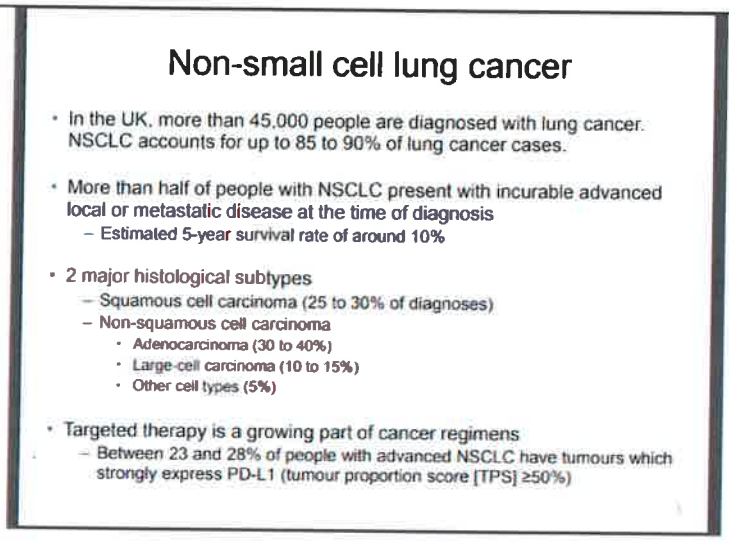


***Precedent in the appraisal of pembrolizumab***

As mentioned in the final appraisal determination for pembrolizumab, after incorporating the March 2016 data cut, 9.6% of patients in the pembrolizumab arm were anticipated to be alive at 5 years. This value already included a 'waning of treatment effect' and had been deemed reasonable from consultation comments from clinical experts. Whilst the committee could not agree on a single clinically plausible scenario, any treatment waning scenario earlier than from year 10 onwards which reduced this 5 year OS estimate was not cost effective (see Table 4 of company response to ACD dated 24th October 2016 – also included in Appendix 3). As such, only under assumptions whereby 5 year OS estimates for pembrolizumab were approximately 10% (rounding up), was this product deemed a cost effective option and therefore recommended for use. Where atezolizumab has demonstrated at least non-inferiority to this comparator, precedence and a consistent approach would confirm that the Roche extrapolation is a suitable analysis for decision making. Artificially manipulating the survival projection downwards by choosing a survival extrapolation that goes against the available evidence is not reasonable and not best practice.

In conclusion, Roche would like to highlight that none of the available evidence results in survival estimates as low as 1.2% for docetaxel patients, nor suggest that immunotherapy overall survival is likely to be as low as 4%. It is important to reiterate that the estimate of 5-year overall survival deemed clinically plausible by clinical experts with decades of experience in the field and by the Committee when evaluating pembrolizumab in the same indication, is significantly higher than that currently used in this appraisal. Roche strongly believe that the available evidence summarised above provides extensive validation of the estimates derived from the Kaplan-Meier plus log-logistic

# Atezolizumab for treating non-small-cell lung cancer after platinum-based chemotherapy [ID970]

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| | survival distribution. |
| 2 | **Implementation of a 2-year stopping rule**<br><br>The ACD states:<br><br>*"The committee heard from the company that there was an ongoing study investigating the effect of a 1-year maximum treatment length, the interim results of which showed that patients who discontinued therapy after 1 year had statistically significantly worse progression-free survival than those who continued therapy until they no longer benefited clinically … The committee heard from the Cancer Drugs Fund clinical lead that the long-term consequences of stopping treatment are unknown, but clinical experience of immunotherapies in other indications suggests that significant treatment-related toxicities may occur while the disease is still responding. There is growing concern among clinicians about the use of immunotherapies beyond 2 years … The Cancer Drugs Fund clinical lead clarified that a 2-year stopping rule is acceptable to both patients and clinicians, and would be implementable. Having determined this, the committee concluded that it would have liked to have seen a 2-year stopping rule applied in the economic model".*<br><br>Roche acknowledges that such a stopping rule could improve the cost effectiveness of atezolizumab. However, such a rule makes a marginal difference in the ICER, as demonstrated in Appendix 4.<br><br>Roche believes that a recommendation based on an arbitrary stopping rule is unreasonable in light of evidence submitted and will not be acceptable to patients and clinicians, given the new evidence now available.<br><br>Results from CheckMate 153, a randomised trial exploring the impact of continuous versus 1-year fixed duration of an immunotherapy in patients with advanced NSCLC, were presented at the ESMO congress in September 2017. These data demonstrated that patients who stopped treatment had a statistically significant higher risk of progressing (HR: 0.42 [95% CI: 0.25, 0.71]), and a numerically higher risk of dying (HR: 0.63 [95% CI: 0.33, 1.20]) (Spigel D, 2017) (see Appendix 4, and diagram below). Since this data were published, there has been growing concerns among the clinical community regarding a stopping rule that has shown a detrimental effect on patients. |

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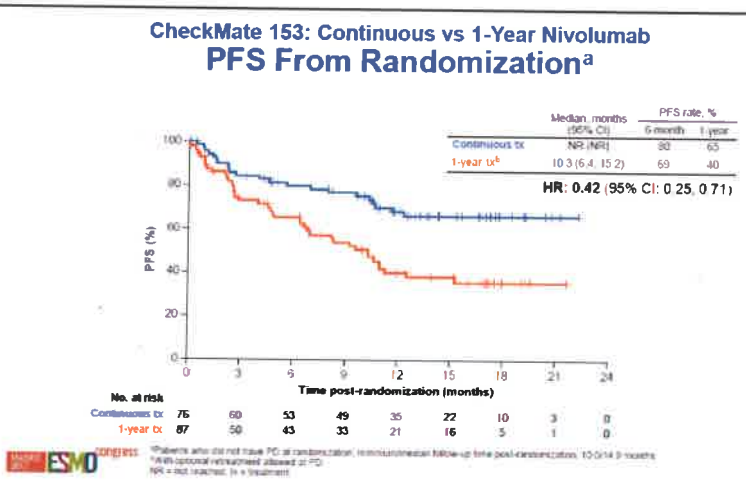


Previous NICE recommendations on stopping rules for other immunotherapies were made before this evidence became available, thus was considered a reasonable approach. However, now the CheckMate evidence is available, Roche are concerned NICE is disregarding available new information and the hierarchy of evidence to impose such a stopping rule. Regarding potential future "significant treatment-related toxicities", Roche would like to highlight atezolizumab's stopping rules already account for these, as listed in the SmPC: "until loss of clinical benefit or **unmanageable toxicity**." Discontinuation should be dealt with case by case by clinicians who are best positioned to decide when to discontinue treatment and if toxicities outweigh the benefits.
Roche have ensured the Patient Access Scheme (PAS) provided to the NHS accounts for the long term budget concerns.

To conclude, a stopping rule is not in the best interests of patients, the NHS and is unreasonable in light of published RCT evidence.

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**Indirect treatment analysis**

The ACD states:

"*The ERG noted that the heterogeneity was such that atezolizumab may not increase overall survival compared with nintedanib plus docetaxel. The analysis estimated a difference in overall survival for atezolizumab (whole population) compared with nintedanib plus docetaxel (in people with adenocarcinoma) of 3.33 months (95% CI -0.15 to 6.81) … The indirect treatment comparison estimated a difference in overall survival for atezolizumab (whole population) compared with pembrolizumab (PD-L1 expression ≥1%) of –0.18 months (95% CI –5.58 to 4.60) … The committee agreed to use the company's updated network, but noted the uncertainty associated with all the*

# Atezolizumab for treating non-small-cell lung cancer after platinum-based chemotherapy [ID970]

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| | *indirect analyses. It could not conclude with any certainty that atezolizumab is clinically equivalent to pembrolizumab."*<br><br>As such, the committee preferred assumptions were to disregard the comparison with pembrolizumab, and conclude atezolizumab does not provide >3 months extension to life over nintedanib + doctetaxel, and therefore the end of life criteria were not met.<br><br>As highlighted in our response to the first ACD, we recognise there is uncertainty in the network driven by the inconsistent populations and thus a potential overestimation of benefit of nintedanib + docetaxel. Nevertheless, as highlighted by clinical experts, real world usage of nintedanib + docetaxel is minimal, thus should not be considered an appropriate comparator: docetaxel and pembrolizumab are the appropriate comparators for decision making purposes in this appraisal.<br><br>With regard to the comparison to pembrolizumab, Roche are disappointed the committee did not consider this comparison further and remain confident it demonstrates atezolizumab as at least non-inferior to pembrolizumab and likely cost saving to the NHS. Nevertheless, Roche are reassured by the statement in the ACD: "*The committee concluded that a comparison in people with PD-L1-positive NSCLC as defined by the tests would be appropriate, given that there was likely overlap in the patients identified*", demonstrating NICE would be willing to utilise an indirect comparison in the equivalent populations, even if it is anticipated to have limited difference given the efficacy across subgroups for atezolizumab. |
| 4 | **Subgroup analysis**<br><br>The ACD states:<br><br>*"The marketing authorisation for atezolizumab is for adults with locally advanced or metastatic NSCLC after chemotherapy, and after chemotherapy and targeted treatment in people with EGFR- or ALK-positive tumours; it does not specify treatment based on PD-L1 expression … Comments from consultation stated that it was inappropriate to make a recommendation based on PD-L1 expression because PD-L1 is not a perfect biomarker and atezolizumab has shown benefit regardless of PD-L1 expression. Nevertheless, although PD-L1 is not a perfect biomarker, the committee considered it to be a reasonable guide as to those who may benefit from targeted treatment. Consequently, it was disappointed that the company did not present clinical and cost-effectiveness results for all of the relevant PD-L1 subgroups (including TC3 or IC3 and TC2/3 or IC 2/3)"*<br><br>As also highlighted in the ACD: "*any cost-effectiveness estimates by PD-L1 subgroup would be even* |

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| | *more uncertain than the estimates for the whole population because atezolizumab has shown benefit in people with both PD-L1-positive and PD-L1-negative tumours."*<br><br>Roche recognises the benefit of atezolizumab increases as the level of PD-L1 expression increases. However, similarly, it is unethical to restrict access only to these patients, when atezolizumab has demonstrated a statistically significant and clinically meaningful improvement in OS for the low and negative PD-L1 expressors, of a similar order to that delivered by immunotherapies already approved for PDL-1 positive patients. The low and negative PD-L1 expressors are the population with the greatest unmet need in current practice. Roche encourage the committee to consider any clinical rationale for not providing access for these patients, especially in consideration of NICE's commitment to advancing equality of opportunity.<br><br>In this response to ACD, Roche has provided full clinical results of all subgroups of interest for the committee to consider (please see Appendix 5). As these data show, atezolizumab has demonstrated statistically significant results, irrespective of PD-L1 expression. In addition, the confidence intervals for each subgroup overlap, demonstrating each subgroup could be considered as equally benefitting from treatment.<br><br>In addition, Roche has also provided economic results for the following subgroups:<br>• PD-L1 positive (TC/IC 1/2/3)<br>• PD-L1 low, negative or unidentifiable expression (TC/IC 0)<br>• All-comers, as based on our marketing authorisation<br><br>Roche appreciates the committee's eagerness to see cost-effectiveness in the high expressors (TC/IC 3); however the OAK primary data cut was not statistically powered for the TC/IC 3 subgroup, and as a result the patient numbers are small, and confidence intervals (CI) large. Based on the OAK data, patients with high expression may benefit more from treatment with atezolizumab, compared to low expressors, but the additional benefit is uncertain, and could overlap with the benefit seen in other groups (see CI of all subgroups below) (Barlesi F et al., 2016). |

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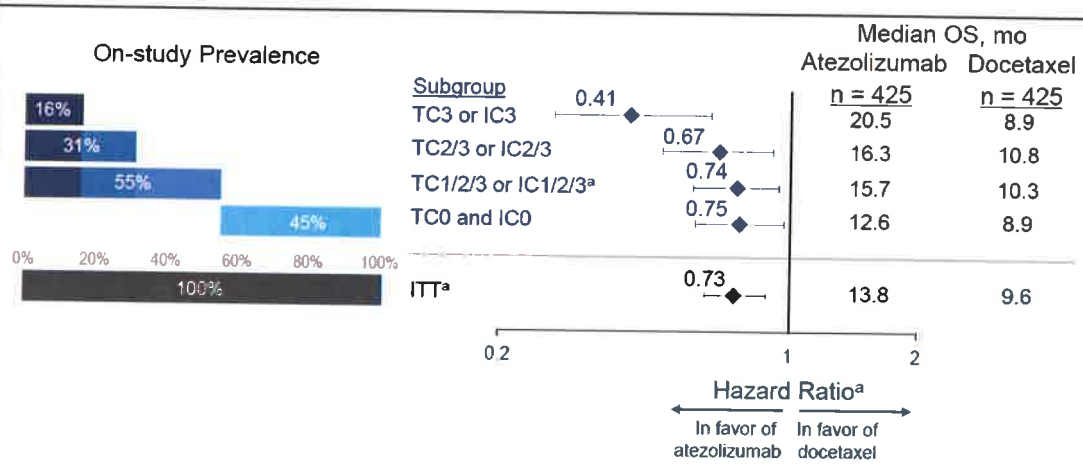
Consultation on the appraisal consultation document – deadline for comments **5pm on Wednesday 1 November 2017 via NICE Docs.**




We would also highlight that the TC/IC 3 and TC/IC 1/2/3 results are in line with other immunotherapies, as demonstrated in the ITCs provided (Appendix 6). Other immunotherapies have been recommended for funding in a wider population (TC/IC 1/2/3, >1% TPS) despite similar efficacy gains in the highest expressors (Herbst et al., 2016, National Institute for Health and Care Excellence, 2016). The ITC provided in these high expressors, we hope, will encourage NICE to focus on the more complete and appropriately powered subgroups and ITT, including where the unmet need currently is: the patients with no or low PD-L1 expression who currently have no access to immunotherapy, yet who receive essentially the same benefit from atezolizumab as those with higher levels of PD-L1 that currently have access to immunotherapies.

As discussed above, due to the limited real world usage of nintedanib+docetaxel, Roche do not believe it is an appropriate comparator in the ITT population. Thus is further emphasised in the subgroup analyses due to heterogeneity in the study populations. As discussed by the committee in the appraisal of pembrolizumab (National Institute for Health and Care Excellence, 2016), the LUME-LUNG 1 trial did not assess PD-L1 expression. Therefore, the committee concluded that the trial populations were too different, thus an indirect treatment comparison was not appropriate for decision-making. The same is true for the appraisal of atezolizumab. Therefore, this comparison is not provided for either the PD-L1 positive or negative subgroups.

***PD-L1 positive (TC/IC 1/2/3)***

For the PD-L1 positive (TC/IC 1/2/3) patients, there are two appropriate comparators: docetaxel, and pembrolizumab (>1% TPS). As such, an ITC was conducted (see Appendix 6). As NICE were hesitant to accept "equivalence" or "non-inferiority" statements in the previous analysis, a CEA has been conducted for both comparators.

# Atezolizumab for treating non-small-cell lung cancer after platinum-based chemotherapy [ID970]

Consultation on the appraisal consultation document – deadline for comments **5pm on Wednesday 1 November 2017 via NICE Docs.**

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| | As agreed with NICE, results of this analysis will be provided by 3rd November (Appendix 9).<br><br>***PD-L1 low and negative (TC/IC 0)***<br>Regarding the low and negative expressors, for whom pembrolizumab is not an appropriate comparator, a cost effectiveness analysis versus docetaxel is provided. As docetaxel is the only comparator, and was also the comparator in the OAK trial, only the OAK data is utilised.<br>See Appendix 7 for full results of this analysis.<br><br>***All-comer population***<br>We reiterate, the all-comer population should be deemed as the appropriate population to base decision making on. Therefore, results utilising the all-comer population are presented in Appendix 8. In addition, a comparison of all populations will be provided by 3rd November in Appendix 10.<br><br>Atezolizumab is the only immunotherapy to have demonstrated statistically significant benefit, irrespective of PDL1 expression. Patients who identify as PD-L1 positive, even at the lowest level of expression (>1% TPS, TC/IC 1/2/3) currently have immunotherapy treatment options available to them (pembrolizumab and nivolumab). Conversely, except for a small proportion of squamous patients, patients with low positivity or negative expression have no immunotherapy option available and thus are a population with clear unmet need, which atezolizumab is able to meet. |
| 5 | **Consideration of clinical expert opinion**<br><br>The clinical expert community (BTOG-NCRI-ACP-RCP-RCR) have actively contributed to this appraisal, either through consulting with Roche to validate the economic model inputs, attendance at the committee meetings or in responding to the ACDs.<br><br>As experts in this field, they have provided their view on the value of immunotherapies and the treatment pathway as it stands currently. Most importantly, they have also examined and scrutinised the predicted survival resulting from both the ERG's and Roche's extrapolation.<br><br>The process guide states "the processes are designed to produce robust guidance for the NHS with appropriate contribution from stakeholders". We ask the Committee to demonstrate the value clinical experts contribute to the NICE process, by considering their point of view also in this appraisal, particularly on OS extrapolation, where clinical experts are best positioned to validate statistical modelling based on their vast experience in the area. In a situation where limited follow-up results in uncertainty over long-term outcomes it is important that the interpretation of extrapolation is informed |

# Atezolizumab for treating non-small-cell lung cancer after platinum-based chemotherapy [ID970]

Consultation on the appraisal consultation document – deadline for comments **5pm on Wednesday 1 November 2017 via NICE Docs.**

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| | by the experience of clinical experts both with lung cancer and immunotherapy experience |
| 6 | **Duration of treatment effect**<br><br>The ACD states:<br><br>*"The company explained that atezolizumab's mechanism of action suggests that its effects on tumours would continue after treatment stopped. The committee considered this assumption to be biologically plausible, but it was concerned about the lack of evidence to support this. The committee considered that the treatment effect was unlikely to last more than 5 years after treatment had stopped. It concluded that although it was biologically plausible for treatment effects to continue after stopping treatment, the length of any continued effect was uncertain."*<br><br>Roche appreciates the uncertainty regarding the long term duration of treatment effect for immunotherapies and it acknowledges that the Committee routinely takes decisions in situations of uncertainty. As demonstrated in the results accompanying Roche's response to the first ACD, atezolizumab is cost effective in all duration-of-treatment effect scenarios.<br><br>However, we would like to highlight that such a cap on duration-of-treatment effect is in contrast to a potential 2 year stopping rule. We would encourage NICE to take a pragmatic approach by allowing patients to fully benefit from immunotherapies and not implementing a stopping rule. If a stance is taken on capping duration of treatment effect, it is perverse to then encourage patients to discontinue treatment at 2 years and, vice versa, if treatment benefit is not capped an increased impact on overall survival is to be expected on the long term, compared to chemotherapy. |
| 7 | **Use of cross-over adjustment**<br><br>The ACD states:<br><br>*"In response to consultation, the company provided analyses that adjusted for this subsequent treatment. These analyses used the rank-preserving structural failure time method, which the ERG stated was not suitable for adjusting for subsequent therapies (it is normally used to adjust for treatment crossover). Therefore the committee agreed that it would use the estimates from the unadjusted trial data."*<br><br>In Roche's response to the previous ACD, full cost effectiveness results adjusting for treatment switching in the OAK trial were provided. As detailed in the original submission, 5% of patients randomized to atezolizumab and 17% of patients in the docetaxel arm went on to receive subsequent cancer immunotherapies. By not adjusting for treatment switching, Roche were taking a conservative |

# Atezolizumab for treating non-small-cell lung cancer after platinum-based chemotherapy [ID970]

Consultation on the appraisal consultation document – deadline for comments **5pm on Wednesday 1 November 2017 via NICE Docs.**

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| | estimate of the OS benefit of atezolizumab, and thus the cost effectiveness. This is in contrast with the approach taken by other appraisals, including pembrolizumab. Thus, the analysis was presented for transparency and clarity purposes for the committee.<br><br>The rank-preserving structural failure time (RPSFT) method was used and previously accepted by the NICE committee as an appropriate method in the appraisal of pembrolizumab (National Institute for Health and Care Excellence, 2016). In the pembrolizumab clinical trial, similarly to OAK, cross-over was not permitted, but patients switched to other immunotherapies. Given the subsequent therapies received were "similar" to pembrolizumab, it was deemed the RPSFT method could be used for adjusting for subsequent therapies – not just treatment crossover, as it is normally used for. In this precedent, the RPSFT method was endorsed for treatment switching by the Committee. A consistent approach would confirm that this is a suitable analysis for decision making. |
| 8 | **Conclusion**<br><br>A full conclusion will be provided with the additional evidence on 3rd November. |

Insert extra rows as needed

## Atezolizumab for treating non-small-cell lung cancer after platinum-based chemotherapy [ID970]

Consultation on the appraisal consultation document – deadline for comments **5pm on Wednesday 1 November 2017 via NICE Docs.**

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NICE National Institute for Health and Care Excellence

# Atezolizumab for treating non-small-cell lung cancer after platinum-based chemotherapy [ID970]

Consultation on the appraisal consultation document – deadline for comments **5pm on Tuesday 21 November 2017 via NICE Docs.**

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|---|---|
| **Organisation name – Stakeholder or respondent** (if you are responding as an individual rather than a registered stakeholder please leave blank): | **Roche Products Ltd**; hereinafter "Roche" |
| **Disclosure** Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry. | **N/A** |
| **Name of commentator person completing form:** | [redacted] |

| Comment number | Comments<br><br>Insert each comment in a new row.<br>Do not paste other tables into this table, because your comments could get lost – type directly into this table. |
|---|---|
| 8 | **Conclusion**<br><br>In summary, Roche have provided significant further validation that the company preferred OS extrapolation is the most appropriate to appraise the cost effectiveness of atezolizumab, driven by:<br>• expert opinion and pharmacodynamic plausibility<br>• comparability to relevant clinical trial evidence for atezolizumab and other immunotherapies<br>• evidence from natural history datasets including NLCA, SEER and FlatIron<br>• consistency with previous committee assumptions and decisions including the committee briefing book, and precedent in the appraisal of pembrolizumab<br><br>In addition, Roche have provided critical evidence suggesting that a two year stopping rule may be detrimental to patients, thus calling into question the imposition of a stopping rule.<br><br>Finally, Roche have provided clinical and economic results for the PD-L1 positive and negative |

# Atezolizumab for treating non-small-cell lung cancer after platinum-based chemotherapy [ID970]

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| | subgroups, as well as a comparison of outcomes across the subgroups (See Appendix 10). As demonstrated consistently, atezolizumab has clinical benefit irrespective of PD-L1 expression, and is currently the only immunotherapy option that can meet a clear unmet need in the population with low positivity or negative expression, who have no immunotherapy option available.<br><br>Following an update to the appraisal of atezolizumab in metastatic urothelial cancer (National Institute for Health and Care Excellence, 2017), the PAS for atezolizumab has increased to [redacted]%. For full details, please see Appendix 7-9, however a summary is provided below:<br>• TC/IC 0: docetaxel as the relevant comparator, the ICER is [redacted];<br>• TC/IC 1/2/3: upon positive NICE guidance in Januray 2017, pembrolizumab has become standard of care. Atezolizumab has demonstrated non-inferiority and an opportunity to provide cost savings for the NHS versus pembrolizumab. The ICER versus docetaxel is [redacted].<br><br>Given the similarities in benefits, ICERs, and the unmet need of the PD-L1 negative population, the all-comer population should be deemed as the appropriate population to base decision making on, with an ICER of [redacted] when accounting for treatment switching adjustment, and [redacted] without.<br><br>Atezolizumab is a cost effective treatment for NSCLC after prior chemotherapy irrespective of PD-L1 expression, and has an opportunity to:<br>• Meet a considerable unmet need in the low and negative expressors population, as well as a significant number of patients who do not have tissue available for PD-L1 testing, and<br>• Provide cost-savings to the NHS: obviating treatment delays whilst testing is undertaken and reducing resources expended in procuring tissue samples, testing and reporting them.<br><br>Roche urge the committee to utilise the full set of evidence available to enable all patients who can benefit from treatment, access to atezolizumab, given the clinical evidence supporting the all-comer population. |

Insert extra rows as needed

## Atezolizumab for treating non-small-cell lung cancer after platinum-based chemotherapy [ID970]

Consultation on the appraisal consultation document – deadline for comments **5pm on Tuesday 21 November 2017 via NICE Docs.**

## References

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NICE National Institute for Health and Care Excellence

# Atezolizumab for treating non-small-cell lung cancer after platinum-based chemotherapy [ID970]

Consultation on the appraisal consultation document – deadline for comments **5pm on Wednesday 1 November 2017 via NICE Docs.**

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|---|---|
| **Organisation name – Stakeholder or respondent** (if you are responding as an individual rather than a registered stakeholder please leave blank): | **Roche Products Ltd**; hereinafter "Roche" |
| **Disclosure** Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry. | **N/A** |
| **Name of commentator person completing form:** | [redacted] |

| Comment number | Comments<br><br>Insert each comment in a new row.<br>Do not paste other tables into this table, because your comments could get lost – type directly into this table. |
|---|---|
| 7 | **Use of treatment-switch adjustment**<br><br>The ACD states:<br><br>*"In response to consultation, the company provided analyses that adjusted for this subsequent treatment. These analyses used the rank-preserving structural failure time method, which the ERG stated was not suitable for adjusting for subsequent therapies (it is normally used to adjust for treatment crossover). Therefore the committee agreed that it would use the estimates from the unadjusted trial data."*<br><br>In Roche's response to the previous ACD, full cost effectiveness results adjusting for treatment switching in the OAK trial were provided. As detailed in the original submission, 5% of patients randomized to atezolizumab and 17% of patients in the docetaxel arm went on to receive subsequent cancer immunotherapies. By not adjusting for treatment switching, Roche were taking a conservative |

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| | estimate of the OS benefit of atezolizumab, and thus the cost effectiveness. This is in contrast with the approach taken by other appraisals, including pembrolizumab. Thus, the analysis was presented for transparency and clarity purposes for the committee.<br><br>The rank-preserving structural failure time (RPSFT) method was used and previously accepted by the NICE committee as an appropriate method in the appraisal of pembrolizumab (National Institute for Health and Care Excellence, 2016). In the pembrolizumab clinical trial, similarly to OAK, cross-over was not permitted, but patients switched to other immunotherapies. Given the subsequent therapies received were "similar" to pembrolizumab, it was deemed the RPSFT method could be used for adjusting for subsequent therapies – not just treatment crossover, as it is normally used for. In this precedent, the RPSFT method was endorsed for treatment switching by the Committee. A consistent approach would confirm that this is a suitable analysis for decision making. |

Insert extra rows as needed

**Atezolizumab for treating non-small-cell lung cancer after platinum-based chemotherapy [ID970]**

Consultation on the appraisal consultation document – deadline for comments **5pm on Wednesday 1 November 2017 via NICE Docs.**

## References

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE 2016. Pembrolizumab for treating PD-L1-positive non-small-cell lung cancer after chemotherapy [TA428].

NICE National Institute for Health and Care Excellence

# Atezolizumab for treating non-small-cell lung cancer after platinum-based chemotherapy [ID970]

Consultation on the appraisal consultation document – deadline for comments **5pm on Wednesday 1 November 2017 via NICE Docs.**

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|---|---|
| **Organisation name – Stakeholder or respondent** (if you are responding as an individual rather than a registered stakeholder please leave blank): | NCRI-ACP-RCP-RCR |
| **Disclosure** Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry. | None |
| **Name of commentator person completing form:** | [redacted] RCP registrar |

| Comment number | Comments<br><br>Insert each comment in a new row.<br>Do not paste other tables into this table, because your comments could get lost – type directly into this table. |
|---|---|
| 1 | The NCRI-ACP-RCP-RCR is grateful for the opportunity to response to the above consultation. We have liaised with our experts and would like to make the following comments. |
| 2 | With regard to the committee's comments on overall survival with atezolizumab, the committee has heard from a number of experts that there is little to distinguish between the PD-1/PD-L1 inhibitors in terms of safety and efficac; this view appears to have been accepted in the absence of head to head data. However, in reviewing the estimates of longer term survival used for modelling, it has chosen to disregard the previously discussed 3 and 5 year survival data for pembrolizumab and nivolumab (see previous response) and accept the ERGs proposed 4% 5 year survival which is not based on any data from NSCLC patients treated with immunotherapy. We would take the view that the committee's accepted view on longer term survival is unduly pessimistic and not supported by the available data. |

Insert extra rows as needed

Please return via NICE DOCS.

Dear Stephanie,
Please see my answers below:
Dr Yvonne Summers FRCP, PhD
Consultant Medical Oncologist
The Christie Hospital NHS Trust & University Hospital South Manchester

On 18 Jan 2018, at 11:39, National Institute for Health and Care Excellence <tacommc@nice.org.uk> wrote:

18/01/2018
Level 1A, City Tower
Piccadilly Plaza
Manchester
M1 4BT

Dear Yvonne,

In anticipation of next week's committee meeting for atezolizumab for previously treated NSCLC the technical team at NICE and the committee chair have a few questions for you which will help focus the committee in its discussions. Please can I ask you to assist and provide a response by 2pm on Monday 22 January? We will then be able to include your responses in the presentation to the committee on Tuesday 23 January 2018.

**Relevance of nintedanib + docetaxel as a comparator**

We have received comments at this consultation and the previous one that for this population (previously treated NSCLC) nintedanib + docetaxel is rarely used and therefore should not be considered a relevant comparator.

**1. In your opinion is this an accurate reflection of clinical practice?**

-It is still used in clinical practice (albeit in very small numbers now), but if docetaxel is being used in a patient with adenocarcinoma and there are no contraindications to nintedanib, the outcomes are improved with the combination

**2. Who would receive nintedanib + docetaxel?**

- This is a subject of much debate. Some oncologists are not using any Docetaxel Nintedanib in non-squamous patients now and have entirely switched to immunotherapy, but not all. The answer is multifactorial for me and involves a number of factors: bulky disease, never smoked/ very light ex smoker, low PD-L1. It takes much more time and energy to consider all of these elements and explain them to a patient in addition to explaining why you might want to consider what is undoubtedly a more toxic treatment (chemotherapy), and so perhaps it is not surprising that many physicians have changed wholesale to immunotherapy.

**Pembrolizumab and atezolizumab**

**3. Would it be reasonable to assume that atezolizumab could be considered clinically equivalent to pembrolizumab?**

-Yes - despite different MoA the drugs appear to have similar toxicity and efficacy.
Use of docetaxel in clinical practice

**4. In the post-pembrolizumab era, is docetaxel used in anyone other than PDL-1 negative expressers ? Same answer as questions 1 & 2**

**Long term use of immunotherapies**

**5. Is a 2 year stopping rule reasonable in light of comments made in previous meetings that there is growing concern among clinicians about the use of immunotherapies beyond 2**

**years and that the best length of treatment with immunotherapies such as atezolizumab is uncertain, with clinicians stopping treatment anywhere between 6 months and 2 years?**

- As you know we are lacking data, some clinicians are uncomfortable with stopping at 2 years. I am unaware of any clinician stopping treatment earlier than 2 years, outside of a clinical trial, for any reason other than toxicity, PD or patient choice. We need to utilise the SACT database to inform decisions - it frustrates me that we potentially have so much real world NHS data on treatment duration, subsequent therapies and survival but are unable to access it for appraisals.

**6. Please provide an update on the current view of duration of likely continued treatment duration after stopping PD-L1 immunotherapies.**

- I'm not quite sure what you mean by this one? If you mean how long is PD-L1 therapy continued after PD, on average it would be 1-2 cycles, but there are some circumstances where PD by RECIST criteria is not reflective of what is happening to the disease globally, eg the disease might be responding well in a number of sites on the first scan but one new lesion appears - this is PD by RECIST but most clinicians would continue and this individual may continue treatment for very many cycles.

**7. Does this differ depending on which treatment is used (ie. atezolizumab, pembrolizumab, nivolumab)?**

- No scientific reason to other that the fact that some studies did have a stopping rule others did not

**Overall survival assumptions**

We have received comments from clinical experts, royal colleges and the company about the committee's preferred assumptions about the proportion of patients still alive at 5 years on atezolizumab (in the ITT of OAK). Currently the committee's preferred assumption is that 4.9% patients on atezolizumab would be alive at year 5. The company argue that it would be nearer 10%. In addition the company have now included a cost-effectiveness analysis looking specifically at the PD-L1 positive (TC/IC 1/2/3) subgroup with pembrolizumab as the comparator. For this group they predict survival at 5 years is 12%.

**8. Is the assumption that 4.9% or 10% of patients would survive at 5 years in the all comers population most clinically plausible?**

- 4.9% is too low for this group. We are beginning to see longer term survival is improved, as is being reflected in longer follow up of trial data. 10% is probably closer to reality.

**9. Does the predicted survival of 12% at 5 years for the PD-L1 positive sub group seem clinically plausible?**

- A few years ago I would have been highly sceptical about such a prediction, but follow-up data is indicating that this is not unreasonable, and anecdotally I increasingly have a clinic with many more longer term survivors (who are not just the EGFR and ALK positive patients). Interestingly the patients who do very well with immunotherapy are often still in good shape when the immunotherapy stops working (partly due to not having all the cytotoxic side effects that they would have had with chemo) are are in a favourable position to receive other treatments or trials.

Kind regards,

Stephanie Callaghan (formerly Stephanie Yates)

Project Manager, Technology Appraisals – Committee C
Centre for Health Technology Evaluation
National Institute for Health and Care Excellence
Level 1A | City Tower | Piccadilly Plaza | Manchester M1 4BT | United Kingdom
Tel: 44 (0)161 870 3248 | Fax: 44 (0)845 003 7785

**Comments on the ACD Received from the Public through the NICE Website**

| | |
|---|---|
| **Name** | [redacted] |
| **Role** | NHS Professional |
| **Other role** | Consultant Medical Oncology |
| **Organisation** | [redacted] |
| **Location** | England |
| **Conflict** | No |
| **Notes** | |
| **Comments on individual sections of the ACD:** | |
| **Section 1** (Appraisal Committee's preliminary recommendations) | Survival from advanced NSCLC continues to be very poor with many patients in my clinics declining docetaxel chemotherapy due to its toxicity. Atezolizumab action against the PD-L1 axis is mechanistically different from pembrolizumab and nivolumab and has been shown in the OAK and POPLAR trials to have greater efficacy than docetaxel in an unselected population.<br><br>The proportion of patients with high levels of PD-L1 expression on immune cells and tumour cells in these clinical trials was only 16% and so is not relevant to the vast majority of patients suffering from this disease. The proportion of patients suitable for nintedanib and docetaxel in my clinics is small and is not a useful comparator.<br><br>Approval of atezolizumab for advanced NSCLC, especially squamous cell carcinoma patients who have previously received chemotherapy would provide people with a chance to extend their survival using a treatment with a more favourable side effect profile. I urge the committee to approve this indication for atezolizumab. |
| **Section 2** (The technology) | |
| **Section 3** (The manufacturer's submission) | |
| **Section 4** ( Consideration of the evidence) | |
| **Section 5** ( Implementation) | |
| **Section 6** ( Related NICE guidance) | |
| **Section 7** (Proposed date of review of guidance) | |

| | |
|---|---|
| **Name** | [redacted] |
| **Role** | NHS Professional |
| **Other role** | Honorary Consultant and Professor of Respiratory Medicine |
| **Organisation** | [redacted] |
| **Location** | England |
| **Conflict** | No |
| **Notes** | |
| **Comments on individual sections of the ACD:** | |
| **Section 1** (Appraisal Committee's preliminary recommendations) | As a physician with long experience in the management of patients with lung cancer, I am disappointed that if the negative decision of NICE expressed in the ACD on the use of Atezolizumab in advanced NSCLC (issued October 2017) is upheld, NHS patients will be denied access to a very effective agent. As the committee recognises, patients with advanced NSCLC have both a very poor prognosis and a high symptom burden. The current "standard" second-line treatment for this group of patients is Docetaxel and the other comparator regimen of docetaxel plus nintedanib is, in my experience very little used, so I would question the decision to use this as a comparator regimen.<br><br>I believe that single agent docetaxel is in many ways a very poor comparator regime in this context, from the point of views both of patient experience and in terms of it mod of action. Docetaxel is a very unpleasant drug, especially in this group of patients who are often very unwell and, in my experience, tolerate that drug poorly. The response rates to single agent docetaxel are poor and I can think of very few patients in my clinical experience who I would judge to have benefited significantly from it; the side effect burden in this patients group is very high.<br><br>The statement in the ACD that: "..a small proportion of patients who decline docetaxel or cannot tolerate it" is, in my view highly misleading and does not reflect clinical practice or experience.<br><br>Also the biological action of both docetaxel and nintedanib are completely different from immunotherapies (as they are form each other, of course) and I believe it is incorrect, from a biological mechanistic standpoint, to use the same exponential curve method to assess the likelihood of longer term survival with the chemotherapy agent, docetaxel and the immunotherapies in general and atezolizumab in particular. The major advance we are seeing with atezolizumab and some of the other immunotherapies is what looks highly likely to be a significant proportion of very long term survivors in a group of patients who have universally had a dire prognosis and a certain death sentence with previous therapeutic options. Clearly we do not have hard evidence of the proportion of such patients likely to be alive after therapies such as atezolizumab, but from my detailed knowledge of the survival patterns of lung cancer patients and what I have seen of the data from relevant trials, I firmly believe the idea of a 10% 5 year survival rate to be entirely plausible; indeed even a 5% survival rate (deemed "plausible" by the committee) in this group of patients with stages IIIB/IV NSCLC who have relapsed after first line therapy should be seen as a major advance!<br><br>With regards the issue of PD-L1 status, whilst it is very likely that response rates are higher in patients with greater levels of PD-L1 positivity, this correlates less well with long term survival benefit. In addition, in the group of patients for whom we have very little effective second line therapies, namely those with relapsed Squamous Cell Carcinoma, I consider immunotherapy with agents such as |

| | |
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| | atezolizumab to be a very major advance, with very reasonable response rates even in PD-L1 negative patients, so that any arbitrary threshold would deny such patients the chance for significant benefit.<br><br>I would ask the committee to take these clinically-based comments into account when considering their final decision.<br><br>[redacted]<br><br>Hon Consultant and Professor of Respiratory Medicine,<br>[redacted] |
| **Section 2**<br>(The technology) | |
| **Section 3**<br>(The manufacturer's submission) | |
| **Section 4**<br>( Consideration of the evidence) | |
| **Section 5**<br>( Implementation) | |
| **Section 6**<br>( Related NICE guidance) | |
| **Section 7**<br>(Proposed date of review of guidance) | |

# Appendix 1: Overall Survival: Relevant clinical trial evidence

**Table 1: Comparison of modelled, observed, and real world data: docetaxel**

| Data source | 2 year OS | 3 year OS | 4 year OS | 5 year OS |
|---|---|---|---|---|
| Company base case OS: KM+ log logistic | 16% | 7% | 4% | 2% |
| ERG and committee preferred OS: KM+exponential | 17% | 7% | 3% | 1% |
| POPLAR (F. Hoffmann-La Roche Ltd, 2017b) | 17% | 10% | | - |
| KEYNOTE-010 [TPS ≥1%] (Herbst RS, 2015) | 15% | - | - | |
| Checkmate-017 [Squamous histology] (Barlesi F et al., 2016) | 8% | 6% | - | - |
| Checkmate-057 [Non-squamous histology] (Barlesi F et al., 2016) | 16% | 9% | - | - |

**Table 2: Comparison of modelled and observed clinical data: atezolizumab (with supportive data from the PD-1 inhibitors nivolumab and pembrolizumab)**

| Data source | 2 year OS | 3 year OS | 4 year OS | 5 year OS |
|---|---|---|---|---|
| Company preferred OS: KM+ log logistic | 30% | 19% | 13% | 10% |
| ERG and committee preferred OS: KM+exponential | 29% | 16% | 8% | 4% |
| POPLAR (F. Hoffmann-La Roche Ltd, 2017b) | 32% | 19% | - | - |
| CA209-003 (Velcheti, 2017, Brahmer J et al, 2017) | 24% | 18% | - | 16% |
| KEYNOTE-001 (Includes unknown PD-L1 status and TPS <1%) (Velcheti, 2017) | 30% | 19% | - | - |
| Checkmate-017 [Squamous histology] (Barlesi F et al., 2016), (Felp Font E, 2017) | 23% | 16% | - | - |
| Checkmate-057 [Non-squamous histology] (Barlesi F et al., 2016), (Felp Font E, 2017) | 29% | 18% | - | - |
| KEYNOTE-010 (TPS ≥1%) [TPS ≥1%] (Herbst RS, 2015) | 30% | - | - | - |

# Appendix 2: Overall Survival: Natural history datasets

## Natural history OS milestone comparison

**Table 3: Natural history data for locally advanced/metastatic NSCLC**

| | Overall survival milestone (% surviving) | | | |
|---|---|---|---|---|
| | 2 year | 3 year | 4 year | 5 year |
| ***First-line*** | | | | |
| NLCA (Stage IV; all PS; chemotherapy-eligible and -ineligible) (Beckett P, 2013) | 7% | 4% | - | 3% |
| NLCA (IIIB/IV; PS0-1; chemotherapy-treated) (Beckett P, 2013) | 20% | 13% | - | 7% |
| SEER (distant) (EJ; Cronin KA (eds),, 2014) | N/R | N/R | N/R | 5.2% |
| SEER (regional/distant) (EJ; Cronin KA (eds),, 2014) | N/R | N/R | N/R | 32.3% |
| ***Atezolizumab-eligible population (IIIB/IV; second-line NSCLC; docetaxel-treated)*** | | | | |
| Flatiron-database (Enrollment Jan 2011 – Mar 2017) N=797 (F. Hoffmann-La Roche Ltd [data on file], 2017) | 14.4% | 10.3% | 6.2% | **3.7%** |

## FlatIron database analyses (F. Hoffmann-La Roche Ltd [data on file], 2017)

I. **Aim**:

To estimate the overall survival (OS) of advanced non-small cell lung cancer (aNSCLC) patients treated in clinical practice docetaxel monotherapy

II. **Method**:

This retrospective observational cohort study utilized Flatiron Health's longitudinal, demographically and geographically diverse database containing electronic health record (EHR) data from over 265 cancer clinics (~800 sites of care) including more than 2 million U.S. cancer patients available for analysis. The de-identified patient-level data in the EHRs includes structured data (e.g., laboratory values, and prescribed drugs) in addition to unstructured data collected via technology-enabled chart abstraction from physician's notes and other unstructured documents (e.g., detailed biomarkers). At the time of the analysis data was available from January 1, 2011 until September 30, 2017 (Flatiron Health, 10 2017). Institutional Review Board approval of the study protocol was obtained prior to study conduct. Informed consent was waived as this was a non-interventional study and the anonymized data in the Flatiron EHR database are protected against breach of confidentiality.

**a. Patients**

Patients considered for this study were newly diagnosed patients with stage IIIB or IV non-small cell lung cancer on or after January 1, 2011 or diagnosed with early-stage NSCLC and subsequently developed recurrent or progressive disease on or after January 1, 2011. Two separate treatment arms were then constructed based on treatment with second-line docetaxel.

All patients initiating docetaxel monotherapy treatment in the second-line between January 1, 2011 and March 30, 2017 were extracted into one **Docetaxel** treatment arm. Line of treatment was derived using a step-wise algorithm by Flatiron from abstracted information from the medical chart on anticancer therapy treatment dates and prescribing regimens (drug names, route, dosage, and units)

(Abernethy et al., 2017). The cut-off of March 30, 2017 was set to allow for at least 6-months of follow-up; data cut-off September 30, 2017. Any patient using docetaxel in combination with another regimen was excluded.

A sub-group analysis was also conducted in the period when anti-PD1/PD-L1 checkpoint inhibitors were available in the US. A second docetaxel treatment arm was constructed (**Docetaxel II**) by extracting patients initiating second-line docetaxel treatment between December 22, 2014 and March 30, 2017. Nivolumab was the first check-point inhibitor available in the US, with FDA approval on December 22, 2014 for the treatment of metastatic melanoma. This date was chosen to represent a time period with potential off-label use of nivolumab in the treatment of aNSCLC patients.

### b. Primary Endpoint

The primary endpoint was OS, defined as the time from the date of initiation of docetaxel until death from any cause. If a patient did not die during the follow-up they were censored on their last activity date at the Flatiron network. This could be a treatment administration or visit date, which ever was most recent.

### c. Statistical Analysis

Demographic and clinical characteristics were summarized for each of the treatment arms at the date of second-line treatment initiation. Descriptive statistics were conducted including frequency distributions for categorical variables and mean values with standard deviations (SD) and median values with range for continuous variables. Median OS and corresponding 95% confidence intervals (CI) were calculated for each treatment arm with Kaplan Meier methods. 6-month landmark survival was calculated as the proportion of patients that were alive at 6-months intervals after second-line treatment initiation. Landmarks were calculated up to 5-years (60 months) after initiation of treatment for the Docetaxel arm.

All statistical analyses were conducted in-house at Roche by an experienced Real World Data analyst using R version 3.3.2 on the internal Roche server.

## III. Results

Among 36,678 patients diagnosed with advanced or metastatic NSCLC, 797 patients were idenitified as initiating second-line treatment with docetaxel monotherapy between January 1, 2011 and March 30, 2017 and included in the primary cohort. Among the 797 patients, 224 initiated treatment from the 22$^{nd}$ of December 2014 for the subgroup Docetaxel II analysis. Demographic and clinical characteristics are summarised in Table 4. Flow diagrams highlighting patient eligibility are found in Figure 1 and

Figure **2**. One hundred and forty-one of 797 patients (17.7%) in the Docetaxel group subsequently received an anti-PD-1/PD-L1 agent, which increased proportionately to 85 of 224 patients (37.9%) in the Docetaxel II subgroup.

**Table 4: Patient demographic and clinical characteristics by treatment arm at initiation of second-line treatment**

| **Characteristic** | | **Docetaxel (n= 797)** | **Docetaxel II (n=224)** |
|---|---|---|---|
| **Age** | **Median age (IQR)** | 67.00 [59.00, 73.00] | 67.00 [59.00, 73.00] |
| **Gender** | **Male, N (%)** | 443 (55.6) | 125 (55.8) |
| **Region (%)** | Northeast | 184 (23.1) | 42 (18.8) |

| | | | |
|---|---|---|---|
| | South | 238 (29.9) | 66 (29.5) |
| | North Central | 184 (23.1) | 55 (24.6) |
| | West | 125 (15.7) | 40 (17.9) |
| | White | 515 (64.6) | 136 (60.7) |
| | Asian | 11 ( 1.4) | 6 ( 2.7) |
| **Race (%)** | Black or African American | 69 ( 8.7) | 23 (10.3) |
| | Other Race | 79 ( 9.9) | 28 (12.5) |
| **Year of advanced diagnosis (%)** | 2011 | 131 (16.4) | 0 ( 0.0) |
| | 2012 | 172 (21.6) | 3 ( 1.3) |
| | 2013 | 220 (27.6) | 26 (11.6) |
| | 2014 | 178 (22.3) | 99 (44.2) |
| | 2015 | 66 ( 8.3) | 66 (29.5) |
| | 2016 | 30 ( 3.8) | 30 (13.4) |
| | 2017 | 0 ( 0.0) | 0 ( 0.0) |
| **Histology (%)** | Non-squamous cell carcinoma | 591 (74.2) | 170 (75.9) |
| | NSCLC histology NOS | 23 ( 2.9) | 5 ( 2.2) |
| | Squamous cell carcinoma | 183 (23.0) | 49 (21.9) |
| **Smoking status** | **History of Smoking, N (%)** | 703 (88.2) | 193 (86.2) |
| **Practice type (%)** | Community | 54 ( 6.8) | 17 ( 7.6) |
| | Academic | 743 (93.2) | 207 (92.4) |
| **ALK rearrangement (%)** | Tested | 508 (63.7) | 157 (70.1) |
| | Rearrangement Present[2] | 3 ( 0.59) | 0 ( 0.0) |
| **EGFR (%)** | Tested | 502 (63.0) | 157 (70.1) |
| | Mutation Present[2] | 34 ( 6.77) | 9 ( 5.73) |
| **Follow-up** | **Months, Mean (SD)** | 18.69 (13.07) | 18.27 (11.46) |

[1]Proportions may not add up to 100% due to missing data. [2]Proportion taken out of patients with tests.

**Figure 1: Patient flow in the Docetaxel group**

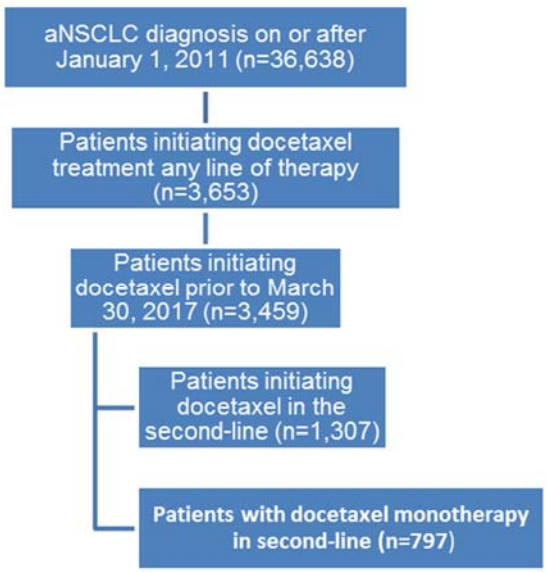
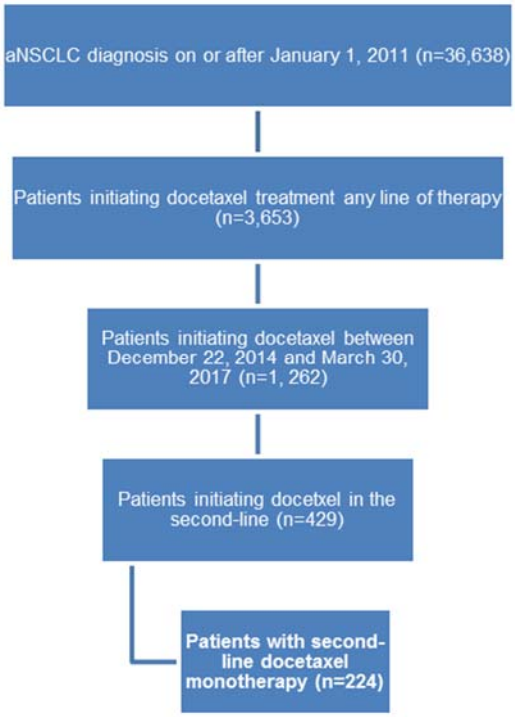


**Figure 2: Patient flow in the Docetaxel II group**




Summary statistics for both Docetaxel and Docetaxel II are described in Table 6. With the available follow-up, 82.4% and 70.1% of patients had died in the respective groups.

**Table 5: Kaplan Meier Summary Statistics**

| | N | Events (%) | Restricted Mean Survival, months (SE) | Median Survival, months (95% CI) |
|---|---|---|---|---|
| **Docetaxel** | 797 | 657 (82.4%) | 9.51 (0.37) | 5.52 (4.83 – 6.18) |
| **Docetaxel II** | 224 | 157 (70.1%) | 10.71 (0.78) | 6.74 (5.59 – 8.05) |

Landmark survival is presented by six-monthly intervals for the Docetaxel group and Docetaxel II subgroup in Table 6. Data are available for the Docetaxel group up to 60 months, whilst Docetaxel II was limited to 30 months at the time of data cut-off.

**Table 6: 6-month Landmark Survival**

| Landmark Date | Docetaxel (n= 797) | Docetaxel II (n=224) |
|---|---|---|
| **6-months** | 47.20% | 54.30% |
| **12-months** | 28.30% | 32.50% |
| **18-months** | 18.90% | 24.10% |
| **24-months** | 14.40% | 17.30% |
| **30-months** | 11.80% | 15.90% |
| **36-months** | 10.30% | -- |

| | | |
|---|---|---|
| **42-months** | 7.70% | -- |
| **48-months** | 6.20% | -- |
| **54-months** | 6.20% | -- |
| **60-months** | 3.70% | -- |

Kaplan-Meier survival curves highlighting the survival of patients in the Docetaxel and Docetaxel subgroups are included below.

**Figure 3: Survival of Docetaxel arm (median OS = 5.52 months, 95% CI: 4.83, 6.18)**

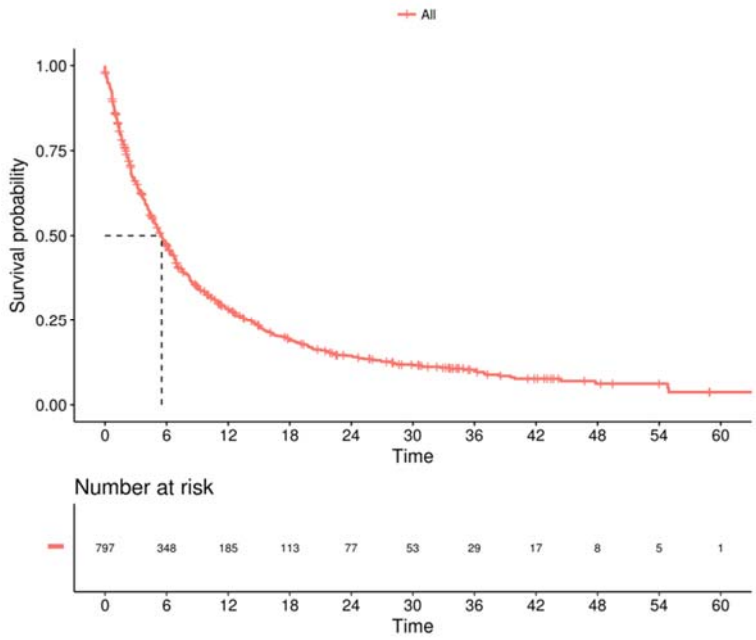
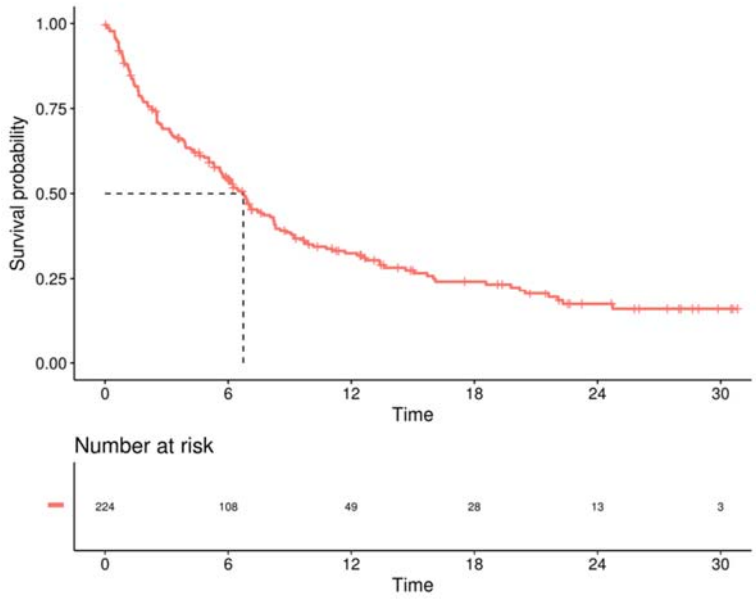



**Figure 4: Survival of Docetaxel II arm (median OS = 6.74 months, 95% CI: 5.59, 8.05)**




## IV. Conclusion

The FlatIron analysis provides consistent results of the overall survival of patients treated with docetaxel to those witnessed in SEER and NLCA. In addition, there is an apparent increase in the survival estimates since anti-PD1/PD-L1 checkpoint inhibitors have become available, suggesting later-line use may be improving the prognosis of these patients.

## Appendix 3: Overall Survival: Precedent from pembrolizumab appraisal

The figures depicted below have been taken directly from the MSD response to ACD for appraisal TA428, dated 24th October. The FAD states:

"The committee recalled that the original modelling projections, using the September 2015 KEYNOTE-010 data and the company's preferred assumptions, suggested that 10.3% and 1.2% of patients in the pembrolizumab arm would be alive at 5 years and 10 years, falling to 9.6% and 1.0% respectively when incorporating the March 2016 data submitted during consultation. Consultation comments from clinical experts noted that immunotherapies are expected to maintain their effect for a subgroup of people and that these values appear reasonable from clinical experience. But the committee considered that the assumption of a constant treatment effect over 20 years, irrespective of the time spent on treatment or disease progression was unlikely based on current clinical understanding of disease progression."

Nevertheless, as demonstrated in Figure 5, pembrolizumab is only deemed cost effective when there is no additional treatment waning, or treatment waning started from year 10 onwards: i.e. when 5 year overall survival is 9.6%.

In the previous response to ACD, Roche demonstrated atezolizumab to be at least non-inferior to pembrolizumab in the all-comer population. In addition, Appendix 3 of this response also demonstrates atezolizumab to be at least non-inferior to pembrolizumab in the PD-L1 positive population (TC/IC 1/2/3, >1% TPS). As such, precedence, and a consistent approach would confirm that the Roche extrapolation is a suitable analysis for decision making, and artificially manipulating the survival projection downwards through the ERG's preferred approach, is not reasonable, and is not reflective of the evidence available.

**Figure 5: Cost Effectiveness Scenario Analyses - pembrolizumab**

Table 4. Deterministic incremental cost-effectiveness results of base-case 2 (discounted, with PAS) – Updated cut-off data (March, 2016)

| Technologies | Total Costs | Total QALYs | Incremental Costs | Incremental QALYs | ICER (£/QALY) |
|---|---|---|---|---|---|
| *Base case – No additional treatment waning* | | | | | |
| 25% of patients receiving treatment after 2 years | | | | | |
| Pembrolizumab | £38,366 | 1.203 | - | - | - |
| Docetaxel | £11,416 | 0.597 | £26,950 | 0.606 | £44,490 |
| 100% of patients receiving treatment after 2 years | | | | | |
| Pembrolizumab | £41,136 | 1.203 | - | - | - |
| Docetaxel | £11,416 | 0.597 | £29,720 | 0.606 | £49,063 |
| *Additional treatment waning from year 3 onwards* | | | | | |
| 25% of patients receiving treatment after 2 years | | | | | |
| Pembrolizumab | £37,893 | 1.024 | - | - | - |
| Docetaxel | £11,416 | 0.597 | £26,477 | 0.427 | £61,954 |
| 100% of patients receiving treatment after 2 years | | | | | |
| Pembrolizumab | £40,662 | 1.024 | - | - | - |
| Docetaxel | £11,416 | 0.597 | £29,246 | 0.427 | £68,433 |
| Technologies | Total Costs | Total QALYs | Incremental Costs | Incremental QALYs | ICER (£/QALY) |
| *Additional treatment waning from year 5 onwards* | | | | | |
| 25% of patients receiving treatment after 2 years | | | | | |
| Pembrolizumab | £38,164 | 1.127 | - | - | - |
| Docetaxel | £11,416 | 0.597 | £26,748 | 0.530 | £50,438 |
| 100% of patients receiving treatment after 2 years | | | | | |
| Pembrolizumab | £40,934 | 1.127 | - | - | - |
| Docetaxel | £11,416 | 0.597 | £29,518 | 0.530 | £55,661 |
| *Additional treatment waning from year 10 onwards* | | | | | |
| 25% of patients receiving treatment after 2 years | | | | | |
| Pembrolizumab | £38,343 | 1.194 | - | - | - |
| Docetaxel | £11,416 | 0.597 | £26,927 | 0.597 | £45,100 |
| 100% of patients receiving treatment after 2 years | | | | | |
| Pembrolizumab | £41,113 | 1.194 | - | - | - |
| Docetaxel | £11,416 | 0.597 | £29,697 | 0.597 | £49,740 |

**Figure 6: Cost Effectiveness Scenario Analyses - pembrolizumab - base case**

Figure 5. OS for pembrolizumab vs. docetaxel based on updated cut-off data (March, 2016) and without implementing additional waning

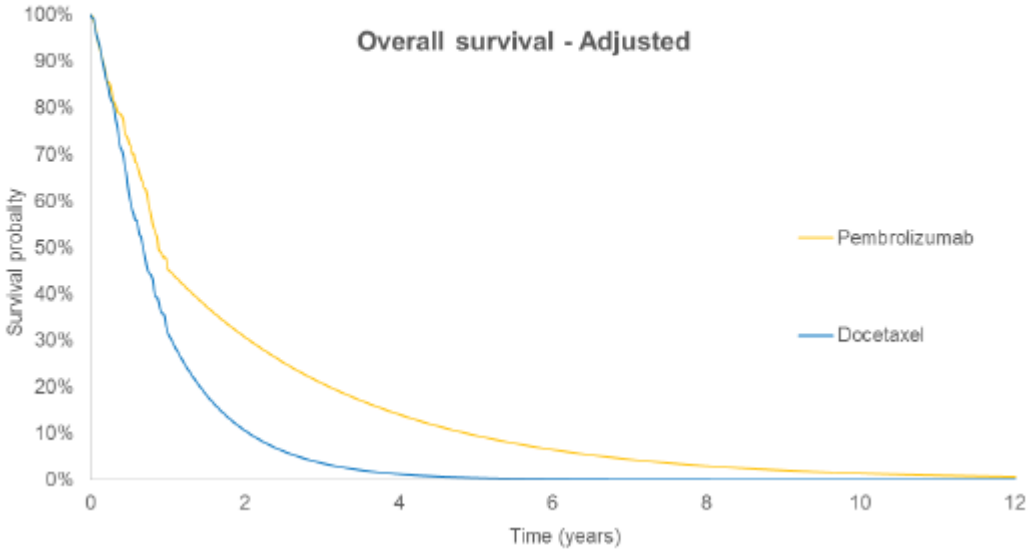



**Figure 7: Cost Effectiveness Scenario Analyses - pembrolizumab - 3 year benefit cap**

Figure 6. OS for pembrolizumab vs. docetaxel based on updated cut-off data (March, 2016), with additional waning beyond year 3

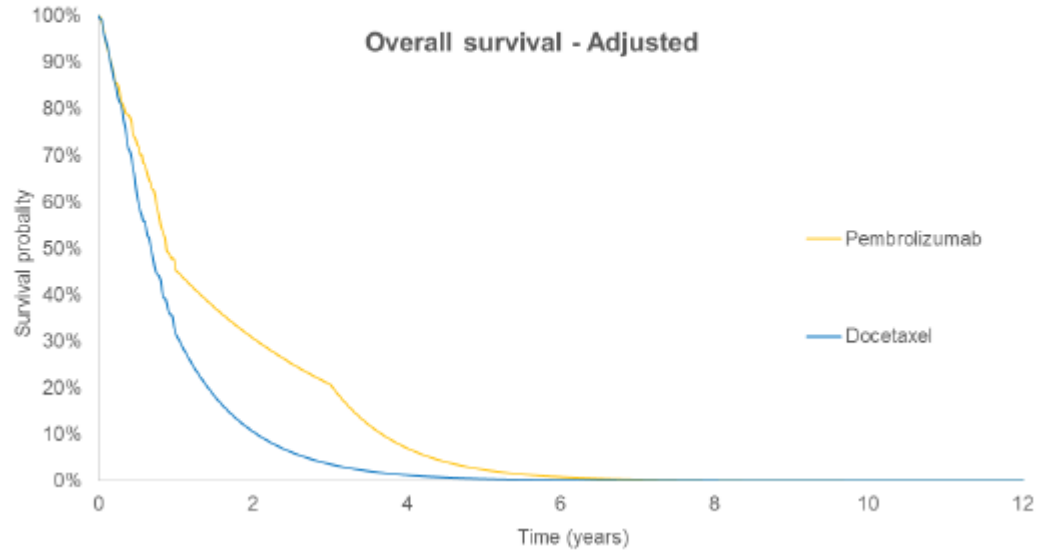


**Figure 8: Cost Effectiveness Scenario Analyses - pembrolizumab - 5 year benefit cap**

Figure 7. OS for pembrolizumab vs. docetaxel based on updated cut-off data (March, 2016), with additional waning beyond year 5

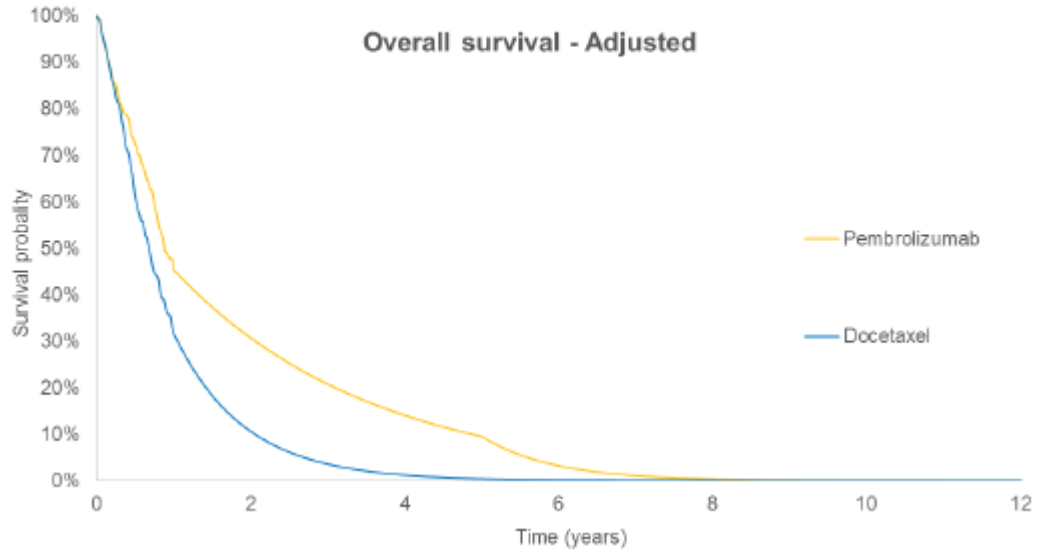
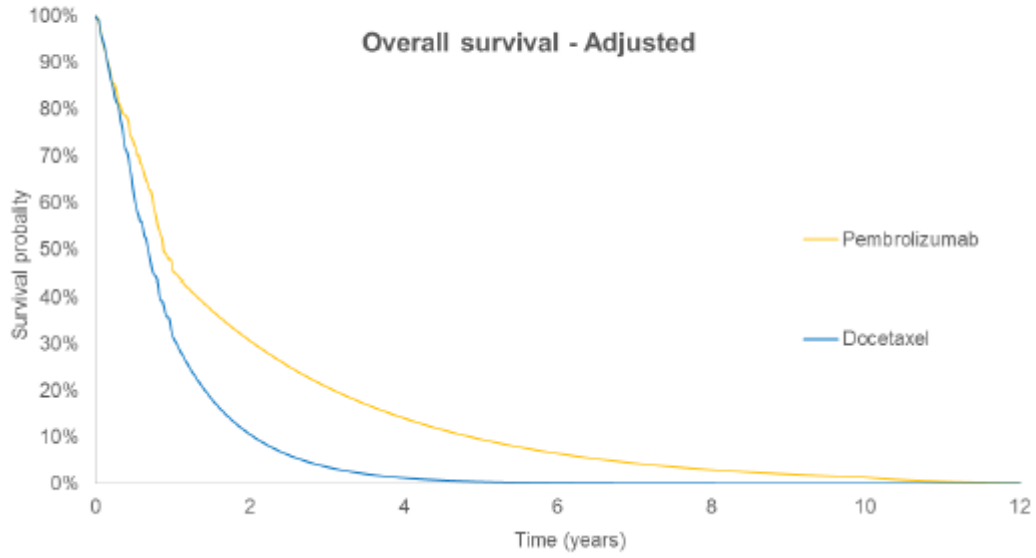



**Figure 9: Cost Effectiveness Scenario Analyses - pembrolizumab - 10 year benefit cap**

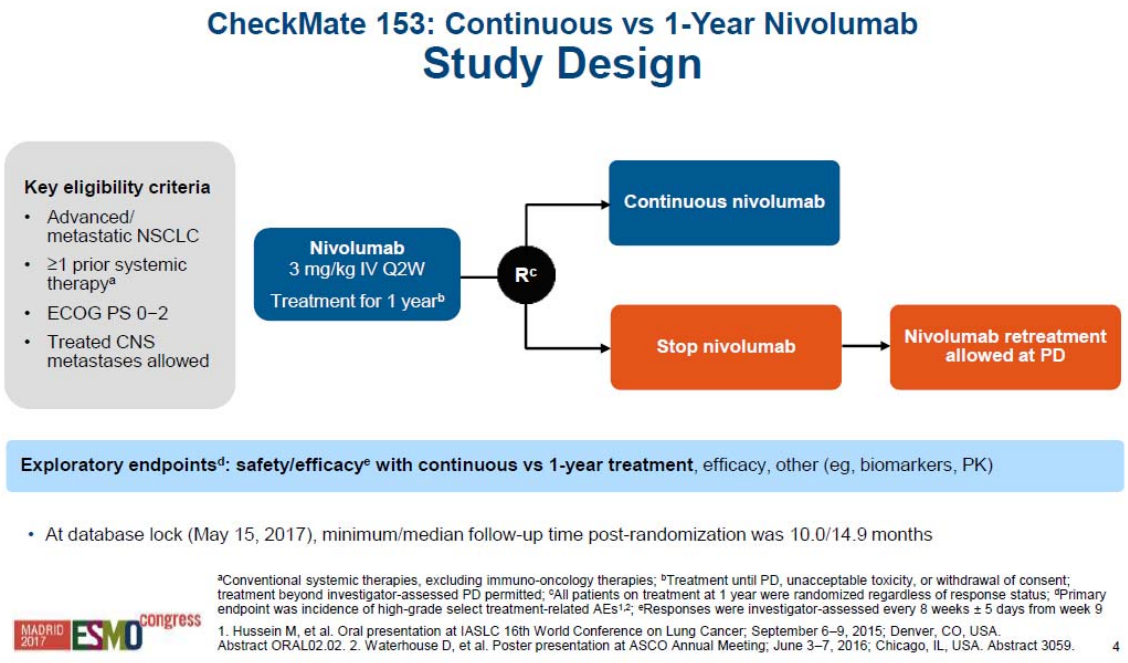
Figure 8. OS for pembrolizumab vs. docetaxel based on updated cut-off data (March, 2016), with additional waning beyond year 10

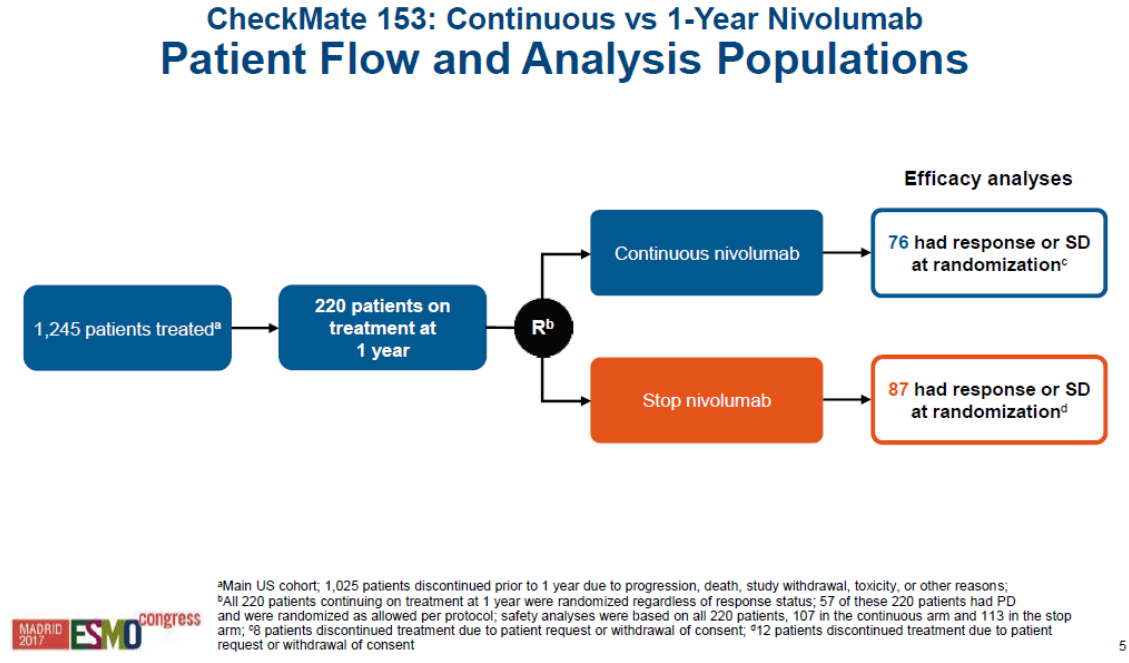


# Appendix 4: 2 year stopping rule

## Results from CheckMate 153

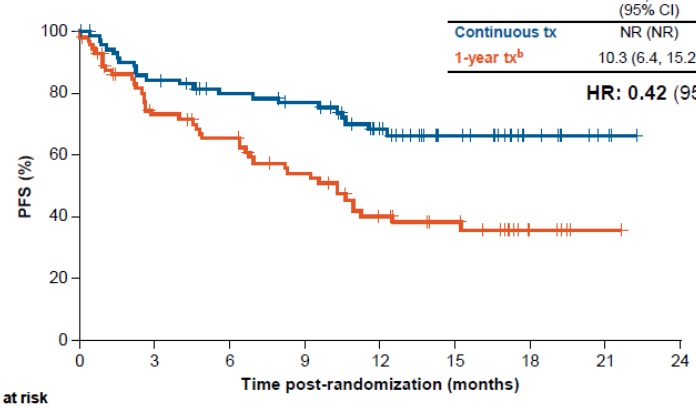
Following important questions regarding the optimal duration of treatment with PD-1 and PD-L1 inhibitors, CheckMate 153 was the first randomised study to evaluate the impact of treatment duration. Patients were randomised to receive continuous nivolumab, or discontinue after 1 year, with retreatment 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. Based on these results, the clinical community have expressed concern about stopping treatment in patients who are otherwise performing well. As such, it is now unreasonable for NICE to implement a stopping rule.



## CheckMate 153: Continuous vs 1-Year Nivolumab

# PFS From Randomization[a]




| | Median, months (95% CI) | PFS rate, % | |
|---|---|---|---|
| | | 6-month | 1-year |
| Continuous tx | NR (NR) | 80 | 65 |
| 1-year tx[b] | 10.3 (6.4, 15.2) | 69 | 40 |

**HR: 0.42** (95% CI: 0.25, 0.71)

| No. at risk | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| Continuous tx | 76 | 60 | 53 | 49 | 35 | 22 | 10 | 3 | 0 |
| 1-year tx | 87 | 50 | 43 | 33 | 21 | 16 | 5 | 1 | 0 |

[a]Patients who did not have PD at randomization; minimum/median follow-up time post-randomization, 10.0/14.9 months
[b]With optional retreatment allowed at PD
NR = not reached; tx = treatment

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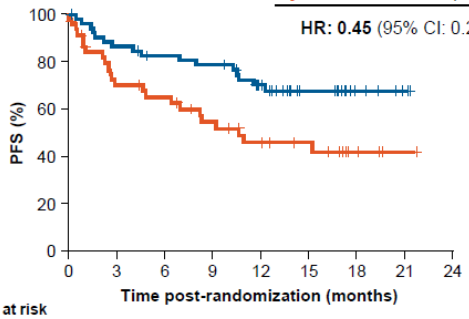
## CheckMate 153: Continuous vs 1-Year Nivolumab

# PFS From Randomization by Response Status[a]

**CR/PR**

| | Median, months (95% CI) |
|---|---|
| Continuous tx | NR (NR) |
| 1-year tx[b,c] | 10.6 (4.8, NA) |

**HR: 0.45** (95% CI: 0.24, 0.85)

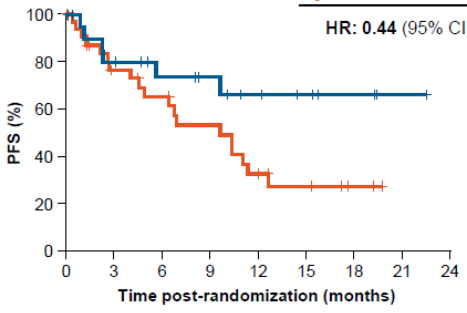



| No. at risk | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| Continuous tx | 53 | 45 | 41 | 39 | 28 | 17 | 7 | 2 | 0 |
| 1-year tx | 49 | 29 | 26 | 20 | 14 | 11 | 3 | 1 | 0 |

**SD**

| | Median, months (95% CI) |
|---|---|
| Continuous tx | NR (5.6, NA) |
| 1-year tx[b] | 9.6 (4.5, 12.6) |

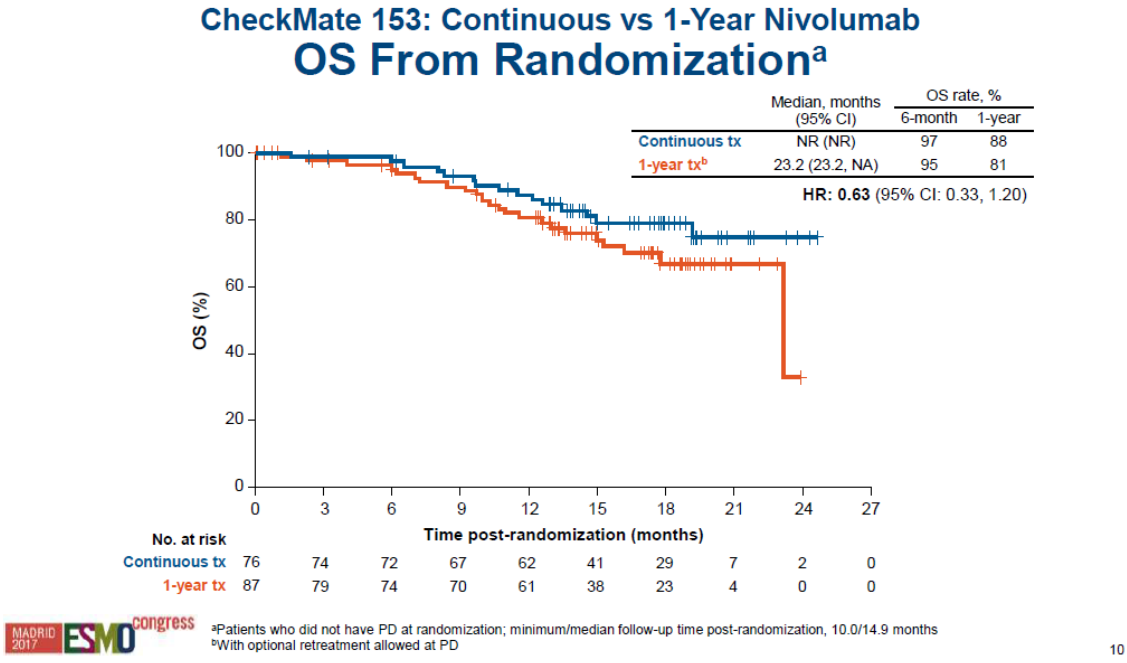
**HR: 0.44** (95% CI: 0.17, 1.09)




| | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | 23 | 15 | 12 | 10 | 7 | 5 | 3 | 1 | 0 |
| | 38 | 21 | 17 | 13 | 7 | 5 | 2 | 0 | 0 |

[a]Best overall response prior to randomization; minimum/median follow-up time post-randomization, 10.0/14.9 months; [b]With optional retreatment allowed at PD; [c]Two patients who stopped treatment had CR prior to randomization; both patients lost CR (6 and 13 months after stopping treatment) with progression due to new lesions; NA = not available

8




## Impact of stopping rule on atezolizumab cost effectiveness

The two year stopping rule has a minimal impact on atezolizumab's ICER, as demonstrated in Table 7, and is unreasonable given the evidence available.

**Table 7: Impact of 2 year stopping rule**

| Technologies | Total Cost | Total QALYs | Incremental Costs | Incremental QALYs | ICER |
|---|---|---|---|---|---|
| **All patients, company base case, no stopping rule: list price** | | | | | |
| Docetaxel | £20,181 | 0.71 | | | |
| Atezolizumab | £74,636 | 1.31 | £54,455 | 0.60 | £91,142 |
| **All patients, company base case, 2 year stopping rule: list price** | | | | | |
| Docetaxel | £20,181 | 0.71 | | | |
| Atezolizumab | £69,526 | 1.31 | £49,345 | 0.60 | £82,590 |
| **All patients, company base case, no stopping rule: PAS price** | | | | | |
| Docetaxel | £20,181 | 0.71 | | | |
| Atezolizumab | [redacted] | 1.31 | [redacted] | 0.60 | [redacted] |
| **All patients, company base case, 2 year stopping rule: PAS price** | | | | | |
| Docetaxel | £20,181 | 0.71 | | | |
| Atezolizumab | [redacted] | 1.31 | [redacted] | 0.60 | [redacted] |
| **All patients, ERG assumptions, no stopping rule: list price** | | | | | |
| Docetaxel | £20,534 | 0.69 | | | |
| Atezolizumab | £71,418 | 0.99 | £50,884 | 0.30 | £168,591 |
| **All patients, ERG assumptions, 2 year stopping rule: list price** | | | | | |
| Docetaxel | £20,534 | 0.69 | | | |
| Atezolizumab | £66,308 | 0.99 | £45,774 | 0.30 | £151,662 |
| **All patients, ERG assumptions, no stopping rule: PAS price** | | | | | |
| Docetaxel | £20,534 | 0.69 | | | |
| Atezolizumab | [redacted] | 0.99 | [redacted] | 0.30 | [redacted] |
| **All patients, ERG assumptions, 2 year stopping rule: PAS price** | | | | | |
| Docetaxel | £20,534 | 0.69 | | | |
| Atezolizumab | [redacted] | 0.99 | [redacted] | 0.30 | [redacted] |

# Appendix 5: Phase III OAK (GO28915) – PD-L1 Expression Subgroup Analyses: Clinical outcomes

Patients were recruited to OAK regardless of PD-L1 expression; however PD-L1 was a pre-determined stratification factor for the study. The prevalence of the PD-L1 expression subgroups in the primary population (PP) in OAK is summarised below (F. Hoffmann-La Roche Ltd, 2016b).

**Table 8: Baseline PD-L1 expression status**

| n (%) | Atezolizumab n=425 | Docetaxel n=425 | All patients N=850 |
|---|---|---|---|
| TC0 and IC0 | 180 (42.4) | 199 (46.8) | 379 (44.6) |
| TC1/2/3 or IC1/2/3 | 241 (56.7) | 222 (52.2) | 463 (54.5) |
| TC2/3 or IC2/3 | 129 (30.4) | 136 (32.0) | 265 (31.2) |
| TC3 or IC3 | 72 (16.9) | 65 (15.3) | 137 (16.1) |
| Unknown | 4 (0.9) | 4 (0.9) | 8 (0.9) |

## Baseline characteristics

Demographic characteristics in the PD-L1 subgroups were generally consistent with observations in the overall PP (Table 9) (F. Hoffmann-La Roche Ltd, 2016b, Rittmeyer et al., 2016).

**Table 9: Patient demographics and baseline characteristics in OAK (PD-L1 subgroups)**

| | TC 0 and IC0 | | TC1/2/3 or IC1/2/3 | | TC2/3 or IC 2/3 | | TC3 or IC3 | | ITT | |
|---|---|---|---|---|---|---|---|---|---|---|
| | Atezo n=180 | Docetaxel n=199 | Atezo n=241 | Docetaxel n=222 | Atezo n=129 | Docetaxel n=136 | Atezo n=72 | Docetaxel n=65 | Atezo n=425 | Docetaxel n=425 |
| Median age, years (range) | 63 (33–82) | 64 (34–84) | 63 (35–82) | 66 (39–85) | 62 (39–82) | 67 (40–85) | 62 (39–82) | 64 (34–85) | 63 (33–82) | 64 (34–85) |
| Age group, n (%) | | | | | | | | | | |
| <65 | 95 (53) | 115 (58) | 138 (57) | 101 (45) | 78 (61) | 55 (40) | 44 (61) | 25 (39) | 235 (55) | 218 (51) |
| ≥65 | 85 (47) | 84 (42) | 103 (43) | 121 (55) | 51 (40) | 81 (60) | 28 (39) | 40 (62) | 190 (45) | 207 (49) |
| Male, n (%) | 102 (57) | 129 (65) | 157 (65) | 126 (57) | 86 (67) | 72 (53) | 50 (69) | 38 (59) | 261 (61) | 259 (61) |
| Race, n (%) | | | | | | | | | | |
| Caucasian | 115 (64) | 134 (67) | 184 (76) | 159 (72) | 106 (82) | 98 (72) | 57 (79) | 49 (75) | 302 (71) | 296 (70) |
| Asian | 52 (29) | 48 (24) | 33 (14) | 46 (21) | 15 (12) | 25 (18) | 11 (15) | 10 (15) | 85 (20) | 95 (22) |
| Black or African American | 1 (1) | 7 (4) | 2 (1) | 4 (2) | 2 (2) | 4 (3) | 1 (1) | 1 (2) | 5 (1) | 11(3) |
| Other | 6 (3) | 4 (2) | 7 (4) | 2 (1) | 3 (2) | 5 (4) | 1 (1) | 3 (5) | 13 (3) | 9 (2) |
| Unknown | 6 (3) | 6 (3) | 13 (5) | 8 (4) | 3 (2) | 4 (3) | 2 (3) | 2 (3) | 20 (5) | 14 (3) |
| Mean weight at BL, kg (SD) | 69.7 (17.5) | 68.5 (14.0) | 75.2 (17.8) | 72.2 (17.4) | 75.6 (17.43) | 71.5 (15.9) | 75.5 (18.8) | 72.9 (14.8) | 72.9 (17.8) | 70.6 (16.1) |
| Tobacco use history, n (%) | | | | | | | | | | |
| Never | 45 (25) | 33 (17) | 39 (16) | 38 (17) | 14 (11) | 18 (13) | 10 (14) | 11 (17) | 84 (20) | 72 (17) |
| Current | 22 (12) | 31 (16) | 37 (15) | 33 (15) | 24 (19) | 22 (16) | 15 (21) | 12 (19) | 59 (14) | 67 (16) |
| Previous | 113 (63) | 135 (68) | 165 (69) | 151 (68) | 91 (71) | 96 (71) | 47 (65) | 42 (65) | 282 (66) | 286 (67) |
| ECOG PS, n (%) | | | | | | | | | | |
| 0 | 64 (36) | 74 (37) | 90 (37) | 85 (38) | 83 (64) | 85 (63) | 27 (38) | 21 (32) | 155 (36) | 160 (38) |
| 1 | 116 (65) | 125 (63) | 151 (63) | 137 (62) | 46 (36) | 51 (38) | 45 (63) | 44 (68) | 270 (64) | 265 (62) |
| Pathology/histology, n (%) | | | | | | | | | | |
| Non-squamous | 140 (78) | 150 (75) | 171 (71) | 162 (73) | 89 (69) | 99 (73) | 49 (68) | 47 (72) | 313 (74) | 315 (74) |
| Squamous | 40 (22) | 49 (25) | 70 (29) | 60 (27) | 40 (31) | 37 (27) | 23 (32) | 18 (28) | 112 (26) | 110 (26) |
| No. of prior therapies, n (%) | | | | | | | | | | |
| 1 | 142 (79) | 152 (76) | 174 (72) | 164 (74) | 92 (71) | 104 (77) | 53 (74) | 52 (80) | 320 (75) | 320 (75) |
| 2 | 38 (21) | 47 (24) | 67 (28) | 58 (26) | 37 (29) | 32 (23) | 19 (26) | 13 (20) | 105 (25) | 105 (25) |
| EGFR mutation, n (%) | | | | | | | | | | |
| Positive | 21 (12) | 28 (14) | 21 (9) | 15 (7) | 9 (7) | 4 (3) | 6 (8) | 3 (5) | 42(10) | 43 (10) |
| Negative | 138 (77) | 139 (70) | 178 (74) | 168 (76) | 98 (76) | 110 (81) | 54 (75) | 47 (72) | 318 (75) | 310 (73) |

| | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| Unknown | 21 (12) | 32 (16) | 42 (17) | 39 (18) | 22 (17) | 22 (16) | 12 (17) | 15 (23) | 65 (15) | 72 (17) |
| EML4-ALK translocation, n (%) | | | | | | | | | | |
| Negative | 101 (56) | 88 (44) | 121 (50) | 110 (49) | 59 (46) | 70 (52) | 39 (54) | 32 (49) | 223 (52) | 201 (47) |
| Unknown | 79 (44) | 111 (56) | 118 (49) | 112 (51) | 69 (54) | 66 (48) | 33 (46) | 33 (51) | 200 (47) | 224 (53) |
| KRAS mutation, n (%) | | | | | | | | | | |
| Positive | 12 (7) | 16 (8) | 13 (5) | 17 (7) | 4 (3) | 12 (9) | 3 (4) | 6 (9) | 26 (6) | 33 (8) |
| Negative | 40 (22) | 52 (26) | 58 (24) | 50 (23) | 33 (26) | 28 (21) | 23 (32) | 11 (17) | 99 (23) | 104 (24) |
| Unknown | 128 (71) | 131 (66) | 170 (71) | 155 (70) | 92 (71) | 96 (71) | 46 (64) | 48 (74) | 300 (71) | 288 (68) |

## Clinical efficacy by PD-L1 subgroups

### Duration of OS by PD-L1 expression subgroups in OAK

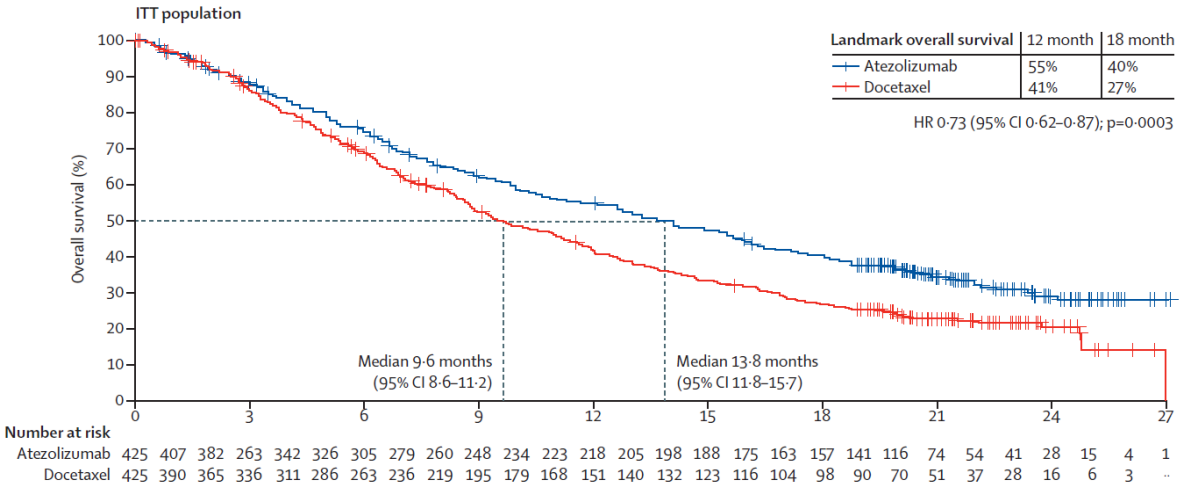
PD-L1 subgroup analysis showed an OS benefit of atezolizumab for all patients regardless of PD-L1 expression (F. Hoffmann-La Roche Ltd, 2016b, Rittmeyer et al., 2016).

**Table 10: Overall survival by PD-L1 expression subgroups**

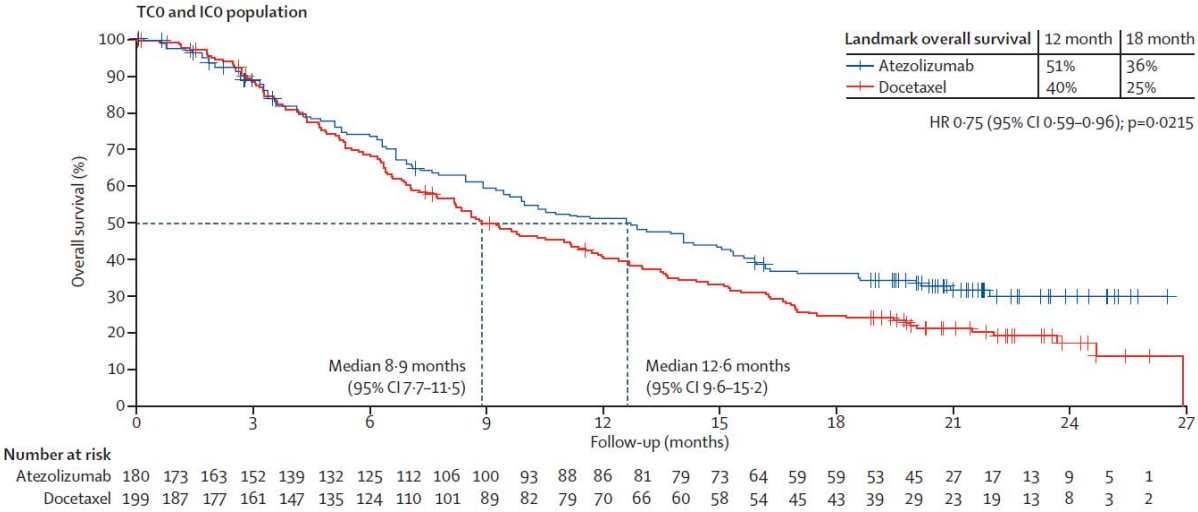
| | **Atezolizumab** | **Docetaxel** |
|---|---|---|
| **ITT population** | **n=425** | **n=425** |
| Patients with event (%) | 271 (63.8) | 298 (70.1) |
| Median duration of survival, months (95% CI) | 13.8 (11.8, 15.7) | 9.6 (8.6, 11.2) |
| Unstratified HR (95% CI)<br>p value | 0.73 (0.62, 0.86)<br>p=0.0002 | |
| **TC0 and IC0** | **n=180** | **n=199** |
| Patients with event (%) | 116 (64.4) | 146 (73.4) |
| Median duration of survival, months (95% CI) | 12.6 (9.6, 15.2) | 8.9 (7.7, 11.5) |
| Unstratified HR (95% CI)<br>p value | 0.75 (0.59, 0.96)<br>p=0.0215 | |
| **TC1/2/3 or IC1/2/3** | **n=241** | **n=222** |
| Patients with event (%) | 151 (62.7) | 149 (67.1) |
| Median duration of survival, months (95% CI) | 15.7 (12.6, 18.0) | 10.3 (8.8, 12.0) |
| Unstratified HR (95% CI)<br>p value | 0.72 (0.58, 0.91)<br>p=0.0102 | |
| **TC2/3 or IC2/3** | **n=129** | **n=136** |
| Patients with event (%) | 79 (61.2) | 92 (67.6) |
| Median duration of survival, months (95% CI) | 16.3 (13.3, 20.1) | 10.8 (8.8, 12.7) |
| Unstratified HR (95% CI)<br>p value | 0.67 (0.49, 0.90)<br>P=0.0080 | |
| **TC3 or IC3** | **n=72** | **n=65** |
| Patients with event (%) | 37 (51.4) | 49 (75.4) |
| Median duration of survival, months (95% CI) | 20.5 (17.5, NE) | 8.9 (5.6, 11.6) |
| Unstratified HR (95% CI)<br>p value | 0.41 (0.27, 0.64)<br>P<0.0001 | |

The KM curves showed a clear separation from 3 months onwards, in favour of the atezolizumab arm, for all PD-L1 expression subgroups, similar to those for the ITT population.

## Figure 10: Kaplan-Meier plot of OS - ITT




## Figure 11: Kaplan-Meier plot of OS – TC0 and IC0




## Figure 12: Kaplan-Meier plot of OS – TC1/2/3 or IC1/2/3

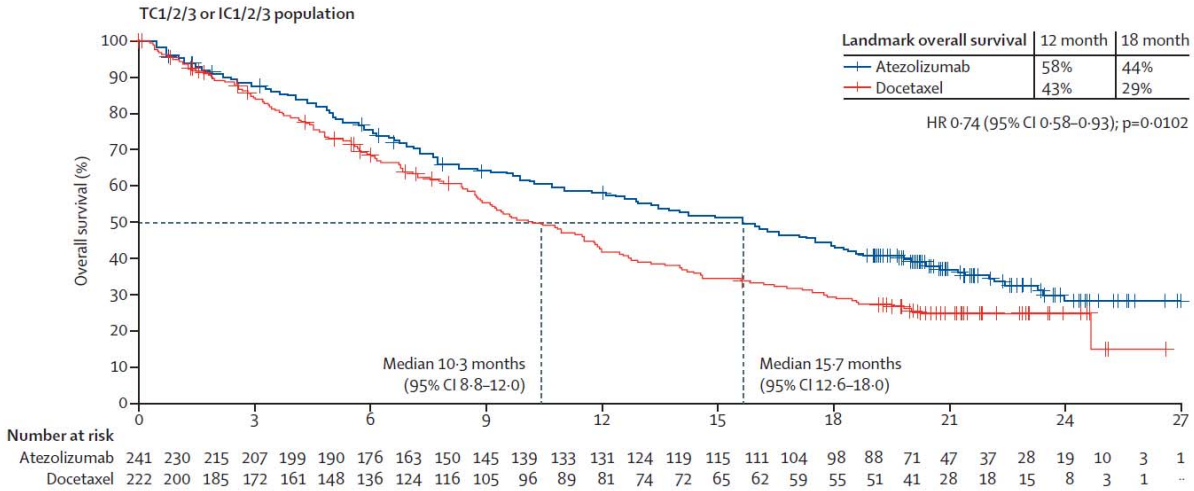


**Figure 13: Kaplan-Meier plot of OS – TC2/3 or IC2/3**

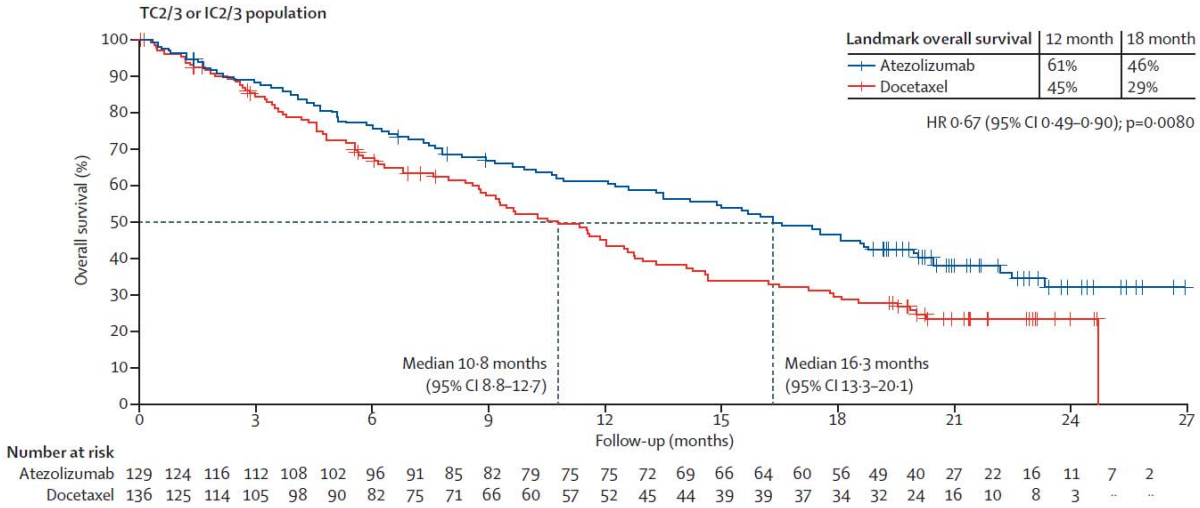
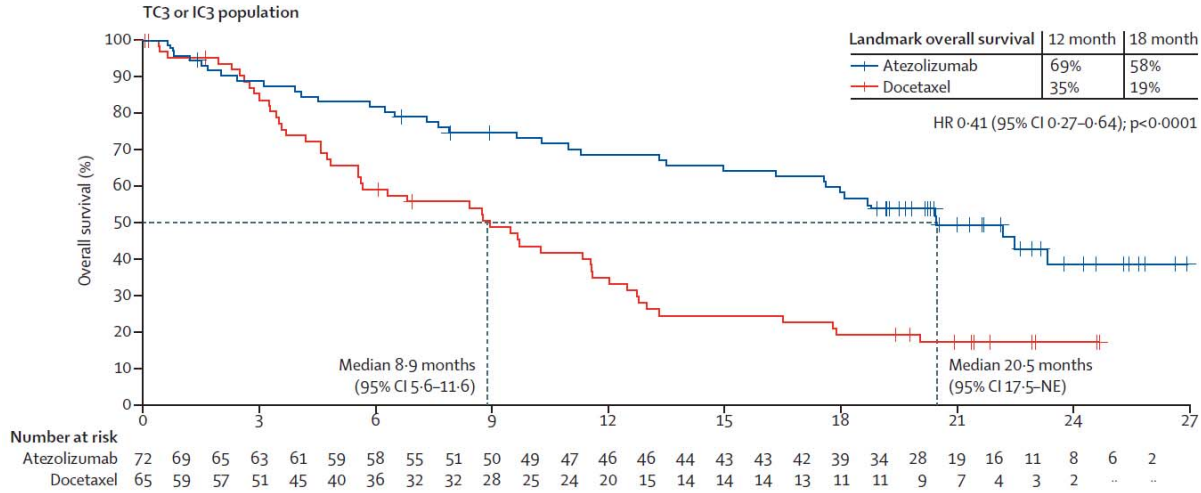



**Figure 14: Kaplan-Meier plot of OS – TC3 or IC3**



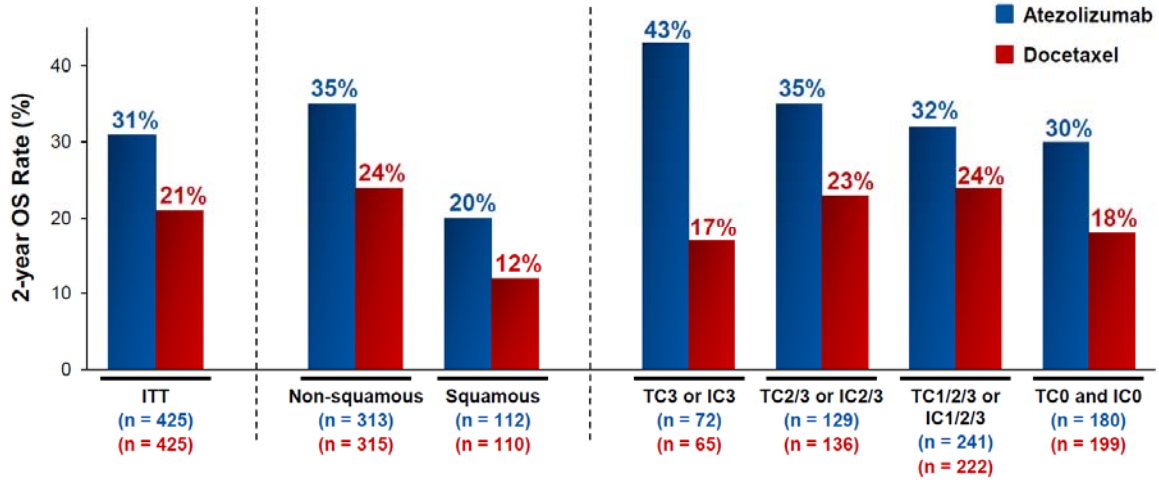

**Landmark 2-year overall survival data in OAK**

An analysis of the long term survivors (LTS) from the OAK study was presented at the International Association for the Study of Lung Cancer World Conference on Lung Cancer (WCLC) in October 2017. Long term survivors were defined as those alive ≥24 months since randomisation. In this analysis, atezolizumab provided a superior 2-year OS benefit over docetaxel (31% vs 21%), a finding that was consistent across all histologies and PD-L1 subgroups (Satouchi M et al., 2017). It is also important to note that 40% of the 119 LTSs treated with atezolizumab in OAK were in the TC0 and IC0 PD-L1 subgroup, which again reiterates the benefit that atezolizumab demonstrates in this group of patients, for which there remains a high unmet need. These data are presented below.

**Table 11: Baseline characteristics of LTS and non-LTS**

| Baseline characteristic | Atezolizumab n=398 | | Docetaxel n=376 | |
|---|---|---|---|---|
| | LTS n=119 | Non-LTS n=279 | LTS n=77 | Non-LTS n=299 |
| Median age, years (range) | 63 (35–81) | 64 (33–82) | 62 (41–84) | 64 (34–85) |
| Female, % | 49 | 34 | 42 | 38 |
| Non-squamous histology, % | 85 | 70 | 84 | 69 |
| ECOG PS 0, % | 50 | 32 | 62 | 32 |
| Never smoker, % | 24 | 17 | 18 | 15 |
| One prior line of therapy, % | 75 | 75 | 71 | 77 |
| Positive EGFR mutation status, % | 9 | 9 | 13 | 8 |
| PD-L1 expression, % | | | | |
| TC3 or IC3 | 24 | 14 | 13 | 16 |
| TC1/2/3 or IC1/2/3 | 60 | 56 | 58 | 50 |
| TC0 and IC0 | 40 | 43 | 42 | 49 |

**Figure 15: 2-year OS benefit by histology and PD-L1 expression subgroups (OAK)**




Landmark 3-year overall survival data for POPLAR were also presented at WCLC in October 2017, which showed that a superior OS benefit was observed with atezolizumab vs docetaxel at all landmark timepoints (3-year survival rates: 19% and 10%, respectively) (Figure 16). As for the 2-year landmark OS rate in the latest OAK analyses, the 3-year landmark OS rate in POPLAR was observed across all histology and PD-L1 subgroups, including TC0 and IC0 (Figure 17) (Park K et al., 2017).

**Figure 16: 3-year landmark overall survival in POPLAR**

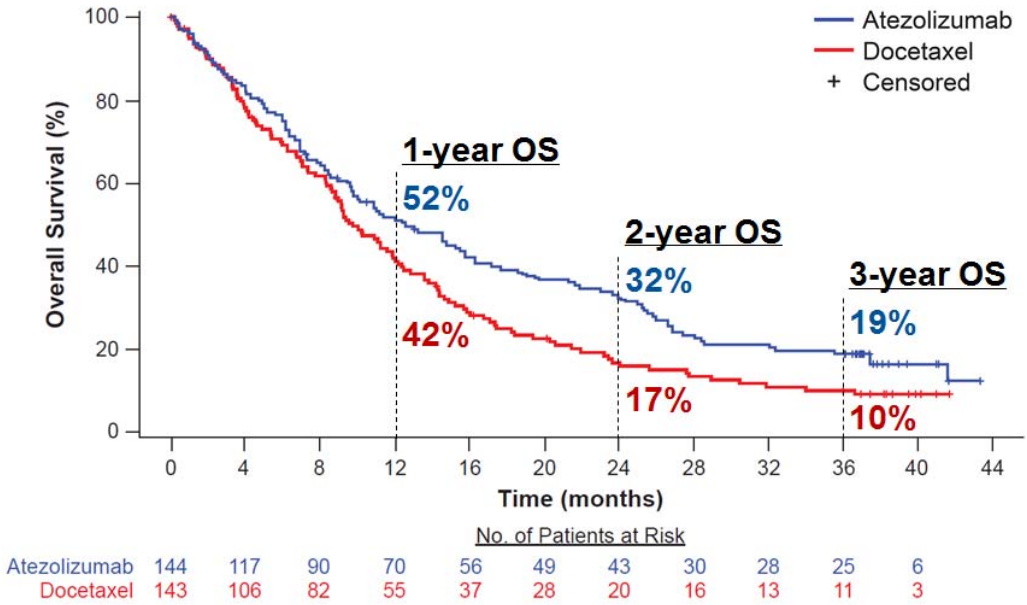
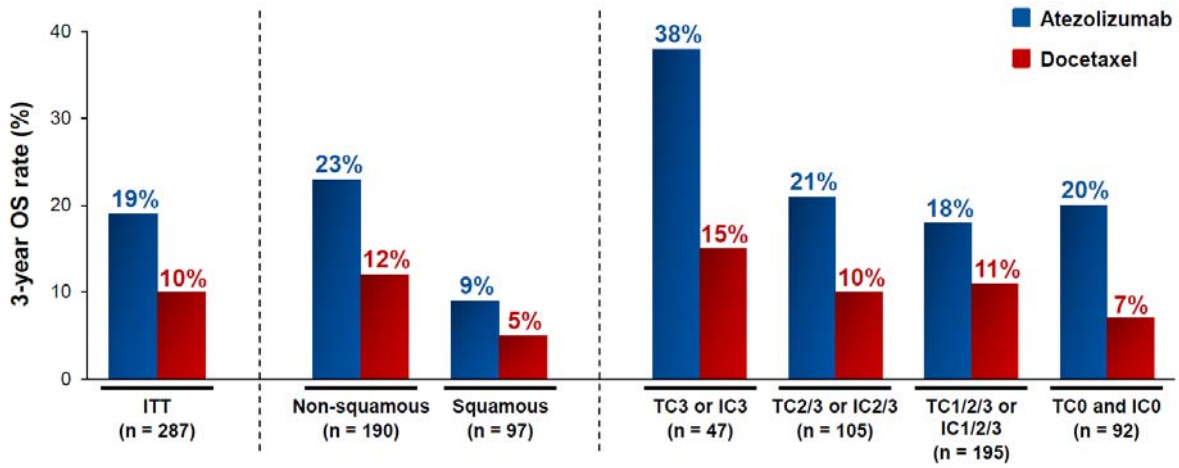



**Figure 17: 3-year OS benefit by histology and PD-L1 expression subgroups (POPLAR)**




**Duration of response by PD-L1 subgroups in OAK**

PD-L1 expression subgroup analysis showed an improvement in DOR for patients treated with atezolizumab regardless of PD-L1 expression (F. Hoffmann-La Roche Ltd, 2016b).

**Table 12: Duration of response by PD-L1 subgroups (OAK)**

| | Atezolizumab | Docetaxel |
|---|---|---|
| **ITT population** | **n=58** | **n=57** |
| Time to event, months (95% CI) | 16.3 (10.0, NE) | 6.2 (4.9, 7.6) |
| Unstratified HR (95% CI) | 0.34 (0.21, 0.55) | |
| **TC0 and IC0** | **n=14** | **n=21** |
| Time to event, months (95% CI) | NE (13.8, NE) | 6.2 (2.9, 9.0) |

| | | |
|---|---|---|
| Unstratified HR (95% CI) | 0.20 (0.07, 0.63) | |
| **TC1/2/3 or IC1/2/3** | **n=43** | **n=36** |
| Time to event, months (95% CI) | 16.0 (9.7, NE | 6.2 (4.9, 9.2) |
| Unstratified HR (95% CI) | 0.38 (0.22, 0.65) | |
| **TC2/3 or IC2/3** | **n=29** | **n=17** |
| Time to event, months (95% CI) | [redacted] | [redacted] |
| Unstratified HR (95% CI) | [redacted] | |
| **TC3 or IC3** | **n=22** | **n=7** |
| Time to event, months (95% CI) | [redacted] | [redacted] |
| Unstratified HR (95% CI) | [redacted] | |

Data from the secondary analyses in OAK (N=1225, clinical cut-off January 2017) demonstrate that the median duration of response for atezolizumab increased to [redacted] with the upper bound not estimable (as observed in the primary analysis), demonstrating the responses are still ongoing ([redacted]) (F. Hoffmann-La Roche Ltd, 2017a).

This increase in the duration of response as the data matures is consistent with the POPLAR analyses, which has shown an increase in duration of response from 14.3 months (11.6 NE) in the primary analysis to 18.6 months (11.6, NE) in the updated analysis (Fehrenbacher et al., 2016, Smith et al., 2016). At the most recent analysis (clinical cut off April 2017) the median duration of response had further increased to 22.3 months (Park K et al., 2017).

## OAK PD-L1 subgroup analyses discussion

Improved OS with atezolizumab relative to docetaxel was observed across all PD-L1 expression subgroups, with a potentially more pronounced improvement seen in patients with the highest PD-L1 expression (TC3 or IC3 subgroup), consistent with what was observed in POPLAR. However, it is important to note that the primary analysis population of the OAK study was not powered to establish efficacy in the TC3 or IC3 subgroup; as such, the confidence intervals are wide and overlap considerably with those of the other PD-L1 subgroups. Importantly, clinically significant benefit extended to patients with the lowest PD-L1 expressing tumours (TC0 and IC0, HR 0.75, 95% CI: 0.59, 0.96). The substantial OS benefit in this subgroup (HR 0.75, 95% CI: 0.59, 0.96) was not seen in the smaller POPLAR study (HR 1.04, 95% CI: 0.62, 1.75 for the primary analysis; HR 0.88, 95% CI: 0.55, 1.42 for the updated analysis) (F. Hoffmann-La Roche Ltd, 2015, F. Hoffmann-La Roche Ltd, 2016a, Fehrenbacher et al., 2016). Since the OAK study had a much larger sample size and the narrower 95% confidence intervals for the HR in the TC0 and IC0 subgroup did not cross 1, the studies in aggregate are strongly indicative of an all-comer treatment effect with significant OS benefit even among patients with low or no PD-L1 expression, which is supported by the OAK LTS analysis.

Further analyses from the OAK study will be published as the data matures. Given the similarities in the study designs, it is anticipated that analyses of the OAK study will mirror that seen in the Phase II POPLAR study, which has shown a superior OS benefit with atezolizumab vs docetaxel at all landmark timepoints, with an increase in the median duration of response with atezolizumab at each analysis. These data demonstrate that a proportion of patients treated with immunotherapy achieve a sustained, durable response which translates into elevated long-term overall survival.

# Appendix 6: ITC

*Updated Appendix distinguishing between treatment-switching adjustment, as opposed to cross-over adjustment.*

## ***Atezolizumab TC/IC 3 versus pembrolizumab >50% TPS and docetaxel***

The reduced network diagram is shown in Figure 18 and includes OAK, POPLAR and KEYNOTE-010. As demonstrated in Figure 19, atezolizumab does not provide statistically significant superior efficacy compared to pembrolizumab. If we assume the same approach preferred by NICE for the comparison of nintedanib+docetaxel, overall survival would be assumed to be the same between the two products. Despite the superior efficacy demonstrated by pembrolizumab in this population, it has been recommended for funding in a wider population. Therefore we encourage NICE to rather focus on the more complete subgroups, and the unmet need experienced in other subgroups such as the negative and low expressors.

**Figure 18: Network diagram TC/IC 3, >50% TPS: Overall Survival (OS) (FE fractional polynomials model, first order p1=0)**

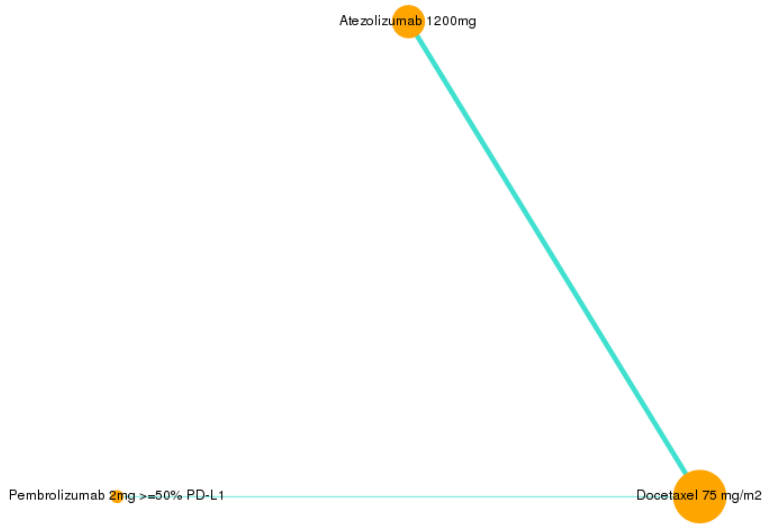



**Table 13: Trials and Drugs included: Overall survival (OS) (FE fractional polynomials model, first order p1=0)**

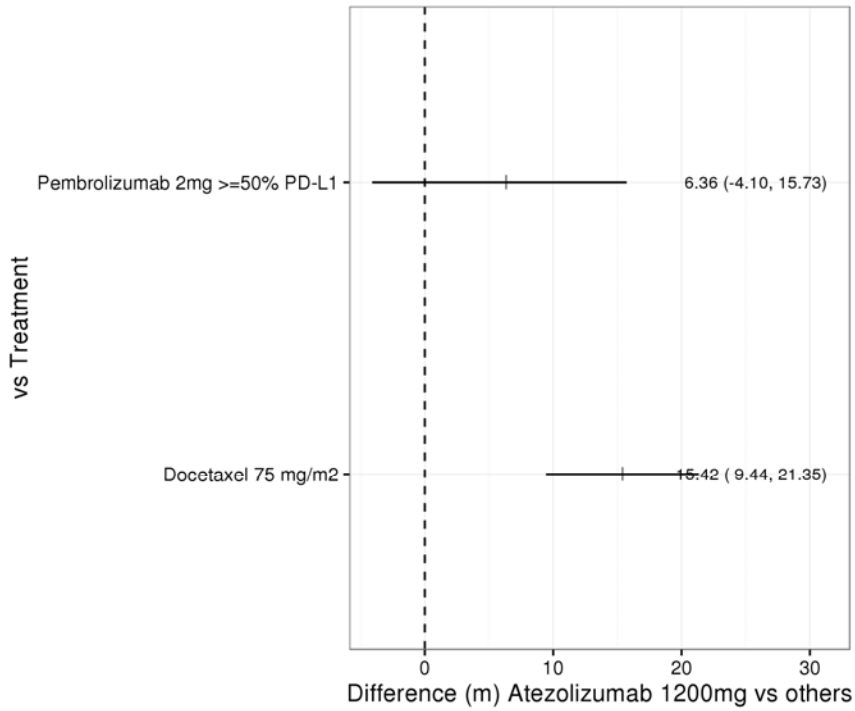
| Study | Reference Treatment | Comparator 1 |
|---|---|---|
| Herbst 2015 (KEYNOTE 010) | Pembrolizumab 2mg >=50% PD-L1 | Docetaxel 75 mg/m2 |
| POPLAR IPD | Docetaxel 75 mg/m2 | Atezolizumab 1200mg |
| OAK IPD | Docetaxel 75 mg/m2 | Atezolizumab 1200mg |

**Table 14: Expected survival (months) by treatment TC/IC 3, >50% TPS: Overall survival (OS) (FE fractional polynomials model, first order p1=0) (Time horizon: 5 years)**

| | Expected survival (95% CrI), months |
|---|---|
| **Docetaxel 75 mg/m2** | 12.83<br>(10.25, 16.72) |
| **Pembrolizumab 2mg >=50% PD-L1** | 21.97<br>(14.49, 31.06) |

| | Expected survival (95% CrI), months |
|---|---|
| **Atezolizumab 1200mg** | 28.31<br>(22.96, 34.16) |

**Figure 19: Forest Plot of Expected survival difference (months) and 95% credible intervals (CrI) of Atezolizumab versus Other Comparators TC/IC 3, >50% TPS: Overall survival (OS) (FE fractional polynomials model, first order p1=0)**




## ***Atezolizumab TC/IC 1/2/3 versus pembrolizumab >1% TPS and docetaxel: treatment-switch adjustment***

Similar to the pembrolizumab appraisal (National Institute for Health and Care Excellence, 2016) and in-line with the NICE DSU guidance (Latimer, 2014), the Rank Preserving Structural Failure Time (RPSFT) method was used to assess the impact of treatment switching on OS estimates. Whereas Latimer recommends utilising in trial data to obtain an estimate of the survival time gained/lost by receiving active treatment (i.e. either randomized or “cross-over” active treatment), this assumes treatment is acting by multiplying survival time by a given factor once patient starts receiving active treatment. Rather, an alternative method was explored utilising the December 2015 data cut of the phase II RCT of atezolizumab versus docetaxel, POPLAR. This trial, identical in design to OAK, had experienced very little treatment switching, thus was considered a much cleaner data set. As such, an estimation of the multiplicative factor (interpreted as relative increase/decrease in survival if one took active treatment compared to taking control) could be obtained to allow us to reconstruct the survival duration of patients, as if they had never received active treatment. Such an approach allows for a more robust adjustment for cross over.

The reduced network diagram is shown in Figure 20 and includes OAK, POPLAR and KEYNOTE-010. This ITC is utilised in the CEA of atezolizumab in PD-L1 positive patients.

**Figure 20: Network diagram TC/IC 1/2/3, >1% TPS: Overall Survival (OS) (FE fractional polynomials model, first order p1=0)**

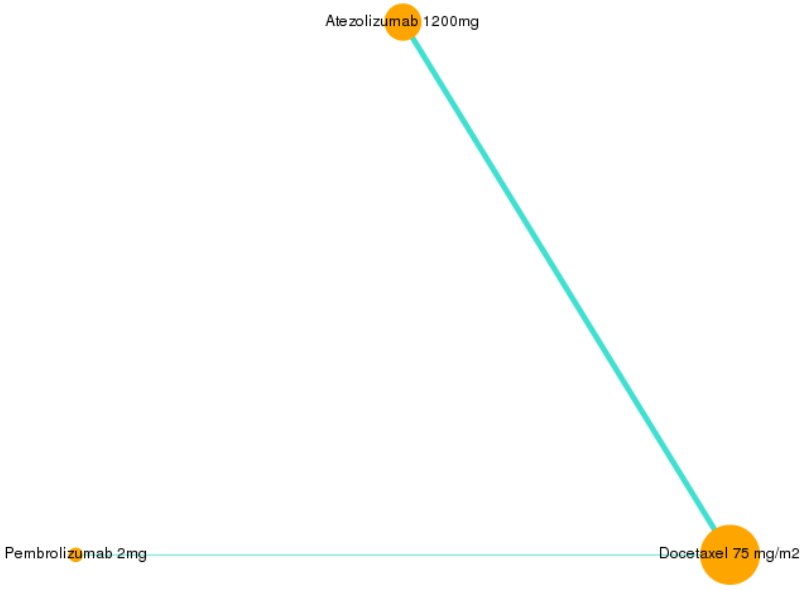



**Table 15: Expected survival (months) by treatment TC/IC 1/2/3, >1% TPS, with adjustment: Overall survival (OS) (FE fractional polynomials model, first order p1=0) (Time horizon: 5 years)**

| | Expected survival (95% CrI), months |
|---|---|
| **Docetaxel 75 mg/m2** | 13.32<br>(11.66, 15.52) |
| **Pembrolizumab 2mg** | 19.36<br>(14.80, 25.04) |
| **Atezolizumab 1200mg** | 21.37<br>(18.78, 24.26) |

**Figure 21: Forest Plot of Expected survival difference (months) and 95% credible intervals (CrI) of Atezolizumab versus Other Comparators TC/IC 1/2/3, >1% TPS, with adjustment: Overall survival (OS) (FE fractional polynomials model, first order p1=0)**

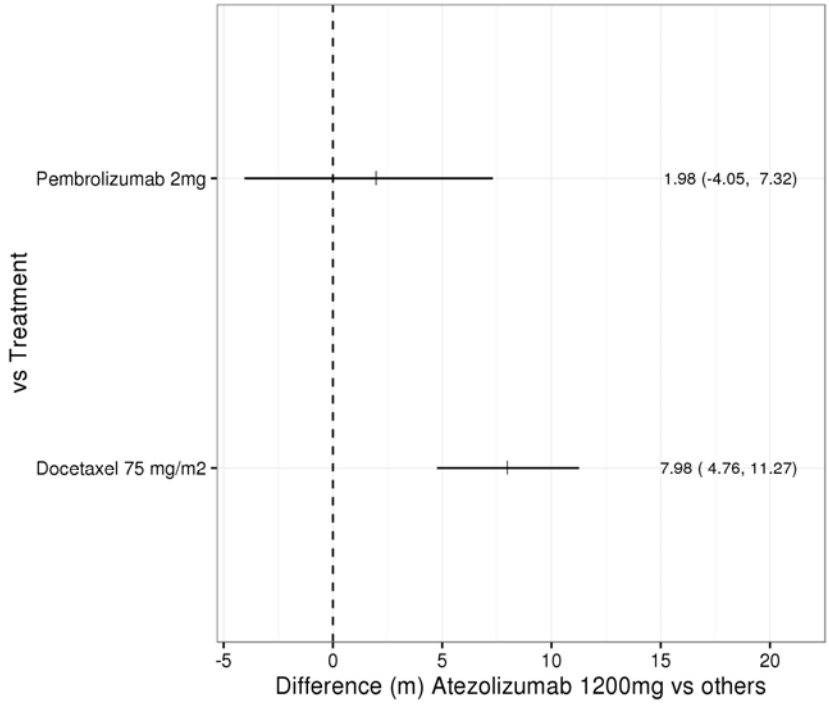
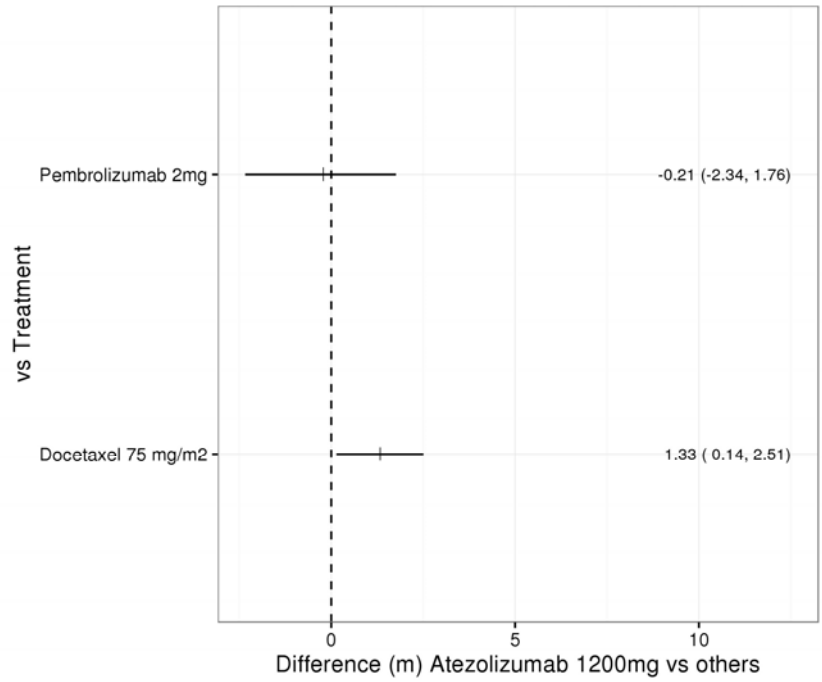



**Table 16: Expected survival (months) by treatment TC/IC 1/2/3, >1% TPS, with adjustment: Progression Free survival (OS) (FE fractional polynomials model, first order p1=1) (Time horizon: 2.5 years)**

| | **Expected survival (95% CrI), months** |
|---|---|
| **Docetaxel 75 mg/m2** | 5.37<br>(4.68, 6.19) |
| **Pembrolizumab 2mg** | 6.91<br>(5.19, 8.90) |
| **Atezolizumab 1200mg** | 6.71<br>(5.76, 7.72) |

**Figure 22: Forest Plot of Expected survival difference (months) and 95% credible intervals (CrI) of Atezolizumab versus Other Comparators TC/IC 1/2/3, >1% TPS, with adjustment: Progression Free survival (OS) (FE fractional polynomials model, first order p1=1)**



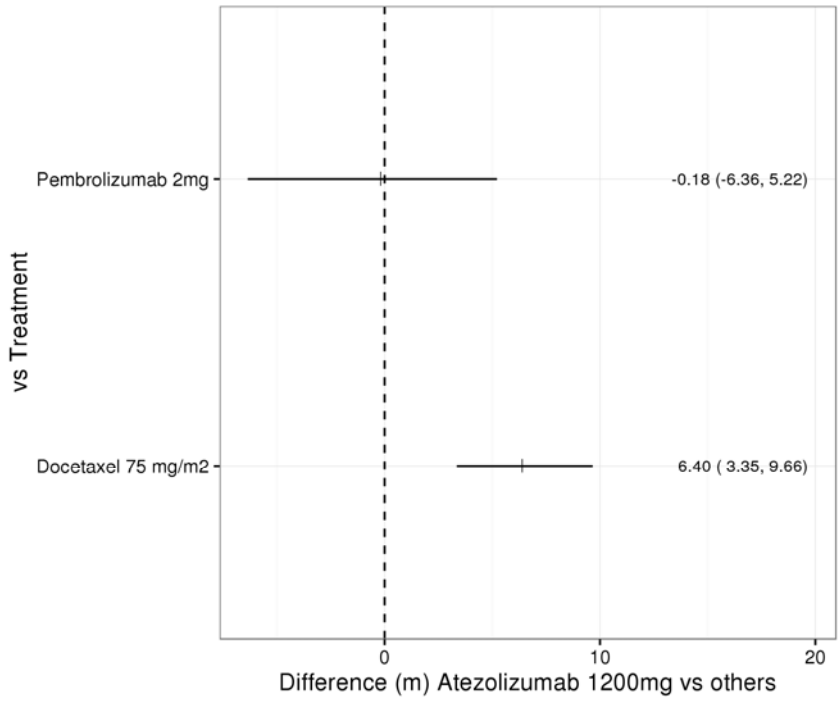

## ***Atezolizumab TC/IC 1/2/3 versus pembrolizumab >1% TPS and docetaxel: without adjustment***

The same network to the above has been utilised: only the OS estimates have varied without treatment-switch adjustment.

**Table 17: Expected survival (months) by treatment TC/IC 1/2/3, >1% TPS, without adjustment: Overall survival (OS) (FE fractional polynomials model, first order p1=0) (Time horizon: 5 years)**

| | **Expected survival (95% CrI), months** |
|---|---|
| **Docetaxel 75 mg/m2** | 14.62<br>(12.84, 16.77) |
| **Pembrolizumab 2mg** | 21.19<br>(16.40, 26.75) |
| **Atezolizumab 1200mg** | 21.03<br>(18.50, 23.72) |

**Table 18: Forest Plot of Expected survival difference (months) and 95% credible intervals (CrI) of Atezolizumab versus Other Comparators TC/IC 1/2/3, >1% TPS, without adjustment: Overall survival (OS) (FE fractional polynomials model, first order p1=0)**



# Appendix 7: Phase III OAK (GO28915) – PD-L1 Expression Subgroup Analyses: Economic results: TC/IC 0

*Updated Appendix driven by errors identified in the economic model:*

- *Corrections for ERG-identified errors from ITT economic model*
- *Updated OS analyses.*

Unless otherwise stated below, the TC/IC 0 economic model utilises the same assumptions as has been presented in the ITT population. It should be noted, the cost of testing for PD-L1 expression has not been included in the analysis. As atezolizumab has shown benefit irrespective of expression, and has achieved a license for the treatment of all patients, there is no requirement of a diagnostic test. By applying the cost of testing to this and the positives population, the benefits of atezolizumab as an effective treatment in all subgroups, thus no requirement for testing, is not appropriately captured.

As the proportional hazards assumption is violated, separate parameterisations of the OAK data have been conducted.

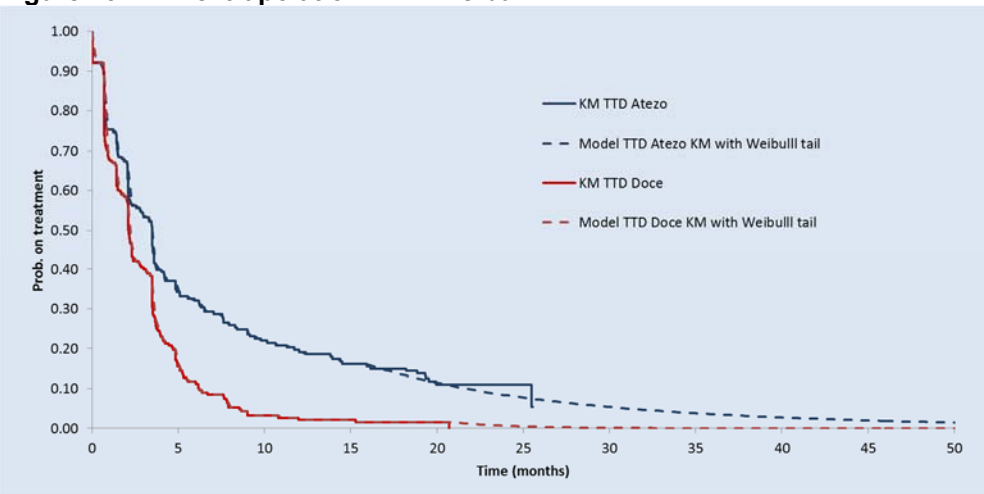
### *TTD extrapolation*

The AIC/BIC statistics for both atezolizumab and docetaxel are provided in Table 19. NICE DSU guidance specifies that where the proportional hazards assumption has not been met, or does not need to be assumed, fitting separate types of parametric models to individual treatment arms requires substantial justification, and rather it is most sensible to fit separate parametric models of the same type, allowing a two-dimensional treatment effect on both the shape and scale parameters of the parametric distribution (Latimer, 2013a). When assessing the best statistical fit a difference of five or more is generally considered important, therefore the Weibull, as the second best fitting curve to both treatment arms, and a minimial difference in AIC/BIC was chosen. Consistent with the approach taken in the ITT population, the KM data was utilised until 15% at risk for atezolizumab, and 1% at risk for docetaxel.

**Table 19: AIC/BIC TTD: atezolizumab and docetaxel**

| | Atezolizumab | | | Docetaxel | | |
|---|---|---|---|---|---|---|
| Distribution | AIC | BIC | Rating | AIC | BIC | Rating |
| EXPONENTIAL | 715.22 | 718.41 | 6 | **621.95** | **625.19** | **1** |
| WEIBULL | 680.53 | 686.89 | 2 | 623.03 | 629.50 | 2 |
| LNORMAL | 692.26 | 698.62 | 5 | 673.81 | 680.29 | 4 |
| GAMMA | 681.03 | 690.57 | 4 | 624.92 | 634.63 | 5 |
| LLOGISTIC | **679.95** | **686.31** | **1** | 646.93 | 653.40 | 6 |
| GOMPERTZ | 717.22 | 723.59 | 7 | 623.95 | 630.43 | 4 |
| NPH WEIBULL | 680.53 | 686.89 | 2 | 623.03 | 629.50 | 2 |

**Figure 23: TTD extrapolation: KM+Weibull**



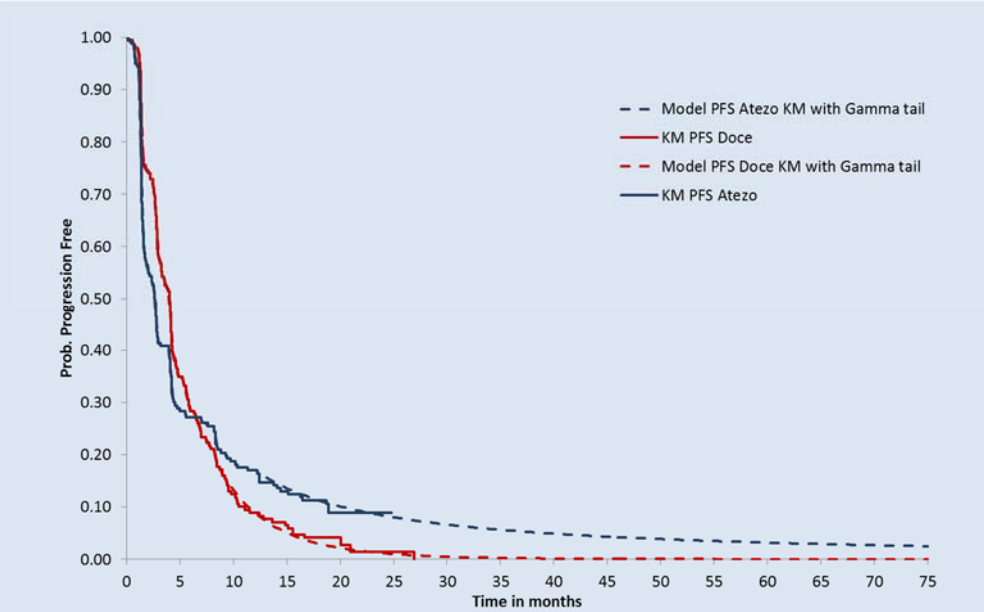

### *PFS extrapolation*

The AIC/BIC statistics for both atezolizumab and docetaxel are provided in Table 20. Consistent with the ITT population, the gamma is the best statistical fit for atezolizumab. It is also the second best statistical to docetaxel, therefore it is deemed appropriate to use. As above, and in line with the approach taken in the ITT population, the KM with Gamma tail applied upon 15% at risk for atezolizumab, and 1% at risk for docetaxel. It should be noted: PFS is not a driver in the economic analysis, thus alternative distributions have minimal impact on the results.

**Table 20: AIC/BIC PFS: atezolizumab and docetaxel**

| | Atezolizumab | | | Docetaxel | | |
|---|---|---|---|---|---|---|
| Distribution | AIC | BIC | Rating | AIC | BIC | Rating |
| EXPONENTIAL | 594.22 | 597.41 | 6 | 517.77 | 521.06 | 6 |
| WEIBULL | 590.77 | 597.15 | 4 | 508.99 | 515.57 | 4 |
| LNORMAL | 539.62 | 546.01 | 2 | 494.85 | 501.43 | 3 |
| GAMMA | **517.68** | **527.26** | **1** | 492.90 | 502.78 | 2 |
| LLOGISTIC | 540.56 | 546.95 | 3 | **487.70** | **494.29** | **1** |
| GOMPERTZ | 596.22 | 602.60 | 7 | 519.30 | 525.89 | 7 |
| NPH WEIBULL | 590.77 | 597.15 | 4 | 508.99 | 515.57 | 4 |

**Figure 24: PFS extrapolation: KM+Gamma**




### *OS extrapolation*

The AIC/BIC statistics for both atezolizumab and docetaxel are provided in Table 21. Consistent with the ITT population, the log logistic is the best statistical fit for both atezolizumab and docetaxel. As the committee have expressed a preference for a KM plus parametric distribution, consistent with the ITT, it is this that is explored.

**Table 21: AIC/BIC OS: atezolizumab and docetaxel**

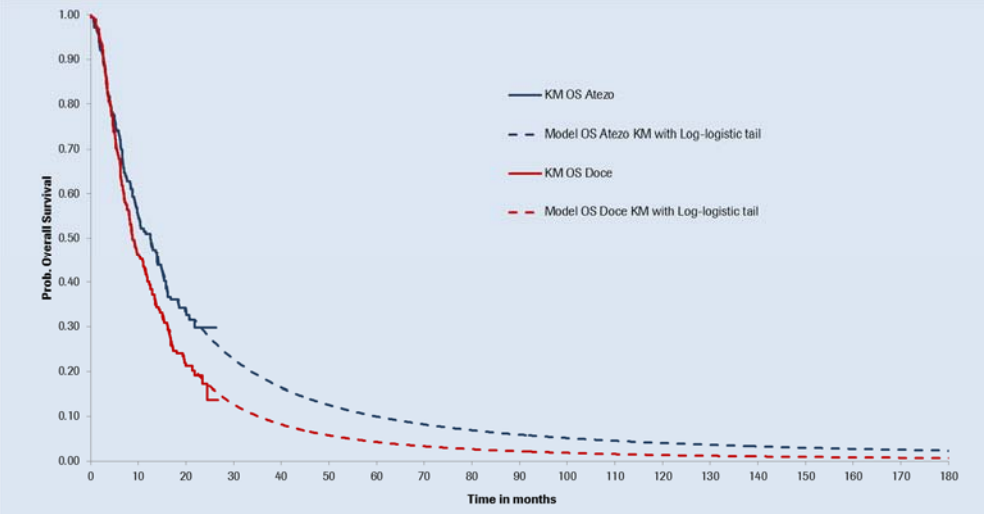
| | Atezolizumab | | | Docetaxel | | |
|---|---|---|---|---|---|---|
| Distribution | AIC | BIC | Rating | AIC | BIC | Rating |
| EXPONENTIAL | 488.22 | 491.42 | 3 | 513.27 | 516.57 | 5 |
| WEIBULL | 489.28 | 495.67 | 5 | 506.48 | 513.07 | 3 |
| LNORMAL | 483.91 | 490.30 | 2 | 511.38 | 517.96 | 5 |
| GAMMA | 485.41 | 494.98 | 4 | 504.17 | 514.05 | 2 |
| LLOGISTIC | **483.28** | **489.67** | **1** | **499.97** | **506.55** | **1** |
| GOMPERTZ | 490.22 | 496.61 | 7 | 512.95 | 519.54 | 7 |
| NPH WEIBULL | 489.28 | 495.67 | 5 | 506.48 | 513.07 | 3 |

When assessing the the resulting distributions (Figure 25), the curve fits atezolizumab well, predicting 5-year OS of 10%, consistent with the ITT population, clinical expert opinion, relevant clinical trial evidence, and precedence with the appraisal of pembrolizumab.

However, the distribution for docetaxel appears to significantly overestimate the anticipated survival of patients, as demonstrated by the large proportion of patients still alive at 5 years (4.3%), and the long ‘tail’ of the curve. This is inconsistent with:

1. The real world survival of docetaxel treated patients, as presented in Appendix 2 and Table 22.
2. The mechanism of action of docetaxel, and lack of pharmacodynamic plausibility as compared to immunotherapies

**Figure 25: OS extrapolation: KM+Log logistic distributions**




NICE DSU guidance specifies that where the proportional hazards assumption has not been met, or does not need to be assumed, fitting separate types of parametric models to individual treatment arms requires substantial justification, and rather it is most sensible to fit separate parametric models of the same type, allowing a two-dimensional treatment effect on both the shape and scale parameters of the parametric distribution (Latimer, 2013b). However, as explained in our response to ACD2 comments form, the mechanism of action of the PD-1 and PD-L1 checkpoint inhibitors, including atezolizumab, is very different from that of chemotherapy, which results in very different efficacy and safety outcomes, and particularly in behaviour of the hazard over time. As such, it is considered appropriate in the absence of the fractional polynomial ITC, to fit separate types of parametric models to each arm. As such, other distributions were assessed for clinical plausibility.

**Table 22: Docetaxel clinical plausibility assessment: model predictions versus available data**

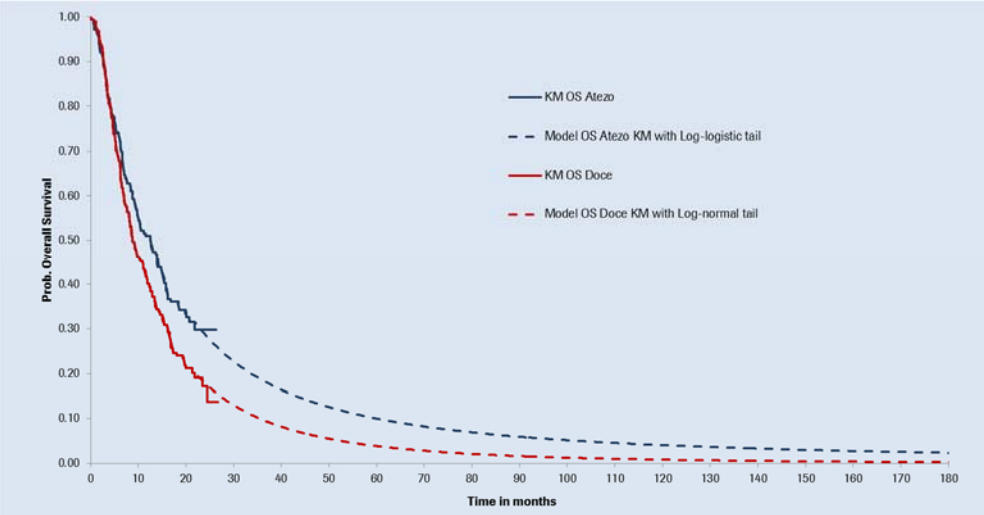
| | 2 years | 3 years | 4 years | 5 years |
|---|---|---|---|---|
| OAK (docetaxel) | 21%* | | | |
| POPLAR (docetaxel) | 17% | 10%* | | |
| NLCA (Stage IV; all PS; chemotherapy-eligible and -ineligible) (Beckett P, 2013) | 7% | 4% | - | 3% |
| Flatiron-database (Enrollment Jan 2011 – Mar 2017) N=797 | 14.4% | 10.3% | 6.2% | 3.7% |

| | | | | | |
|---|---|---|---|---|---|
| (F. Hoffmann-La Roche Ltd [data on file], 2017) | | | | | |
| Parametric distributions | KM+Exponential | 17.4% | 7.3% | 3.1% | 1.3% |
| | KM+Weibull | 16.4% | 4.6% | 1.2% | 0.3% |
| | KM+Log normal | 17.9% | 9.8% | 6.0% | 3.9% |
| | KM+Gamma | 17.1% | 6.8% | 2.8% | 1.3% |
| | KM+Log logistic | 17.8% | 9.7% | 6.2% | 4.3% |
| | KM+Gompertz | 16.5% | 4.3% | 0.8% | 0.1% |

*Subject to significant cross-over

As demonstrated in Table 22, the log-logistic and log-normal curves appear to provide the closest approximations to the available evidence. Nevertheless, when assessing the long term survival curves, both the log–logistic (Figure 25) and the log-normal (Figure 26) curves appear to overestimate survival on chemotherapy, with approximately 1% patients alive at 10 years.

**Figure 26: OS extrapolation: KM+Log normal docetaxel distribution**




However, despite this perceived over-estimation of long term survival, the distribution providing the closest fit to the available RCT and RW evidence, KM+Log Normal has been chosen as the base case distribution for docetaxel, with the KM+ Log logistic utilised for the atezolizumab distribution.

### *Results: List Price*

Adjustment for treatment switching has not been conducted. A lower proportion of PD-L1 negative patients switched treatment to another immunotherapy, as fewer immunotherapies are available in this population.

In the PD-L1 low and negative expressors, atezolizumab provided a QALY gain of 1.27, and a life-year gain of 1.97, at a total drug cost of £44,174, and total overall cost of £71,816 at list price. In contrast, docetaxel provides a QALY gain of 0.77, and a life-year gain of 1.27, at a total cost of £20,842.

As such, the atezolizumab resulting ICER is £102,116 versus docetaxel. See Table 23.

### *Results: PAS Price*

Following an update to the appraisal of atezolizumab in metastatic urothelial cancer (National Institute for Health and Care Excellence, 2017), the PAS for atezolizumab has increased to [redacted].

Utilising this discount, atezolizumab provided a QALY gain of 1.27, and a life-year gain of 1.97, at a total drug cost of [redacted], and total overall cost of [redacted]. In contrast, docetaxel provides a QALY gain of 0.77, and a life-year gain of 1.27, at a total cost of £20,842.

As such, the atezolizumab resulting ICER is [redacted] versus docetaxel. See Table 25.

**Table 23: TC/IC 0 base case results (list price)**

| Technologies | Total costs (£) | Total LYG | Total QALYs | Incremental costs (£) | Incremental LYG | Incremental QALYs | ICER (£) incremental (QALYs) |
|---|---|---|---|---|---|---|---|
| Docetaxel | £20,842 | 1.27 | 0.77 | - | - | - | - |
| Atezolizumab | £71,816 | 1.97 | 1.27 | £50,974 | 0.70 | 0.50 | £102,116 |

**Table 24: TC/IC 0 PSA results compared to base-case (list price)**

| | Costs | | QALYs | | ICERs | |
|---|---|---|---|---|---|---|
| | Base case | PSA | Base case | PSA | Base case | PSA |
| Docetaxel | £20,842 | £21,582 | 0.77 | 0.77 | - | - |
| Atezolizumab | £71,816 | £72,825 | 1.27 | 1.27 | £102,116 | £103,298 |

**Figure 27: TC/IC 0 CE Plane (list price)**

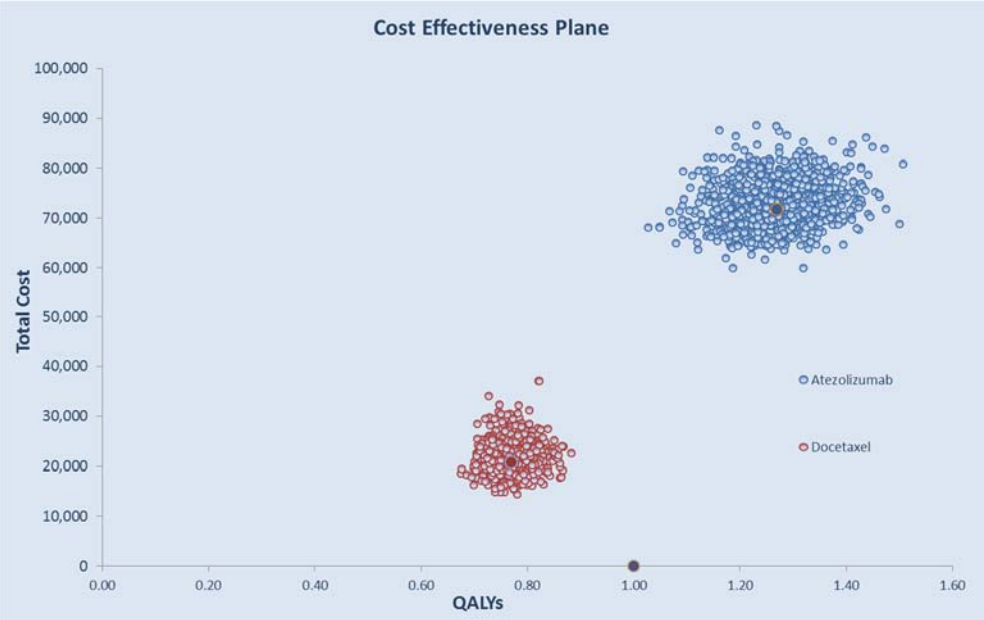



**Table 25: TC/IC 0 base case results (PAS price)**

| Technologies | Total costs (£) | Total LYG | Total QALYs | Incremental costs (£) | Incremental LYG | Incremental QALYs | ICER (£) incremental (QALYs) |
|---|---|---|---|---|---|---|---|
| Docetaxel | £20,842 | 1.27 | 0.77 | - | - | - | - |
| Atezolizumab | [redacted] | 1.97 | 1.27 | [redacted] | 0.70 | 0.50 | [redacted] |

**Table 26: TC/IC 0 PSA results compared to base-case (PAS price)**

| | Costs | | QALYs | | ICERs | |
|---|---|---|---|---|---|---|
| | Base case | PSA | Base case | PSA | Base case | PSA |
| Docetaxel | £20,842 | £21,432 | 0.77 | 0.77 | - | - |
| Atezolizumab | [redacted] | [redacted] | 1.27 | 1.27 | [redacted] | [redacted] |

**Figure 28: TC/IC 0 CE Plane (PAS price)**

## Appendix 8: Phase III OAK (GO28915) – PD-L1 Expression Subgroup Analyses: Economic results: All-comer

As demonstrated by the economic and clinical results for the positives and negatives subgroup, the ITT population – "allcomers" remains the most appropriate population for decision making. The results below utilise the company preferred distributions as depicted in the previous response to ACD.

Following an update to the appraisal of atezolizumab in metastatic urothelial cancer, the PAS for atezolizumab has increased to [redacted]. Therefore the with-PAS results incorporate this discount.

### *List Price*

Without adjusting for crossover, atezolizumab provided a QALY gain of 1.31, and a life-year gain of 2.02, at a total drug cost of £46,438, and total overall cost of £74,636 at list price. In contrast, docetaxel provides a QALY gain of 0.71, and a life-year gain of 1.17, at a total cost of £20,181; and nintedanib (plus docetaxel) provides a QALY gain of 0.91, and a life-year gain of 1.46, at a total cost of £36,261 at list price.

As such, the atezolizumab resulting ICER versus docetaxel is £91,142, and versus nintedanib (plus docetaxel) is £92,587.

When adjusting for crossover, atezolizumab provided an incremental QALY gain of 0.66 versus docetaxel, and 0.49 versus nintedanib (plus docetaxel), resulting in an ICER of £83,049 and £75,751 at list price, respectively.

Nintedanib is associated with a PAS, at an unknown level of discount; therefore the analysis could not be conducted at the with-PAS price level. Usage of nintedanib in the real world is limited, thus caution should be exercised utilizing this comparator.

See Table 27 for a summary of the base case results.

### *Updated PAS Price*

Without adjusting for crossover, atezolizumab provided a QALY gain of 1.31, and a life-year gain of 2.02, at a total drug cost of [redacted], and total overall cost of [redacted] at PAS price. In contrast, docetaxel provides a QALY gain of 0.71, and a life-year gain of 1.17, at a total cost of £20,181; and nintedanib (plus docetaxel) provides a QALY gain of 0.91, and a life-year gain of 1.46, at a total cost of £30,734 at list price.

As such, the atezolizumab resulting ICER versus docetaxel is [redacted], and versus nintedanib (plus docetaxel) is [redacted].

When adjusting for crossover, the ICER reduces to [redacted] and [redacted] respectively.

However, nintedanib is associated with a PAS, at an unknown level of discount; therefore the analysis could not be conducted at the with-PAS price level.

See Table 28 for a summary of the base case results with PAS.

**Table 27: All-comer base case results (list price)**

| | | | | | Versus Docetaxel | | | | Versus N+D | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Analysis | Technologies | Total costs (£) | Total LYG | Total QALYs | Incremental costs (£) | Incremental LYG | Incremental QALYs | ICER (£) incremental (QALYs) | Incremental costs (£) | Incremental LYG | Incremental QALYs | ICER (£) incremental (QALYs) |
| With crossover adjustment | Docetaxel | £19,536 | 1.07 | 0.64 | - | - | - | - | - | - | - | - |
| | Nintedanib + Docetaxel | £37,265 | 1.31 | 0.81 | £17,730 | 0.24 | 0.17 | £104,210 | - | - | - | - |
| | **Atezolizumab** | **£74,636** | **2.02** | **1.31** | **£55,100** | **0.95** | **0.66** | **£83,049** | **£37,370** | **0.71** | **0.49** | **£75,751** |
| Without crossover adjustment | Docetaxel | £20,181 | 1.17 | 0.71 | - | - | - | - | - | - | - | - |
| | Nintedanib + Docetaxel | £36,261 | 1.46 | 0.91 | £18,080 | 0.29 | 0.20 | £88,367 | - | - | - | - |
| | **Atezolizumab** | **£74,636** | **2.02** | **1.31** | **£54,455** | **0.85** | **0.60** | **£91,142** | **£36,375** | **0.56** | **0.39** | **£92,587** |

Note: results versus N+D provided for consistency. As per consultation comments form, this is not deemed an appropriate comparator

**Table 28: All-comer base case results (PAS price)**

| | | | | | Versus Docetaxel | | | | Versus N+D | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Analysis | Technologies | Total costs (£) | Total LYG | Total QALYs | Incremental costs (£) | Incremental LYG | Incremental QALYs | ICER (£) incremental (QALYs) | Incremental costs (£) | Incremental LYG | Incremental QALYs | ICER (£) incremental (QALYs) |
| With crossover adjustment | Docetaxel | £19,536 | 1.07 | 0.64 | - | - | - | - | - | - | - | - |
| | Nintedanib + Docetaxel | £37,265 | 1.31 | 0.81 | £17,730 | 0.24 | 0.17 | £104,210 | - | - | - | - |
| | **Atezolizumab** | [redacted] | **2.02** | **1.31** | [redacted] | **0.95** | **0.66** | [redacted] | [redacted] | **0.71** | **0.49** | [redacted] |
| Without crossover adjustment | Docetaxel | £20,181 | 1.17 | 0.71 | - | - | - | - | - | - | - | - |
| | Nintedanib + Docetaxel | £36,261 | 1.46 | 0.91 | £18,080 | 0.29 | 0.20 | £88,367 | - | - | - | - |
| | **Atezolizumab** | [redacted] | **2.02** | **1.31** | [redacted] | **0.85** | **0.60** | [redacted] | [redacted] | **0.56** | **0.39** | [redacted] |

Note: results versus N+D provided for consistency. As per consultation comments form, this is not deemed an appropriate comparator

# Appendix 9: Phase III OAK (GO28915) – PD-L1 Expression Subgroup Analyses: Economic results: TC/IC 1/2/3

Unless otherwise stated below, the TC/IC 1/2/3 economic model utilises the same assumptions as have been presented in the ITT population.

As the subgroup populations have been separated out now, there is a distinct difference in appropriate comparators. Since its approval in January 2017, usage of pembrolizumab has increased significantly, with docetaxel now minimally used. Therefore, whilst the CUA results are presented for both comparators, a distinction should be made between the degree of importance placed upon the analyses for decision making purposes, as well as the increased uncertainty associated with the CUA as opposed to a simpler CMA.

## *ITC*

The ITC utilises a reduced network of atezolizumab (TC/IC 1/2/3), pembrolizumab (>1% TPS) and docetaxel. As demonstrated in Figure 29 and Figure 30, overall survival for atezolizumab is non-inferior to pembrolizumab irrespective of adjusting for treatment switching, or not. Similarly, atezolizumab is non-inferior to pembrolizumab in PFS as well (Figure 31).

**Figure 29: Forest Plot of Expected survival difference (months) and 95% credible intervals (CrI) of Atezolizumab versus Other Comparators: Overall survival (OS) (FE fractional polynomials model, first order p1=0), base case – adjusting for treatment switching**

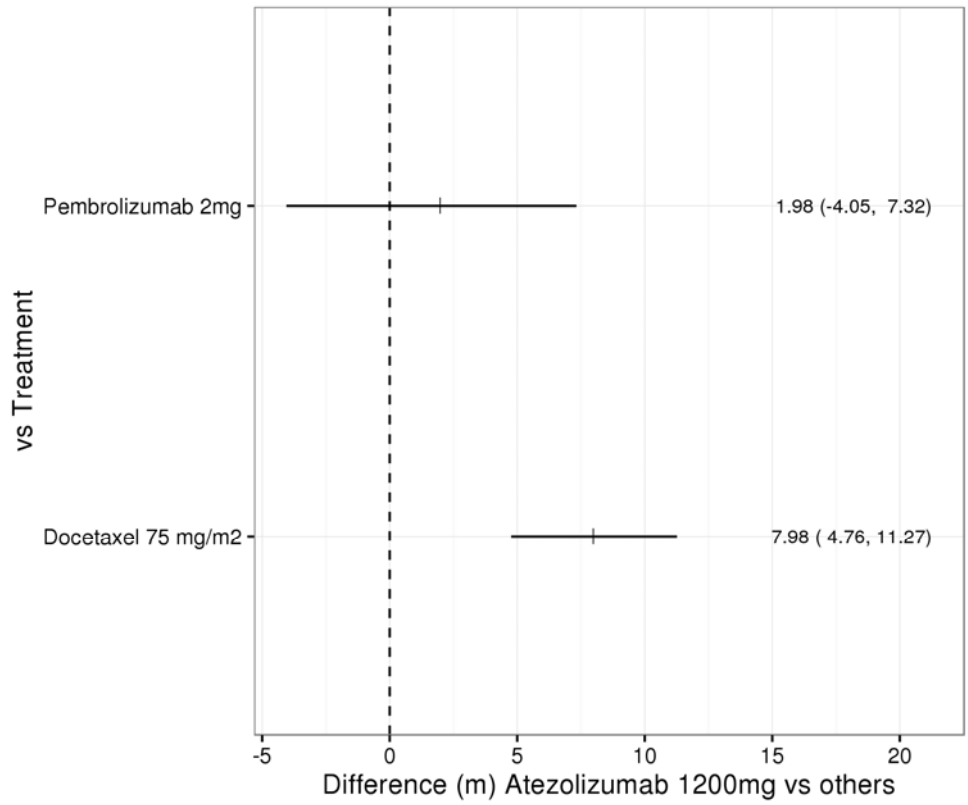


**Figure 30: Forest Plot of Expected survival difference (months) and 95% credible intervals (CrI) of Atezolizumab versus Other Comparators: Overall survival (OS) (FE fractional polynomials model, first order p1=0), no adjustment for treatment switching**

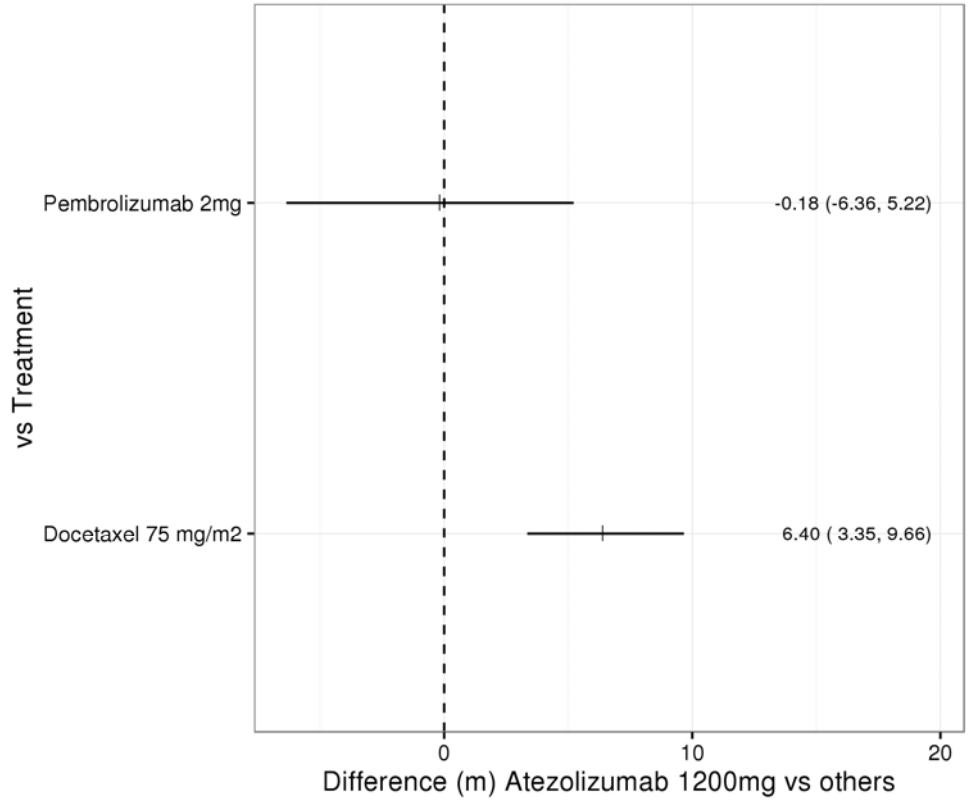
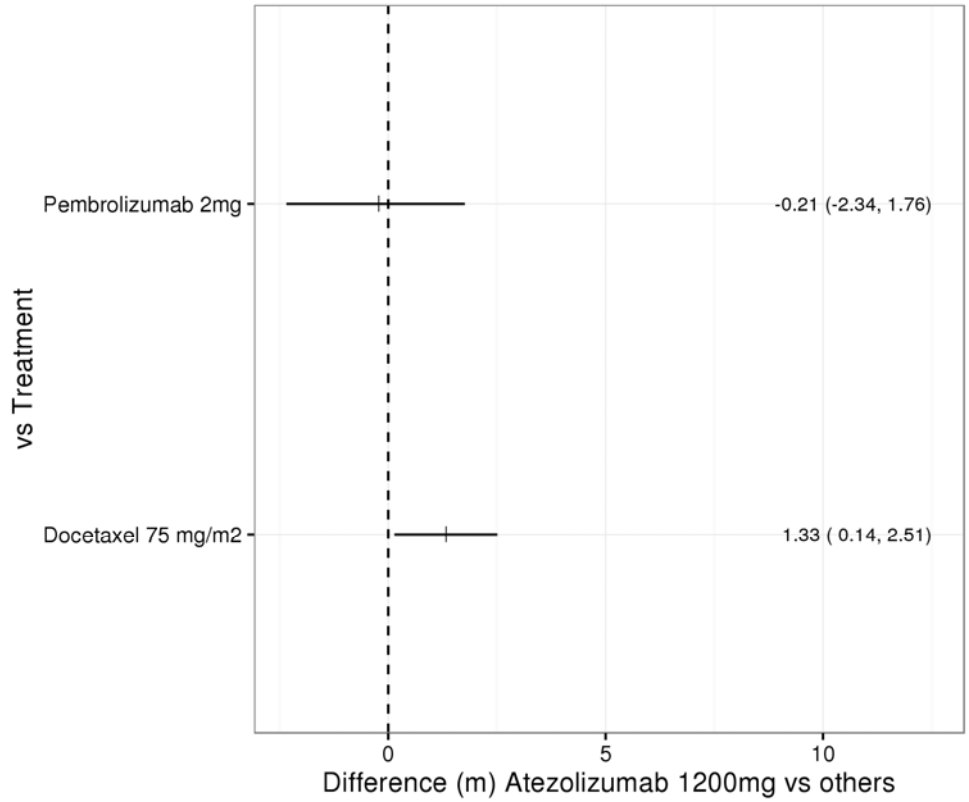


**Figure 31: Forest Plot of Expected survival difference (months) and 95% credible intervals (CrI) of Atezolizumab versus Other Comparators: Progression Free survival (PFS) (FE fractional polynomials model, first order p1=1)**




### *TTD extrapolation*

The AIC/BIC statistics for TTD are provided in Table 29. As the fractional polynomial network meta-analysis is incorporated in this subgroup, separate parameterisations were not required. Rather, the comparator curves are constructed using the atezolizumab curve as a reference, applying the time dependant (i.e. non proportional) hazard ratios. As TTD was not available for pembrolizumab, it is assumed equal to atezolizumab, consistent with the outputs of the ITC. However, in line with the NICE guidance, a two year stopping rule is incorporated for pembrolizumab.

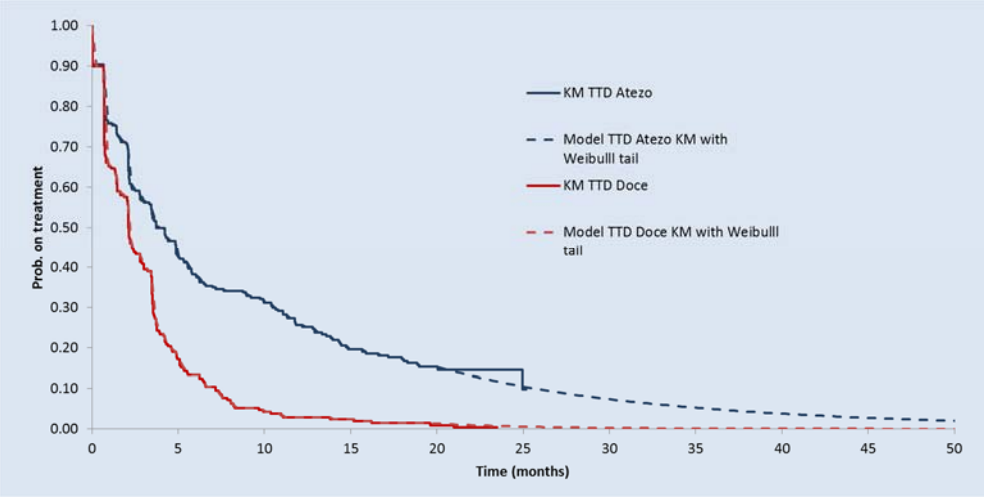
The non proportional hazards weibull is the best statistical fit to the data, however it appears to over-estimate treatment duration in comparison to the KM data. As KM data is almost complete, with 13% and 1% patients still at risk at week 85 for atezolizumab and docetaxel, respectively, the KM+Weibull is utilised in the base case, using the KM until 10% at risk for atezolizumab, and 1% at risk for docetaxel.

**Table 29: AIC/BIC TTD**

| Distribution | AIC | BIC | Rating |
|---|---|---|---|
| EXPONENTIAL | 1728.2 | 1736.4 | 5 |
| WEIBULL | 1674.6 | 1686.9 | 3 |
| LNORMAL | 1756.1 | 1768.4 | 7 |

| | | | |
|---|---|---|---|
| GAMMA | 1672.2 | 1684.5 | 2 |
| LLOGISTIC | 1721.8 | 1734.2 | 4 |
| GOMPERTZ | 1730.2 | 1742.5 | 6 |
| **NPH WEIBULL** | **1662.3** | **1678.8** | **1** |

**Figure 32: TTD extrapolation: KM+ Weibull***




*pembrolizumab = atezolizumab TTD up to 2 years, where the 2 year stopping rule is implemented.

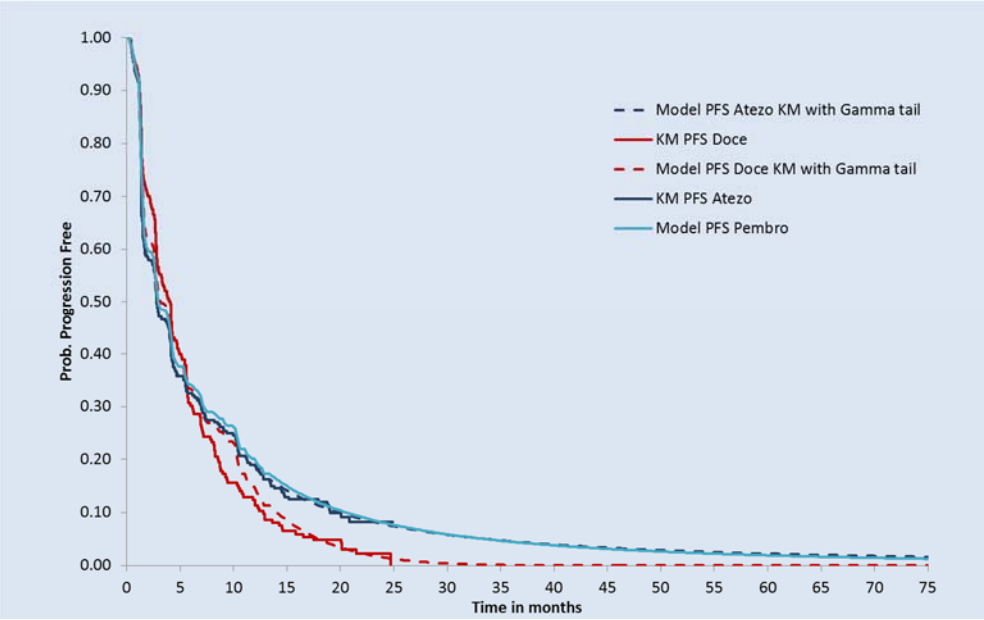
### *PFS extrapolation*

The AIC/BIC statistics are provided in Table 30. Consistent with the ITT population, the gamma is the best statistical fit. In line with the approach taken in the ITT population, the KM with Gamma tail applied upon 15% at risk for atezolizumab, and 2% at risk for docetaxel. It should be noted: PFS is not a driver in the economic analysis, thus alternative distributions have minimal impact on the results.

**Table 30: AIC/BIC PFS**

| Distribution | AIC | BIC | Rating |
|---|---|---|---|
| EXPONENTIAL | 1394.8 | 1403.0 | 5 |
| WEIBULL | 1396.4 | 1408.8 | 6 |
| LNORMAL | 1320.5 | 1333.0 | 2 |
| **GAMMA** | **1308.2** | **1324.8** | **1** |
| LLOGISTIC | 1335.5 | 1347.9 | 3 |
| GOMPERTZ | 1396.8 | 1409.2 | 6 |
| NPH WEIBULL | 1387.0 | 1403.5 | 4 |

**Figure 33: PFS extrapolation: KM+Gamma**




## *OS extrapolation*

The AIC/BIC statistics are provided in Table 31. The outcome is inconsistent with that seen in the ITT and PD-L1 negative population: the log logistic is the third best fit to the data, with exponential and weibull performing better in terms of statistical fit to the observed period. Given this divergence from other populations, assessment of clinical plausibility is paramount.

**Table 31: AIC/BIC OS**

| Distribution | AIC | BIC | Rating |
|---|---|---|---|
| **EXPONENTIAL** | **1251.0** | **1259.3** | **1** |
| WEIBULL | 1251.3 | 1263.7 | 2 |
| LNORMAL | 1259.0 | 1271.4 | 7 |
| GAMMA | 1251.0 | 1267.5 | 5 |
| LLOGISTIC | 1252.8 | 1265.2 | 3 |
| GOMPERTZ | 1252.7 | 1265.2 | 3 |
| NPH WEIBULL | 1253.2 | 1269.8 | 6 |

As longer term atezolizumab, and other immunotherapy data is now available for patients with NSCLC, this was utilised to validate the extrapolations by comparing the survival estimates predicted by all distributions. As the committee have expressed a preference for a KM plus parametric distribution, it is these that are reported.

**Table 32: Atezolizumab clinical plausibility assessment: model predictions versus available data**

| | **2 years** | **3 years** | **4 years** | **5 years** |
|---|---|---|---|---|
| OAK (atezolizumab) – TC/IC 1/2/3 | 32% | - | - | - |

| | | | | | |
|---|---|---|---|---|---|
| POPLAR (atezolizumab) – TC/IC 1/2/3 | | 35% | 18% | - | - |
| CA209-003 (Velcheti, 2017, Brahmer J et al, 2017) - >1% PD-L1 | | 25% | 23% | 23% | 23% |
| CA209-003 (Velcheti, 2017, Brahmer J et al, 2017) – all patients | | 24% | 18% | 17% | 16% |
| Keynote-001 - >1% TPS | | 30% | 19% | - | - |
| Keynote-010 - > 1% TPS | | 30% | - | - | - |
| Parametric distributions | KM+Exponential | 30% | 17% | 8% | 4% |
| | KM+Weibull | 30% | 16% | 7% | 3% |
| | KM+Log normal | 31% | 21% | 15% | 12% |
| | KM+Gamma | 30% | 18% | 11% | 7% |
| | KM+Log logistic | 31% | 21% | 15% | 12% |
| | KM+Gompertz | 30% | 16% | 6% | 2% |

As demonstrated (Table 32), all curves underestimate the two-year survival witnessed for atezolizumab in OAK and POPLAR. Similarly, the exponential, weibull and gompertz significantly underestimate survival at 3 years as compared to atezolizumab POPLAR data, and beyond 3 years as compared to the other available evidence and the pharmacodynamic plausibility assumptions for atezolizumab (see section 1 of our stakeholder comments form, and Appendix 1-3).

As compared to 3 year POPLAR data, the Gamma is the best fitting distribution. However, similarly to the exponential, weibill and gompertz, when comparing to the other available evidence and the pharmacodynamic plausibility assumptions for atezolizumab (see section 1 of our stakeholder comments form, and Appendix 1-3), long term survival assumptions are significantly underestimated.

This is further supported when assessing:

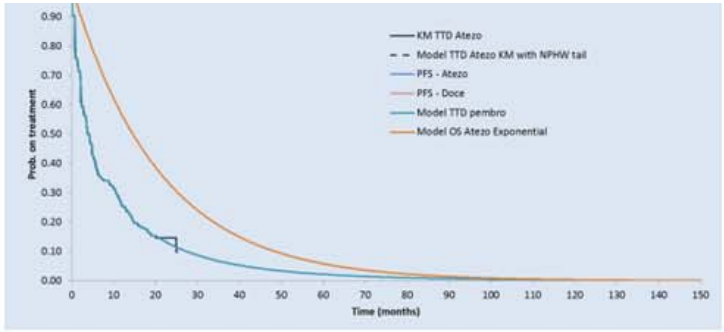
- The survival distributions predicted for pembrolizumab, in comparison to what has previously been accepted in their appraisal (National Institute for Health and Care Excellence, 2016) (Table 33)
- An overlay of the TTD and OS curves demonstrating the exponential, weibull, gamma and gompertz could be deemed as clinically implausible as TTD meets, and is subsequently capped by these OS distributions between 6.5 and 10 years (Figure 6).

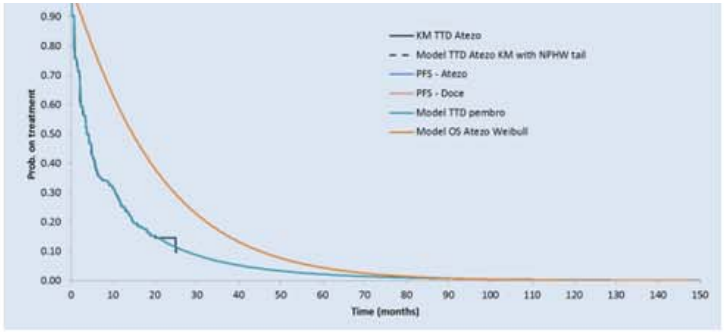
**Table 33: Pembrolizumab clinical plausibility assessment: model predictions versus available data**

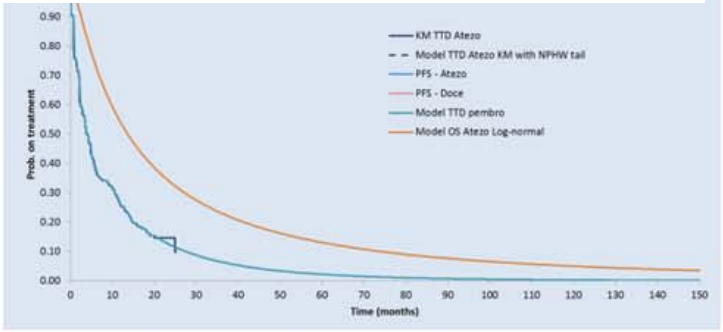
| | | 2 years | 3 years | 4 years | 5 years |
|---|---|---|---|---|---|
| Pembrolizumab NICE committee appraisal * | | 30% * | 19% * | 13% * | 9% * |
| CA209-003 (Velcheti, 2017, Brahmer J et al, 2017) - >1% PD-L1 | | 25% | 23% | 23% | 23% |
| CA209-003 (Velcheti, 2017, Brahmer J et al, 2017) – all patients | | 24% | 18% | 17% | 16% |
| Parametric distributions | KM+Exponential | 27% | 14% | 8% | 4% |
| | KM+Weibull | 26% | 13% | 6% | 3% |
| | KM+Log normal | 27% | 18% | 13% | 9% |
| | KM+Gamma | 27% | 15% | 9% | 5% |
| | KM+Log logistic | 27% | 17% | 12% | 9% |
| | KM+Gompertz | 26% | 13% | 6% | 3% |

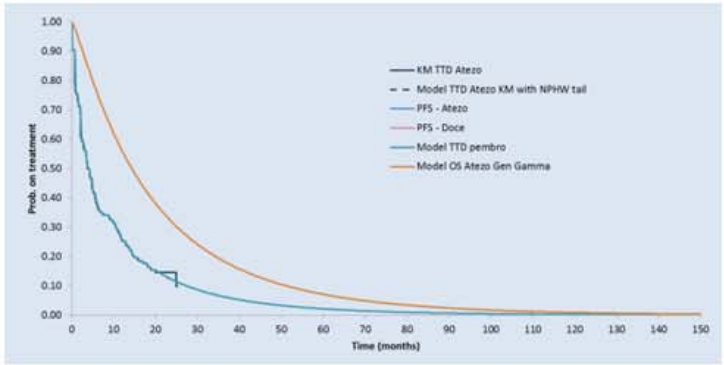
* Digitised curve, subject to a degree of uncertainty

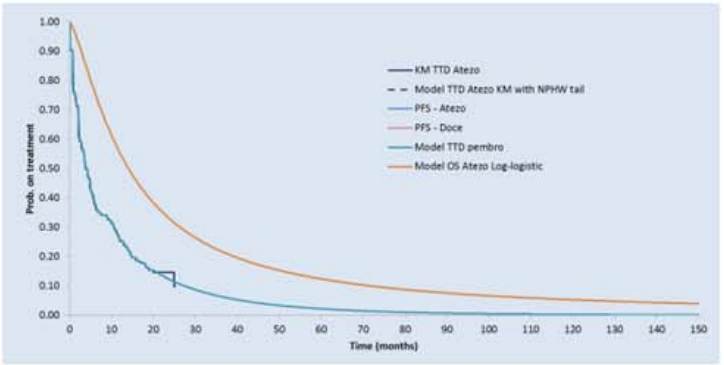
**Figure 34: Visual assessment of OS clinical plausibility against TTD**

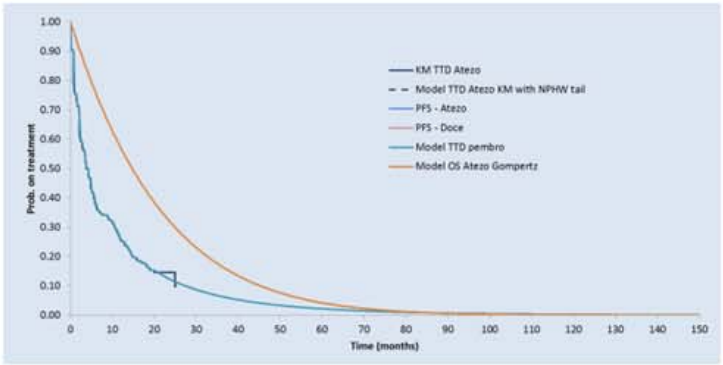


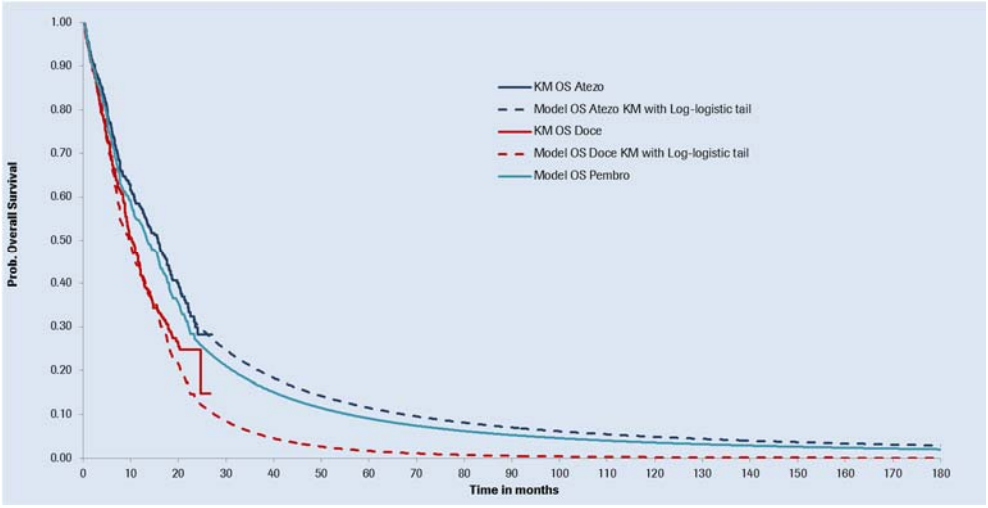
Conversely, whilst it appears the log-logistic and log-normal functions are likely to slightly overestimate atezolizumab survival at 3 years, they otherwise fit the available evidence well: particularly when validating the pembrolizumab curve (Table 33).

As the log-logistic is a better statistical fit, and fits both atezolizumab and the NICE committee-endorsed survival extrapolation of pembrolizumab well, this is the distribution utilised in the base case.

Whilst a 5-year OS prediction of 12% is higher than witnessed in the TC/IC 0 subgroup, and ITT population, it is driven from the separation of the data sets and therefore different parametric fits to the positives data. Whilst the comparison to pembrolizumab validates this estimated survival figure – closely matching the 5 year OS estimate endorsed by the committee, it is important to note Roche still believe an overall survival benefit of approximately 10% for all patients is appropriate, as witnessed in the ITT economic evaluation.

The resulting base case analysis curve can be found in Figure 35.

**Figure 35: OS extrapolation base case: KM+Log logistic**




### *Costs*

Costs utilised in the CUA are predominantly in line with those provided in the CMA provided as part of our response to ACD1 (reported below). There are a small number of adaptions to this:

1. Adverse events and terminal care costs: These were previously excluded as they were deemed to have no differential impact between the interventions. However, as docetaxel is also incorporated in the CUA, they are present in this analysis. Nevertheless, these are equivalent, thus similarly to the CMA, have no impact on the outcome.

2. Drug acquisition costs: Planned individual dosing incorporated as opposed to planned average dosing. Utilising an average of all patient weights in the trial is considered more representative for the NHS perspective, and is more consistent with the assumptions endorsed in the pembrolizumab appraisal (National Institute for Health and Care Excellence, 2016)

**Drug acquisition costs**

Drug acquisition costs used in the model by pack/vial size and by dose for atezolizumab and pembrolizumab are presented in Table 34 and Table 35. Both are presented at list price, but both have patient access schemes in place.
For pembrolizumab, as per the anticipated licence, the model uses a 2mg/kg dose administered as a 30minute IV infusion every three weeks (Q3W). The list price of a 50mg vial is £1,315.00.

**Table 34: Drug acquisition costs (list price)**

| Drug | Vial/pack concentration | Vial/pack volume | Dose per vial/pack | Cost per vial/pack | Source |
|---|---|---|---|---|---|
| Atezolizumab (list) | 1200mg/ml | 20 ml | 1200 mg | £3,807.69 | UK list price |
| Pembrolizumab (list) | | | 50 mg | £1,315.00 | DMD |

Data on the typical weight distribution of patients with NSCLC was not available for the UK. Therefore, the average individual weights from the OAK clinical trial was used to estimate the average drug cost per patient per administration. In line with the assumptions provided in the pembrolizumab appraisal, no vial sharing is assumed within the model (National Institute for Health and Care Excellence, 2016). Based on this assumption, a total of 3.14 vials are required per cycle, at a total drug cost per patient per administration of £4,127.45 at list price.

In contrast, as part of the pembrolizumab NSCLC appraisal, MSD estimated the average number of vials required per patient per cycle was 3.39, resulting in a total drug cost per patient per administration of £4,453.13 at list price. Therefore, whilst the Roche approach is taken as the base case assumption, this should be considered a conservative approach, and a scenario is incorporated using the MSD assumptions.

**Table 35: Drug cost per treatment cycle (list price)**

| Drug | Total dose per administration | No. of vials/pack | Method of administration | Total drug cost per cycle |
|---|---|---|---|---|
| Atezolizumab (list price) | 1,200 mg | 1 x 1200 mg Q3W | IV; no vial sharing | £3807.69 |

| | | | | |
|---|---|---|---|---|
| Pembrolizumab (list price); OAK average weight assumption | 2mg*71.69kg = 143.39mg | 3 x 50mg vial Q3W | IV; no vial sharing | £4,127.45 |
| Pembrolizumab (list price); KEYNOTE-010 average weight assumption *Scenario analysis* | Please refer to Table 36 | 3.39 x 50mg vial Q3W | IV; no vial sharing | £4,453.13 |

**Table 36: pembrolizumab assumptions: Weight distribution from European patients in KEYNOTE-010 and number of vials required: Scenario analysis (National Institute for Health and Care Excellence, 2016)**

| Weight categories | Frequency | % | Total dose per administration (mg) | Vial required (assuming maximum weight in the band) | Cost per infusion (list price) |
|---|---|---|---|---|---|
| 0-50kg | 28 | 5.4% | 0 to 100 | 2 | |
| 50-75kg | 296 | 57.5% | 100 to 150 | 3 | |
| 75-100kg | 158 | 30.7% | 150 to 200 | 4 | |
| 100-125kg | 30 | 5.8% | 200 to 250 | 5 | |
| 125-130kg | 3 | 0.6% | 250 to 300 | 6 | |
| *Total* | 515 | 100% | | 3.39 | £4,453.13 |

### Administration costs

Administration of pembrolizumab is the same as the administration of atezolizumab: IV infusion every three weeks (Q3W). Consistent with the nivolumab and pembrolizumab appraisals, and the initial assumptions of the company submission, the cost associated with administering both treatments are assumed to be that of a simple chemotherapy (as described in the NHS reference costs – see Table 37).

**Table 37: Drug administration costs**

| Drug | Type of administration | | NHS reference code | Cost per administration | Source |
|---|---|---|---|---|---|
| Atezolizumab | Deliver simple Parenteral Chemotherapy at first attendance | Outpatient Setting | SB12Z (outpatient) | £198.94 | NHS reference costs 2015-16 |
| Pembrolizumab | Deliver simple Parenteral Chemotherapy at first attendance | Outpatient setting | SB12Z (outpatient) | £198.94 | NHS reference costs 2015-16 |

### PD-L1 testing

As pembrolizumab is indicated for patients whose tumours express PD-L1, an additional cost of PD-L1 testing is incorporated. In the pembrolizumab appraisal, the cost of a PD-L1 test per patient eligible for treatment was determined by estimating the proportion of patients who would be eligible for treatment, and therefore how many patients would need to be tested for PD-L1 expression to identify one eligible patient. The total cost per eligible patient was estimated at £337.51, accounting for the proportion of patients with assessable samples (Table 38).

It should be noted that the cost of testing for PD-L1 expression has not been included in the analysis of atezolizumab. As atezolizumab has shown benefit irrespective of expression, and has achieved a license for the treatment of all patients, there is no requirement of a diagnostic test. By applying the cost of testing to this and the negatives population, the benefits of atezolizumab as an effective treatment in all subgroups, thus no requirement for testing, is not appropriately captured. However, this cost is applied for the treatment of pembrolizumab, as its license and usage is only in the NSCLC population with TPS>1%, thus a diagnostic test is a requirement.

**Table 38: Cost of PD-L1 testing per patient eligible for treatment with pembrolizumab (National Institute for Health and Care Excellence, 2016)**

| | |
|---|---|
| % of people eligible for treatment with Pembrolizumab among patients with NSCLC stage IIIb/IV | 12% |
| PD-L1 test cost | £40.50 |
| Total PD-L1 cost | £337.51 |

### Other considerations

Pembrolizumab has a two year clinical stopping rule incorporated as part of their NICE guidance. Therefore, all acquisition and administration costs are stopped after two years.

## *Results: List Price*

Adjustment for treatment switching has been included, driven by the large volume of treatment switching in the docetaxel arm to other immunotherapies.

In the PD-L1 positive expressors base case, atezolizumab provided a QALY gain of 1.44, and a life-year gain of 2.20, at a total drug cost of £53,004, and total overall cost of £83,937 at list price. In contrast, pembrolizumab provides a QALY gain of 1.25, and a life-year gain of 1.91, at a total cost of £76,720; and docetaxel provides a QALY gain of 0.67, and a life-year gain of 1.11, at a total cost of £20,132.

As such, the atezolizumab resulting ICER is £83,352 versus docetaxel and pembrolizumab is extendedly dominated (see Table 39).

As anticipated, there is a minimal difference in QALY gain between atezolizumab and pembrolizumab (0.18 in base case, 0.14 in scenario analysis), demonstrating non-inferiority, and supporting the use of a cost minimisation analysis. Thus, an additional table has been provided for the cost comparison results between these products. It should be noted, a simpler cost minimisation analysis is subject to fewer assumptions and thus can be considered a more appropriate and robust method to appraise atezolizumab versus pembrolizumab.

### *Results: PAS Price*

Following an update to the appraisal of atezolizumab in metastatic urothelial cancer (National Institute for Health and Care Excellence, 2017), the PAS for atezolizumab has increased to [redacted].

Utilising this discount, atezolizumab provided a QALY gain of 1.44, and a life-year gain of 2.20, at a total drug cost of [redacted], and total overall cost of [redacted].

As such, the atezolizumab resulting ICER is [redacted] versus docetaxel with pembrolizumab (at list price) being dominated (see Table 45).

Utilising the cost minimisation analysis, atezolizumab is considered cost cost-saving to the NHS over pembrolizumab.

**Table 39: TC/IC 1/2/3 base case results (list price)**

| | | | | | Versus docetaxel | | | | Versus pembrolizumab | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Analysis | Technologies (ranked by total QALYs) | Total QALYs | Total costs (£) | Total LYG | Incremental QALYs | Incremental costs (£) | Incremental LYG | ICER (£) | Incremental QALYs | Incremental costs (£) | Incremental LYG | ICER (£) | Full incremental |
| With adjustment | Docetaxel | 0.67 | £20,159 | 1.11 | - | - | - | - | - | - | - | - | |
| | Pembrolizumab | 1.25 | £76,720 | 1.91 | 0.58 | £56,561 | 0.80 | £97,332 | - | - | - | - | Ext. dominated |
| | **Atezolizumab** | 1.44 | £83,963 | 2.20 | 0.77 | £63,804 | 1.09 | £83,352 | 0.18 | £7,243 | 0.28 | £39,286 | £83,352 |

**Table 40: TC/IC 1/2/3 scenario analysis results – pembrolizumab submission acquisition cost assumption (list price)**

| | | | | | Versus docetaxel | | | | Versus pembrolizumab | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Analysis | Technologies (ranked by total QALYs) | Total QALYs | Total costs (£) | Total LYG | Incremental QALYs | Incremental costs (£) | Incremental LYG | ICER (£) | Incremental QALYs | Incremental costs (£) | Incremental LYG | ICER (£) | Full incremental |
| With adjustment | Docetaxel | 0.67 | £20,159 | 1.11 | - | - | - | - | - | - | - | - | |
| | Pembrolizumab | 1.25 | £80,518 | 1.91 | 0.58 | £60,359 | 0.80 | £103,868 | - | - | - | - | Ext. dominated |
| | **Atezolizumab** | 1.44 | £83,963 | 2.20 | 0.77 | £63,804 | 1.09 | £83,352 | 0.18 | £3,445 | 0.28 | £18,687 | £83,352 |

**Table 41: TC/IC 1/2/3 scenario analysis results - without adjustment (list price)**

| | | | | | Versus docetaxel | | | | Versus pembrolizumab | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Analysis | Technologies | Total QALYs | Total costs (£) | Total LYG | Incremental QALYs | Incremental costs (£) | Incremental LYG | ICER (£) | Incremental QALYs | Incremental costs (£) | Incremental LYG | ICER (£) | Full incremental |
| With adjustment | Docetaxel | 0.78 | £21,267 | 1.28 | - | - | - | - | - | - | - | - | |
| | Pembrolizumab | 1.58 | £80,021 | 2.42 | 0.80 | £58,755 | 1.14 | £73,800 | - | - | - | - | 73,800 |
| | **Atezolizumab** | 1.44 | £83,963 | 2.20 | 0.65 | £62,696 | 0.92 | £95,922 | -0.14 | £3,942 | -0.22 | -£27,661 | Dominated |

**Table 42: TC/IC 1/2/3 cost comparison results: atezolizumab versus pembrolizumab (list price, base case)**

| | | Atezolizumab | Pembrolizumab | Increment | % absolute increment |
|---|---|---|---|---|---|
| Mean costs in PFS/On treatment | Treatment cost | £53,004 | £48,133 | £4,871 | 0.61 |
| | Diagnostic cost | £0 | £338 | -£338 | 0.04 |
| | Drug administration | £2,769 | £2,320 | £449 | 0.06 |
| | Adverse events | £117 | £117 | £0 | 0.00 |
| | Supportive care | £11,392 | £10,661 | £732 | 0.09 |
| Total costs in PFS/On treatment | | £67,283 | £61,568 | £5,715 | |
| Mean costs in PD/Off treatment | Supportive care | £9,528 | £7,954 | £1,574 | 0.20 |
| | Subsequent therapy cost | £3,749 | £3,749 | £0 | 0.00 |
| Total costs in PD/Off treatment | | £13,277 | £11,703 | £1,574 | |
| Terminal care costs | | £3,404 | £3,449 | -£45 | 0.01 |
| Total costs | | £83,963 | £76,720 | £7,243 | 100% |

**Table 43: TC/IC 1/2/3 cost comparison results: atezolizumab versus pembrolizumab (list price, dosing scenario)**

| | | Atezolizumab | Pembrolizumab | Increment | % absolute increment |
|---|---|---|---|---|---|
| Mean costs in PFS/On treatment | Treatment cost | £53,004 | £51,930 | £1,074 | 0.25 |
| | Diagnostic cost | £0 | £338 | -£338 | 0.08 |
| | Drug administration | £2,769 | £2,320 | £449 | 0.11 |
| | Adverse events | £117 | £117 | £0 | 0.00 |
| | Supportive care | £11,392 | £10,661 | £732 | 0.17 |
| Total costs in PFS/On treatment | | £67,283 | £65,366 | £1,917 | |
| Mean costs in PD/Off treatment | Supportive care | £9,528 | £7,954 | £1,574 | 0.37 |
| | Subsequent therapy cost | £3,749 | £3,749 | £0 | 0.00 |
| Total costs in PD/Off treatment | | £13,277 | £11,703 | £1,574 | |
| Terminal care costs | | £3,404 | £3,449 | -£45 | 0.01 |
| Total costs | | £83,963 | £80,518 | £3,445 | 100% |

**Table 44: TC/IC 1/2/3 PSA results compared to base-case (list price)**

| | Costs | | QALYs | | ICERs | |
|---|---|---|---|---|---|---|
| | Base case | PSA | Base case | PSA | Base case | PSA |
| Docetaxel | £20,159 | £20,892 | 0.67 | 0.68 | - | - |
| Pembrolizumab | £76,720 | £79,304 | 1.25 | 1.33 | Ext. dominated | Ext. dominated |
| Atezolizumab | £83,963 | £85,079 | 1.44 | 1.44 | £83,352 | £85,074 |

**Figure 36: TC/IC 1/2/3 CE Plane (list price)**

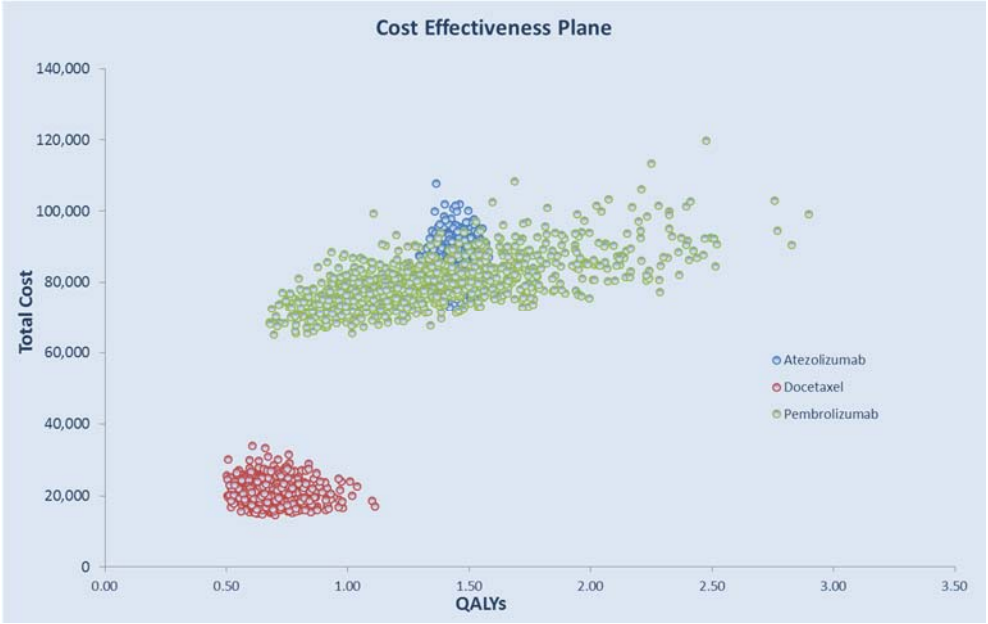


**Table 45: TC/IC 1/2/3 base case results (PAS price)**

| | | | | | Versus docetaxel | | | | Versus pembrolizumab | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Analysis | Technologies (ranked by total QALYs) | Total QALYs | Total costs (£) | Total LYG | Incremental QALYs | Incremental costs (£) | Incremental LYG | ICER (£) | Incremental QALYs | Incremental costs (£) | Incremental LYG | ICER (£) | Full incremental |
| With adjustment | Docetaxel | 0.67 | £20,159 | 1.11 | - | - | - | - | - | - | - | - | |
| | Pembrolizumab | 1.25 | £76,720 | 1.91 | 0.58 | £56,561 | 0.80 | £97,332 | - | - | - | - | [redacted] |
| | **Atezolizumab** | 1.44 | [redacted] | 2.20 | 0.77 | [redacted] | 1.09 | [redacted] | 0.18 | [redacted] | 0.28 | [redacted] | [redacted] |

**Table 46: TC/IC 1/2/3 scenario analysis results – pembrolizumab submission acquisition cost assumption (PAS price)**

| | | | | | Versus docetaxel | | | | Versus pembrolizumab | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Analysis | Technologies (ranked by total QALYs) | Total QALYs | Total costs (£) | Total LYG | Incremental QALYs | Incremental costs (£) | Incremental LYG | ICER (£) | Incremental QALYs | Incremental costs (£) | Incremental LYG | ICER (£) | Full incremental |
| With adjustment | Docetaxel | 0.67 | £20,159 | 1.11 | - | - | - | - | - | - | - | - | |
| | Pembrolizumab | 1.25 | £80,518 | 1.91 | 0.58 | £60,359 | 0.80 | £103,868 | - | - | - | - | [redacted] |
| | **Atezolizumab** | 1.44 | [redacted] | 2.20 | 0.77 | [redacted] | 1.09 | [redacted] | 0.18 | [redacted] | 0.28 | [redacted] | [redacted] |

**Table 47: TC/IC 1/2/3 scenario analysis results - without adjustment (PAS price)**

| | | | | | Versus docetaxel | | | | Versus pembrolizumab | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Analysis | Technologies | Total QALYs | Total costs (£) | Total LYG | Incremental QALYs | Incremental costs (£) | Incremental LYG | ICER (£) | Incremental QALYs | Incremental costs (£) | Incremental LYG | ICER (£) | Full incremental |
| With adjustment | Docetaxel | 0.78 | £21,267 | 1.28 | - | - | - | - | - | - | - | - | |
| | Pembrolizumab | 1.58 | £80,021 | 2.42 | 0.80 | £58,755 | 1.14 | £73,800 | - | - | - | - | [redacted] |
| | **Atezolizumab** | 1.44 | [redacted] | 2.20 | 0.65 | [redacted] | 0.92 | [redacted] | -0.14 | [redacted] | -0.22 | [redacted] | [redacted] |

**Table 48: TC/IC 1/2/3 cost comparison results: atezolizumab versus pembrolizumab (PAS price, base case)**

| | | Atezolizumab | Pembrolizumab | Increment | % absolute increment |
|---|---|---|---|---|---|
| Mean costs in PFS/On treatment | Treatment cost | [redacted] | £48,133 | [redacted] | [redacted] |
| | Diagnostic cost | £0 | £338 | -£338 | [redacted] |
| | Drug administration | £2,769 | £2,320 | £449 | [redacted] |
| | Adverse events | £117 | £117 | £0 | [redacted] |
| | Supportive care | £11,392 | £10,661 | £732 | [redacted] |
| Total costs in PFS/On treatment | | [redacted] | £61,568 | [redacted] | |
| Mean costs in PD/Off treatment | Supportive care | £9,528 | £1,574 | £1,574 | [redacted] |
| | Subsequent therapy cost | £3,749 | £3,749 | £0 | [redacted] |
| Total costs in PD/Off treatment | | £13,277 | £11,703 | £1,574 | |
| Terminal care costs | | £3,404 | £3,449 | -£45 | [redacted] |
| Total costs | | [redacted] | £76,720 | [redacted] | [redacted] |

**Table 49: TC/IC 1/2/3 cost comparison results: atezolizumab versus pembrolizumab (PAS price, dosing scenario)**

| | | Atezolizumab | Pembrolizumab | Increment | % absolute increment |
|---|---|---|---|---|---|
| Mean costs in PFS/On treatment | Treatment cost | [redacted] | £51,930 | [redacted] | [redacted] |
| | Diagnostic cost | £0 | £338 | -£338 | [redacted] |
| | Drug administration | £2,769 | £2,320 | £449 | [redacted] |
| | Adverse events | £117 | £117 | £0 | [redacted] |
| | Supportive care | £11,392 | £10,661 | £732 | [redacted] |
| Total costs in PFS/On treatment | | [redacted] | £65,366 | [redacted] | |
| Mean costs in PD/Off treatment | Supportive care | £9,528 | £1,574 | £1,574 | [redacted] |
| | Subsequent therapy cost | £3,749 | £3,749 | £0 | [redacted] |
| Total costs in PD/Off treatment | | £13,277 | £11,703 | £1,574 | |
| Terminal care costs | | £3,404 | £3,449 | -£45 | [redacted] |
| Total costs | | [redacted] | £80,518 | [redacted] | [redacted] |

**Table 50: TC/IC 1/2/3 PSA results compared to base-case (PAS price)**

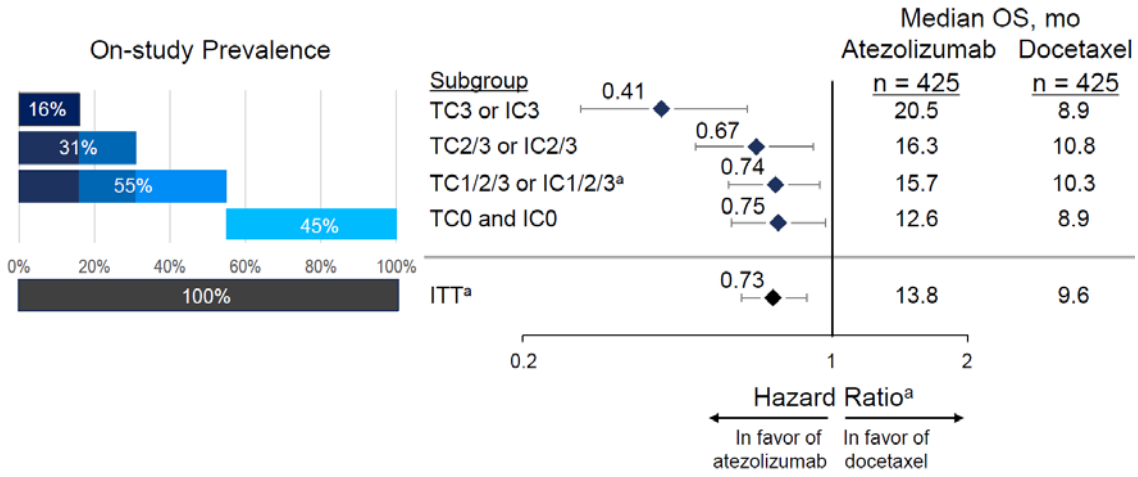
| | Costs | | QALYs | | ICERs | |
|---|---|---|---|---|---|---|
| | Base case | PSA | Base case | PSA | Base case | PSA |
| Docetaxel | £20,159 | £21,119 | 0.67 | 0.68 | - | - |
| Pembrolizumab | £76,720 | £79,476 | 1.25 | 1.34 | Dominated | Dominated |
| Atezolizumab | [redacted] | [redacted] | 1.44 | 1.44 | [redacted] | [redacted] |

**Figure 37: TC/IC 0 CE Plane (PAS price)**

## Appendix 10: Phase III OAK (GO28915) – Economic analysis: Summary and comparison of populations

As demonstrated in our stakeholder comments form, and appendices 5 and 7-9, atezolizumab has demonstrated statistically significant and clinically meaningful benefit irrespective of PD-L1 expression. The minimum improvement witnessed in the OAK trial equated to a median of 3.7 month overall survival benefit in the TC/IC 0 subgroup: the low and negative expressors, the population with the greatest unmet need in current practice.

**Figure 38: Clinical benefit of atezolizumab across subgroups**




When comparing the populations further (Table 51, Table 52 the importance of appraising the full ITT population as the most appropriate and robust population to base decision making on is further emphasised: The similarities across populations in terms of time on treatment (9.55 months versus. 7.85 months), overall survival (30.21 months versus 26.87 months) and incremental QALYs versus docetaxel (0.77 versus 0.60) for the PD-L1 positive versus PD-L1 negative population, respectively, demonstrate consistency with the ITT population, and the importance of making atezolizumab available for all patients, irrespective of expression level.

When appraising cost effectiveness, the two subgroup populations now have different appropriate comparators, driven from the pembrolizumab positive recommendation by NICE in January 2017.

In the TC/IC 1/2/3 (>1% TPS) population, Roche have demonstrated non-inferiority to pembrolizumab, and at the PAS level, cost saving for the NHS. In addition, atezolizumab is also cost effective versus docetaxel.

The majority of the TC/IC 0 (<1% TPS) population currently have no access to an immunotherapy treatment option, thus docetaxel is the appropriate comparator. [redacted]

[redacted], it is imperative to remind the committee the OAK trial was not appropriately powered for an analysis in this population.

In summary, atezolizumab provides cost-savings to the NHS as compared to pembrolizumab, and provides additional clinical benefit to the TC/IC 0 population, where there is the most unmet need. The consistency in outcomes across the populations further supports the ITT as the appropriate population to base decision making on, where atezolizumab is cost effective versus docetaxel, and again cost-saving versus pembrolizumab.

**Table 51: Comparisons of means across populations**

| Population | ITT | +ives (TC/IC 123) | -ives (TC/IC 0) |
|---|---|---|---|
| Mean TOT | 8.25 months | 9.55 months | 7.85 months |
| Mean OS | 27.42 months | 30.21 months | 26.87 months |

**Table 52: Comparison of QALYs across populations**

| Population | ITT | +ives (TC/IC 123) | -ives (TC/IC 0) |
|---|---|---|---|
| Incremental QALYs "on treatment" | 0.29 | 0.36 | 0.26 |
| Incremental QALYs "off treatment" | 0.38 | 0.40 | 0.23 |
| Incremental total QALYs | 0.66 | 0.77 | 0.50 |

**Table 53: Comparison of cost and ICERs across populations (list price, versus docetaxel)**

| Population | ITT | +ives (TC/IC 123) | -ives (TC/IC 0) |
|---|---|---|---|
| Incremental treatment costs | £46,303 | £52,884 | £44,036 |
| Incremental total costs | £55,100 | £63,804 | £50,974 |
| ICER (vs. docetaxel) | £83,049 | £83,352 | £102,116 |

**Table 54: Comparison of cost and ICERs across populations (PAS price, versus docetaxel)**

| Population | ITT | +ives (TC/IC 123) | -ives (TC/IC 0) |
|---|---|---|---|
| Incremental treatment costs | [redacted] | [redacted] | [redacted] |
| Incremental total costs | [redacted] | [redacted] | [redacted] |
| ICER (vs. docetaxel) | [redacted] | [redacted] | [redacted] |

**Table 55: Comparison of costs: atezolizumab versus pembrolizumab PD-L1 positive (base case)**

| | | Atezolizumab | Pembrolizumab | Increment |
|---|---|---|---|---|
| List price | Total costs in PFS/On treatment | £67,283 | £61,568 | £5,715 |
| | Total costs in PD/Off treatment | £13,277 | £11,703 | £1,574 |
| | Total costs | £83,963 | £76,720 | £7,243 |
| Atezolizumab PAS price, Pembrolizumab list price | Total costs in PFS/On treatment | [redacted] | £61,568 | [redacted] |
| | Total costs in PD/Off treatment | £13,277 | £11,703 | £1,574 |
| | Total costs | [redacted] | £76,720 | [redacted] |

# Appendix 11: Additional requested analyses from NICE

## List Price

### ITT

**Table 56: All-comer population – versus docetaxel**

| | Total costs | Total QALYS | Inc. costs | Inc. QALYs | ICER |
|---|---|---|---|---|---|
| **Company basecase (no stopping rule, on-going treatment effect, with switching adjustment, company-preferred extrapolation)** | | | | | |
| Docetaxel | £19,536 | 0.64 | | | - |
| Atezolizumab | £74,636 | 1.31 | £55,100 | 0.66 | £83,049 |
| **1. 2 year stopping rule** | | | | | |
| Docetaxel | £19,536 | 0.64 | | | - |
| Atezolizumab | £69,259 | 1.31 | £49,723 | 0.66 | £74,945 |
| **2a. 2-year treatment effect** | | | | | |
| Docetaxel | £19,469 | 0.64 | | | - |
| Atezolizumab | £74,292 | 1.27 | £54,823 | 0.64 | £86,193 |
| **2b. 3-year treatment effect** | | | | | |
| Docetaxel | £19,517 | 0.64 | | | - |
| Atezolizumab | £74480 | 1.29 | £54,963 | 0.65 | £84,574 |
| **3. without switching adjustment** | | | | | |
| Docetaxel | £20,181 | 0.71 | | | - |
| Atezolizumab | £74,636 | 1.31 | £54,455 | 0.60 | £91,142 |
| **4. Committee preferred OS extrapolation (for all comers)*** | | | | | |
| Docetaxel | £19,279 | 0.62 | | | - |
| Atezolizumab | £71,772 | 1.02 | £52,494 | 0.41 | £129,299 |
| **Committee preferred assumptions (1+2b+3+4)*** | | | | | |
| Docetaxel | £19644 | 0.66 | | | - |
| Atezolizumab | £65,986 | 0.98 | £46,342 | 0.33 | £141,720 |

* The ERG preferred curve is hardcoded in their model, thus is not reproducible in the company model. Therefore the committee preferred extrapolation utilizes the closest analysis: the piecewise distribution in the company economic model, KM until 52 weeks, as preferred, end of piece: 69 weeks (atezo) and 80 weeks (doce).

**Table 57: All-comer population – versus nintedanib+docetaxel**

| | Total costs | Total QALYS | Inc. costs | Inc. QALYs | ICER |
|---|---|---|---|---|---|
| **Company basecase (no stopping rule, on-going treatment effect, with switching adjustment, company-preferred extrapolation)** | | | | | |
| Nintedanib+Docetaxel | £37,265 | 0.81 | | | - |
| Atezolizumab | £74,636 | 1.31 | £37,370 | 0.49 | £75,751 |
| **1. 2 year stopping rule** | | | | | |
| Nintedanib+Docetaxel | £37,265 | 0.81 | | | - |
| Atezolizumab | £69,259 | 1.31 | £31,994 | 0.49 | £64,852 |
| **2a. 2-year treatment effect** | | | | | |
| Nintedanib+Docetaxel | £37,136 | 0.80 | | | - |
| Atezolizumab | £74,292 | 1.27 | £37,156 | 0.47 | £78,699 |

| | | | | | |
|---|---|---|---|---|---|
| **2b. 3-year treatment effect** | | | | | |
| Nintedanib+Docetaxel | £37,220 | 0.81 | | | - |
| Atezolizumab | £74480 | 1.29 | £37,259 | 0.48 | £77,243 |
| **3. without switching adjustment** | | | | | |
| Nintedanib+Docetaxel | £38,261 | 0.91 | | | - |
| Atezolizumab | £74,636 | 1.31 | £36,375 | 0.39 | £92,587 |
| **4. Committee preferred OS extrapolation (for all comers)*** | | | | | |
| Nintedanib+Docetaxel | £36,623 | 0.75 | | | - |
| Atezolizumab | £71,772 | 1.02 | £35,149 | 0.27 | £128,181 |
| **Committee preferred assumptions (1+2b+3+4)*** | | | | | |
| Nintedanib+Docetaxel | £37,022 | 0.79 | | | - |
| Atezolizumab | £65,986 | 0.98 | £28,964 | 0.19 | £151,071 |

* The ERG preferred curve is hardcoded in their model, thus is not reproducible in the company model. Therefore the committee preferred extrapolation utilizes the closest analysis: the piecewise distribution in the company economic model, KM until 52 weeks, as preferred, end of piece: 69 weeks (atezo) and 80 weeks (doce).

## PD-L1 positive

It is imperative to note, the committee have not provided feedback on what they deem the most plausible OS curve. As such, an assumption has been required that the committee will utilize a similar distribution to ITT, hence piecewise distribution is presented.

**Table 58: PD-L1 positive population – versus docetaxel**

| | | Total costs | Total QALYS | Inc. costs | Inc. QALYs | ICER |
|---|---|---|---|---|---|---|
| **Company basecase (no stopping rule, on-going treatment effect, with switching adjustment)** | | | | | | |
| Docetaxel | | £20,159 | 0.67 | | | - |
| Atezolizumab | | £83,963 | 1.44 | £63,804 | 1.09 | £83,352 |
| **1. 2 year stopping rule** | | | | | | |
| Docetaxel | | £20,159 | 0.67 | | | - |
| Atezolizumab | | £74,914 | 1.44 | £54,755 | 1.09 | £71,529 |
| **2a. 2-year treatment effect** | | | | | | |
| Docetaxel | | £20,116 | 0.67 | | | - |
| Atezolizumab | | £83,680 | 1.41 | £63,563 | 0.74 | £85,689 |
| **2b. 3-year treatment effect** | | | | | | |
| Docetaxel | | £20,124 | 0.67 | | | |
| Atezolizumab | | £83,735 | 1.41 | £63,611 | 0.75 | £85,207 |
| **3. without switching adjustment** | | | | | | |
| Docetaxel | | £21,267 | 0.78 | | | |
| Atezolizumab | | £83,963 | 1.44 | £62,696 | 0.65 | £95,922 |
| **4. Include cost of testing it atezolizumab arm** | | | | | | |
| Docetaxel | | £20,159 | 0.67 | | | |
| Atezolizumab | | £84,301 | 1.44 | £64,142 | 0.77 | £83,793 |
| **5. Include all OS extrapolations (repeat these rows as necessary)** | | | | | | |
| KM+Exp | Docetaxel | £19,713 | 0.63 | | | |
| | Atezolizumab | £80,403 | 1.08 | £60,690 | 0.46 | £132,055 |

| | | | | | | |
|---|---|---|---|---|---|---|
| | Docetaxel | £19,645 | 0.62 | | | |
| KM+Weibull | Atezolizumab | £80,051 | 1.05 | £60,406 | 0.43 | £140,076 |
| | Docetaxel | £20,193 | 0.67 | | | |
| KM+Log norm | Atezolizumab | £83,736 | 1.41 | £63,543 | 0.74 | £85,852 |
| | Docetaxel | £19,777 | 0.63 | | | |
| KM+Gamma | Atezolizumab | £80,884 | 1.13 | £61,108 | 0.50 | £121,981 |
| | Docetaxel | £20,159 | 0.67 | | | |
| KM+Log log | Atezolizumab | £83,963 | 1.44 | £63,804 | 0.77 | £83,352 |
| | Docetaxel | £19,644 | 0.62 | | | |
| KM+Gompertz | Atezolizumab | £79,979 | 1.04 | £60,335 | 0.42 | £142,230 |
| | Docetaxel | £20,390 | 0.69 | | | |
| Piecewise* | Atezolizumab | £82,128 | 1.26 | £61,737 | 0.56 | £109,522 |
| | Docetaxel | £20,398 | 0.69 | | | |
| 0% cure log log | Atezolizumab | £84,473 | 1.49 | £64,076 | 0.79 | £80,852 |
| | Docetaxel | £19,844 | 0.64 | | | |
| 0% cure gamma | Atezolizumab | £80,990 | 1.14 | £61,146 | 0.51 | £121,034 |
| **Committee preferred assumptions (1+2b+3+most plausible OS curve)**** | | | | | | |
| Docetaxel | | £20,159 | 0.76 | | | - |
| Atezolizumab | | £72,227 | 1.17 | £51,237 | 0.55 | £122,771 |

* Atezo: KM used to 45 weeks, end of piece: 65 weeks; Doce: KM used til 60 weeks, end of piece: 80 weeks
** Assumes committee will utilize a similar distribution to ITT, hence piecewise distribution included

**Table 59: PD-L1 positive population – versus pembrolizumab**

| | | Total costs | Total QALYS | Inc. costs | Inc. QALYs | ICER |
|---|---|---|---|---|---|---|
| **Company basecase (no stopping rule, on-going treatment effect, with switching adjustment)** | | | | | | |
| Pembrolizumab | | £76,720 | 1.25 | | | - |
| Atezolizumab | | £83,963 | 1.44 | £7,243 | 0.28 | £39,286 |
| **1. 2 year stopping rule** | | | | | | |
| Pembrolizumab | | £76,720 | 1.25 | | | - |
| Atezolizumab | | £74,914 | 1.44 | -£1,806 | 0.28 | -£9,798 |
| **2a. 2-year treatment effect** | | | | | | |
| Pembrolizumab | | £76,491 | 1.23 | | | |
| Atezolizumab | | £83,680 | 1.41 | £7,189 | 0.18 | £40,155 |
| **2b. 3-year treatment effect** | | | | | | |
| Pembrolizumab | | £76,536 | 1.23 | | | |
| Atezolizumab | | £83,735 | 1.41 | £7,200 | 0.18 | £39,981 |
| **3. without switching adjustment** | | | | | | |
| Pembrolizumab | | £80,021 | 1.58 | | | |
| Atezolizumab | | £83,963 | 1.44 | £3,942 | -0.14 | -£27,661 |
| **4. Include cost of testing it atezolizumab arm** | | | | | | |
| Pembrolizumab | | £76,720 | 1.25 | | | |
| Atezolizumab | | £84,301 | 1.44 | £7,581 | 0.18 | £41,120 |
| **5. Include all OS extrapolations (repeat these rows as necessary)** | | | | | | |
| | Pembrolizumab | £73,840 | 0.98 | | | |
| KM+Exp | Atezolizumab | £80,403 | 1.08 | £6,563 | 0.10 | £63,247 |

| | | | | | | |
|---|---|---|---|---|---|---|
| | Pembrolizumab | £73,498 | 0.95 | | | |
| KM+Weibull | Atezolizumab | £80,051 | 1.05 | £6,552 | 0.10 | £68,008 |
| | Pembrolizumab | £76,569 | 1.24 | | | |
| KM+Log norm | Atezolizumab | £83,736 | 1.41 | £7,168 | 0.18 | £40,496 |
| | Pembrolizumab | £74,283 | 1.02 | | | |
| KM+Gamma | Atezolizumab | £80,884 | 1.13 | £6,601 | 0.12 | £57,195 |
| | Pembrolizumab | £76,720 | 1.25 | | | |
| KM+Log log | Atezolizumab | £83,963 | 1.44 | £7,243 | 0.18 | £39,286 |
| | Pembrolizumab | £73,415 | 0.95 | | | |
| KM+Gompertz | Atezolizumab | £79,979 | 1.04 | £6,564 | 0.09 | £69,811 |
| | Pembrolizumab | £75,409 | 1.13 | | | |
| Piecewise* | Atezolizumab | £82,128 | 1.26 | £6,718 | 0.13 | £52,701 |
| | Pembrolizumab | £77,201 | 1.30 | | | |
| 0% cure log log | Atezolizumab | £84,473 | 1.49 | £7,273 | 0.19 | £38,869 |
| 0% cure | Pembrolizumab | £74,379 | 1.03 | | | |
| gamma | Atezolizumab | £80,990 | 1.14 | £6,612 | 0.11 | £57,517 |
| **Committee preferred assumptions (1+2b+3+most plausible OS curve)**** | | | | | | |
| Pembrolizumab | | £76,076 | 1.21 | | | - |
| Atezolizumab | | £72,227 | 1.17 | -£3,849 | -0.05 | £111,522 |

* Atezo: KM used to 45 weeks, end of piece: 65 weeks; Doce: KM used til 60 weeks, end of piece: 80 weeks
** Assumes committee will utilize a similar distribution to ITT, hence piecewise distribution included

## PD-L1 negative

It is imperative to note, the committee have not provided feedback on what they deem the most plausible OS curve. As such, an assumption has been required that the committee will utilize a similar distribution to ITT, hence piecewise distribution is presented.

**Table 60: PD-L1 negative population**

| | Total costs | Total QALYS | Inc. costs | Inc. QALYs | ICER |
|---|---|---|---|---|---|
| **Company basecase (no stopping rule, on-going treatment effect, without switching adjustment)** | | | | | |
| Docetaxel | £20,842 | 0.77 | | | - |
| Atezolizumab | £71,816 | 1.27 | £50,974 | 0.50 | £102,116 |
| **1. 2 year stopping rule** | | | | | |
| Docetaxel | £20,842 | 0.77 | | | - |
| Atezolizumab | £65,223 | 1.27 | £44,380 | 0.50 | £88,907 |
| **2a. 2-year treatment effect** | | | | | |
| Docetaxel | £20,842 | 0.77 | | | - |
| Atezolizumab | £69,495 | 1.04 | £48,653 | 0.34 | £179,834 |
| **2b. 3-year treatment effect** | | | | | |
| Docetaxel | £20,842 | 0.77 | | | - |
| Atezolizumab | £69,979 | 1.09 | £49,137 | 0.32 | £154,159 |
| **3. without switching adjustment** | | | | | |

| | | | | | | |
|---|---|---|---|---|---|---|
| Docetaxel | | NA | NA | NA | NA | NA |
| Atezolizumab | | NA | NA | NA | NA | NA |
| **4. Include cost of testing it atezolizumab arm** | | | | | | |
| Docetaxel | | £20,842 | 0.77 | | | - |
| Atezolizumab | | £72,154 | 1.27 | £51,312 | 0.50 | £102,793 |
| **5. Include all OS extrapolations (repeat these rows as necessary)** | | | | | | |
| Docetaxel | KM+Log norm | £20,842 | 0.77 | | | - |
| Atezolizumab | KM+Exp | £68,575 | 0.95 | £47,733 | 0.18 | £265,957 |
| | KM+Weibull | £68,206 | 0.91 | £47,364 | 0.14 | £332,117 |
| | KM+Log norm | £71,328 | 1.22 | £50,485 | 0.45 | £111,791 |
| | KM+Gamma | £70,322 | 1.12 | £49,480 | 0.35 | £140,342 |
| | KM+Log log | £71,816 | 1.27 | £50,974 | 0.50 | £102,116 |
| | KM+Gompertz | £68,575 | 0.95 | £47,733 | 0.18 | £265,958 |
| | Piecewise* | £71,393 | 1.23 | £50,551 | 0.46 | £109,906 |
| | Cure log logistic | £71,517 | 1.24 | £50,675 | 0.47 | £108,027 |
| Atezolizumab | KM+Log log | £71,816 | 1.27 | | | |
| Docetaxel | KM+Exp | £19,878 | 0.67 | £51,938 | 0.60 | £87,238 |
| | KM+Weibull | £19,445 | 0.63 | £52,371 | 0.64 | £81,976 |
| | KM+Log norm | £20,842 | 0.77 | £50,974 | 0.50 | £102,116 |
| | KM+Gamma | £19,822 | 0.67 | £51,994 | 0.60 | £86,522 |
| | KM+Log log | £21,204 | 0.81 | £50,612 | 0.46 | £109,145 |
| | KM+Gompertz** | £19,395 | NA | £52,422 | NA | NA |
| | Piecewise* | 19,856 | 0.67 | £51,960 | 0.60 | £86,959 |
| **Committee preferred assumptions (1+2b+3+most plausible OS curve)*** ** | | | | | | |
| Docetaxel | | £19,856 | 0.67 | | | - |
| Atezolizumab | | £40,989 | 0.99 | £21,133 | 0.31 | £67,185 |

* Atezo: KM used to 70 weeks, end of piece: 98 weeks; Doce: KM used til 52 weeks, end of piece: 67 weeks
** Gompertz does not converge, therefore unable to return a result
*** Assumes committee will utilize a similar distribution to ITT, hence piecewise distribution included

## PAS Price

### ITT

**Table 61: All-comer population – versus docetaxel**

| | Total costs | Total QALYS | Inc. costs | Inc. QALYs | ICER |
|---|---|---|---|---|---|
| **Company basecase (no stopping rule, on-going treatment effect, with switching adjustment, company-preferred extrapolation)** | | | | | |
| Docetaxel | £19,536 | 0.64 | | | - |
| Atezolizumab | [redacted] | 1.31 | [redacted] | 0.66 | [redacted] |
| **1. 2 year stopping rule** | | | | | |
| Docetaxel | £19,536 | 0.64 | | | - |
| Atezolizumab | [redacted] | 1.31 | [redacted] | 0.66 | [redacted] |

| | | | | | |
|---|---|---|---|---|---|
| **2a. 2-year treatment effect** | | | | | |
| Docetaxel | £19,469 | 0.64 | | | - |
| Atezolizumab | [redacted] | 1.27 | [redacted] | 0.64 | [redacted] |
| **2b. 3-year treatment effect** | | | | | |
| Docetaxel | £19,517 | 0.64 | | | - |
| Atezolizumab | [redacted] | 1.29 | [redacted] | 0.65 | [redacted] |
| **3. without switching adjustment** | | | | | |
| Docetaxel | £20,181 | 0.71 | | | - |
| Atezolizumab | [redacted] | 1.31 | [redacted] | 0.60 | [redacted] |
| **4. Committee preferred OS extrapolation (for all comers)*** | | | | | |
| Docetaxel | £19,279 | 0.62 | | | - |
| Atezolizumab | [redacted] | 1.02 | [redacted] | 0.41 | [redacted] |
| **Committee preferred assumptions (1+2b+3+4)*** | | | | | |
| Docetaxel | £19,644 | 0.66 | | | - |
| Atezolizumab | [redacted] | 0.98 | [redacted] | 0.33 | [redacted] |

* Utilises the piecewise distribution in the company economic model, KM until 52 weeks, as preferred, end of piece: 69 weeks (atezo) and 80 weeks (doce).

**Table 62: All-comer population – versus nintedanib+docetaxel**

| | Total costs | Total QALYS | Inc. costs | Inc. QALYs | ICER |
|---|---|---|---|---|---|
| **Company basecase (no stopping rule, on-going treatment effect, with switching adjustment, company-preferred extrapolation)** | | | | | |
| Nintedanib+Docetaxel | £37,265 | 0.81 | | | - |
| Atezolizumab | [redacted] | 1.31 | [redacted] | 0.49 | [redacted] |
| **1. 2 year stopping rule** | | | | | |
| Nintedanib+Docetaxel | £37,265 | 0.81 | | | - |
| Atezolizumab | [redacted] | 1.31 | [redacted] | 0.49 | [redacted] |
| **2a. 2-year treatment effect** | | | | | |
| Nintedanib+Docetaxel | £37,136 | 0.80 | | | - |
| Atezolizumab | [redacted] | 1.27 | [redacted] | 0.47 | [redacted] |
| **2b. 3-year treatment effect** | | | | | |
| Nintedanib+Docetaxel | £37,220 | 0.81 | | | - |
| Atezolizumab | [redacted] | 1.29 | [redacted] | 0.48 | [redacted] |
| **3. without switching adjustment** | | | | | |
| Nintedanib+Docetaxel | £38,261 | 0.91 | | | - |
| Atezolizumab | [redacted] | 1.31 | [redacted] | 0.39 | [redacted] |
| **4. Committee preferred OS extrapolation (for all comers)*** | | | | | |
| Nintedanib+Docetaxel | £36,623 | 0.75 | | | - |
| Atezolizumab | [redacted] | 1.02 | [redacted] | 0.27 | [redacted] |
| **Committee preferred assumptions (1+2b+3+4)*** | | | | | |
| Nintedanib+Docetaxel | £37,022 | 0.79 | | | - |
| Atezolizumab | [redacted] | 0.98 | [redacted] | 0.19 | [redacted] |

* Utilises the piecewise distribution in the company economic model, KM until 52 weeks, as preferred, end of piece: 69 weeks (atezo) and 80 weeks (doce).

## PD-L1 positive

It is imperative to note, the committee have not provided feedback on what they deem the most plausible OS curve. As such, an assumption has been required that the committee will utilize a similar distribution to ITT, hence piecewise distribution is presented.

**Table 63: PD-L1 positive population: versus docetaxel**

| | | Total costs | Total QALYS | Inc. costs | Inc. QALYs | ICER |
|---|---|---|---|---|---|---|
| **Company basecase (no stopping rule, on-going treatment effect, with switching adjustment)** | | | | | | |
| Docetaxel | | £20,159 | 0.67 | | | - |
| Atezolizumab | | [redacted] | 1.44 | [redacted] | 1.09 | [redacted] |
| **1. 2 year stopping rule** | | | | | | |
| Docetaxel | | £20,159 | 0.67 | | | - |
| Atezolizumab | | [redacted] | 1.44 | [redacted] | 1.09 | [redacted] |
| **2a. 2-year treatment effect** | | | | | | |
| Docetaxel | | £20,116 | 0.67 | | | |
| Atezolizumab | | [redacted] | 1.41 | [redacted] | 0.74 | [redacted] |
| **2b. 3-year treatment effect** | | | | | | |
| Docetaxel | | £20,124 | 0.67 | | | |
| Atezolizumab | | [redacted] | 1.41 | [redacted] | 0.75 | [redacted] |
| **3. without switching adjustment** | | | | | | |
| Docetaxel | | £21,267 | 0.78 | | | |
| Atezolizumab | | [redacted] | 1.44 | [redacted] | 0.65 | [redacted] |
| **4. Include cost of testing it atezolizumab arm** | | | | | | |
| Docetaxel | | £20,159 | 0.67 | | | |
| Atezolizumab | | [redacted] | 1.44 | [redacted] | 0.77 | [redacted] |
| **5. Include all OS extrapolations (repear these rows as necessary)** | | | | | | |
| KM+Exp | Docetaxel | £19,713 | 0.63 | | | |
| | Atezolizumab | [redacted] | 1.08 | [redacted] | 0.46 | [redacted] |
| KM+Weibull | Docetaxel | £19,645 | 0.62 | | | |
| | Atezolizumab | [redacted] | 1.05 | [redacted] | 0.43 | [redacted] |
| KM+Log norm | Docetaxel | £20,193 | 0.67 | | | |
| | Atezolizumab | [redacted] | 1.41 | [redacted] | 0.74 | [redacted] |
| KM+Gamma | Docetaxel | £19,777 | 0.63 | | | |
| | Atezolizumab | [redacted] | 1.13 | [redacted] | 0.50 | [redacted] |
| KM+Log log | Docetaxel | £20,159 | 0.67 | | | |
| | Atezolizumab | [redacted] | 1.44 | [redacted] | 0.77 | [redacted] |
| KM+Gompertz | Docetaxel | £19,644 | 0.62 | | | |
| | Atezolizumab | [redacted] | 1.04 | [redacted] | 0.42 | [redacted] |
| Piecewise* | Docetaxel | £20,390 | 0.69 | | | |
| | Atezolizumab | [redacted] | 1.26 | [redacted] | 0.56 | [redacted] |
| 0% cure log log | Docetaxel | £20,398 | 0.69 | | | |
| | Atezolizumab | [redacted] | 1.49 | [redacted] | 0.79 | [redacted] |
| 0% cure gamma | Docetaxel | £19,844 | 0.64 | | | |
| | Atezolizumab | [redacted] | 1.14 | [redacted] | 0.51 | [redacted] |
| **Committee preferred assumptions (1+2b+3+most plausible OS curve)** | | | | | | |

| | | | | | |
|---|---|---|---|---|---|
| Docetaxel | £20,990 | 0.76 | | | - |
| Atezolizumab | [redacted] | 1.17 | [redacted] | 0.55 | [redacted] |

* Atezo: KM used to 45 weeks, end of piece: 65 weeks; Doce: KM used til 60 weeks, end of piece: 80 weeks
** Assumes committee will utilize a similar distribution to ITT, hence piecewise distribution included

**Table 64: PD-L1 positive population: versus pembrolizumab**

| | | Total costs | Total QALYS | Inc. costs | Inc. QALYs | ICER |
|---|---|---|---|---|---|---|
| **Company basecase (no stopping rule, on-going treatment effect, with switching adjustment)** | | | | | | |
| Pembrolizumab | | £76,720 | 1.25 | | | - |
| Atezolizumab | | [redacted] | 1.44 | [redacted] | 0.28 | [redacted] |
| **1. 2 year stopping rule** | | | | | | |
| Pembrolizumab | | £76,720 | 1.25 | | | - |
| Atezolizumab | | [redacted] | 1.44 | [redacted] | 0.28 | [redacted] |
| **2a. 2-year treatment effect** | | | | | | |
| Pembrolizumab | | £76,491 | 1.23 | | | |
| Atezolizumab | | [redacted] | 1.41 | [redacted] | 0.18 | [redacted] |
| **2b. 3-year treatment effect** | | | | | | |
| Pembrolizumab | | £76,536 | 1.23 | | | |
| Atezolizumab | | [redacted] | 1.41 | [redacted] | 0.18 | [redacted] |
| **3. without switching adjustment** | | | | | | |
| Pembrolizumab | | £80,021 | 1.58 | | | |
| Atezolizumab | | [redacted] | 1.44 | [redacted] | -0.14 | [redacted] |
| **4. Include cost of testing it atezolizumab arm** | | | | | | |
| Pembrolizumab | | £76,720 | 1.25 | | | |
| Atezolizumab | | [redacted] | 1.44 | [redacted] | 0.18 | [redacted] |
| **5. Include all OS extrapolations (repear these rows as necessary)** | | | | | | |
| KM+Exp | Pembrolizumab | £73,840 | 0.98 | | | |
| | Atezolizumab | [redacted] | 1.08 | [redacted] | 0.10 | [redacted] |
| KM+Weibull | Pembrolizumab | £73,498 | 0.95 | | | |
| | Atezolizumab | [redacted] | 1.05 | [redacted] | 0.10 | [redacted] |
| KM+Log norm | Pembrolizumab | £76,569 | 1.24 | | | |
| | Atezolizumab | [redacted] | 1.41 | [redacted] | 0.18 | [redacted] |
| KM+Gamma | Pembrolizumab | £74,283 | 1.02 | | | |
| | Atezolizumab | [redacted] | 1.13 | [redacted] | 0.12 | [redacted] |
| KM+Log log | Pembrolizumab | £76,720 | 1.25 | | | |
| | Atezolizumab | [redacted] | 1.44 | [redacted] | 0.18 | [redacted] |
| KM+Gompertz | Pembrolizumab | £73,415 | 0.95 | | | |
| | Atezolizumab | [redacted] | 1.04 | [redacted] | 0.09 | [redacted] |
| Piecewise* | Pembrolizumab | £75,409 | 1.13 | | | |
| | Atezolizumab | [redacted] | 1.26 | [redacted] | 0.13 | [redacted] |
| 0% cure log log | Pembrolizumab | £77,201 | 1.30 | | | |
| | Atezolizumab | [redacted] | 1.49 | [redacted] | 0.19 | [redacted] |
| 0% cure gamma | Pembrolizumab | £74,379 | 1.03 | | | |
| | Atezolizumab | [redacted] | 1.14 | [redacted] | 0.11 | [redacted] |

| Committee preferred assumptions (1+2b+3+most plausible OS curve) | | | | | |
|---|---|---|---|---|---|
| Pembrolizumab | £76,076 | 1.21 | | | - |
| Atezolizumab | [redacted] | 1.17 | [redacted] | -0.05 | [redacted] |

* Atezo: KM used to 45 weeks, end of piece: 65 weeks; Doce: KM used til 60 weeks, end of piece: 80 weeks
** Assumes committee will utilize a similar distribution to ITT, hence piecewise distribution included

## PD-L1 negative

It is imperative to note, the committee have not provided feedback on what they deem the most plausible OS curve. As such, an assumption has been required that the committee will utilize a similar distribution to ITT, hence piecewise distribution is presented.

**Table 65: PD-L1 negative population**

| | | Total costs | Total QALYS | Inc. costs | Inc. QALYs | ICER |
|---|---|---|---|---|---|---|
| **Company basecase (no stopping rule, on-going treatment effect, with switching adjustment)** | | | | | | |
| Docetaxel | | £20,842 | 0.77 | | | - |
| Atezolizumab | | [redacted] | 1.27 | [redacted] | 0.50 | [redacted] |
| **1. 2 year stopping rule** | | | | | | |
| Docetaxel | | £20,842 | 0.77 | | | - |
| Atezolizumab | | [redacted] | 1.27 | [redacted] | 0.50 | [redacted] |
| **2a. 2-year treatment effect** | | | | | | |
| Docetaxel | | £20,842 | 0.77 | | | - |
| Atezolizumab | | [redacted] | 1.04 | [redacted] | 0.27 | [redacted] |
| **2b. 3-year treatment effect** | | | | | | |
| Docetaxel | | £20,842 | 0.77 | | | - |
| Atezolizumab | | [redacted] | 1.09 | [redacted] | 0.32 | [redacted] |
| **3. without switching adjustment** | | | | | | |
| Docetaxel | | NA | NA | NA | NA | NA |
| Atezolizumab | | NA | NA | NA | NA | NA |
| **4. Include cost of testing it atezolizumab arm** | | | | | | |
| Docetaxel | | £20,842 | 0.77 | | | - |
| Atezolizumab | | [redacted] | 1.27 | [redacted] | 0.50 | [redacted] |
| **5. Include all OS extrapolations (repear these rows as necessary)** | | | | | | |
| Docetaxel | KM+Log norm | £20,842 | 0.77 | | | - |
| Atezolizumab | KM+Exp | [redacted] | 0.95 | [redacted] | 0.18 | [redacted] |
| | KM+Weibull | [redacted] | 0.91 | [redacted] | 0.14 | [redacted] |
| | KM+Log norm | [redacted] | 1.22 | [redacted] | 0.45 | [redacted] |
| | KM+Gamma | [redacted] | 1.12 | [redacted] | 0.35 | [redacted] |
| | KM+Log log | [redacted] | 1.27 | [redacted] | 0.50 | [redacted] |
| | KM+Gompertz | [redacted] | 0.95 | [redacted] | 0.18 | [redacted] |

| | | | | | | |
|---|---|---|---|---|---|---|
| | Piecewise* | [redacted] | 1.23 | [redacted] | 0.46 | [redacted] |
| | Cure log logistic | [redacted] | 1.24 | [redacted] | 0.47 | [redacted] |
| Atezolizumab | KM+Log log | [redacted] | 1.27 | | | |
| Docetaxel | KM+Exp | £19,878 | 0.67 | [redacted] | 0.60 | [redacted] |
| | KM+Weibull | £19,445 | 0.63 | [redacted] | 0.64 | [redacted] |
| | KM+Log norm | £20,842 | 0.77 | [redacted] | 0.50 | [redacted] |
| | KM+Gamma | £19,822 | 0.67 | [redacted] | 0.60 | [redacted] |
| | KM+Log log | £21,204 | 0.81 | [redacted] | 0.46 | [redacted] |
| | KM+Gompertz** | £19,395 | NA | [redacted] | NA | [redacted] |
| | Piecewise* | £19,856 | 0.67 | [redacted] | 0.60 | [redacted] |
| **Committee preferred assumptions (1+2b+3+most plausible OS curve)** | | | | | | |
| Docetaxel | | £19,856 | 0.67 | | | - |
| Atezolizumab | | [redacted] | 0.99 | [redacted] | 0.31 | [redacted] |

* Atezo: KM used to 70 weeks, end of piece: 98 weeks; Doce: KM used til 52 weeks, end of piece: 67 weeks
** Gompertz does not converge, therefore unable to return a result
*** Assumes committee will utilize a similar distribution to ITT, hence piecewise distribution included

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## KEY TAKE-AWAY POINTS

**Secondary analyses in ITT1225 of OAK:**

- **Overall survival benefit is maintained in the larger 1225 population**
  - Survival improvement in both squamous and non-squamous histologies
  - Survival benefit seen across all levels of PD-L1 expression
  - OS improvement maintained across majority of subgroups in ITT1225
- **Similar to the primary population (ITT850):**
  - PFS and ORR do not capture the efficacy of TECENTRIQ in the ITT1225 population
  - Improved PFS and ORR are only seen at higher levels of PD-L1 expression
  - **Responses are durable: mDoR increases further with prolonged follow-up since primary analysis (ITT850) and is still not yet mature**
  - **The favourable safety profile of TECENTRIQ is confirmed with increased overall exposure and no new safety signals were identified**

**Comparison of ITT1225 and ITT850 OAK analysis populations**

- **The overall survival benefit of TECENTRIQ seen in the primary analysis population (ITT850) is maintained with increasing data maturity**
- **HRs for overall survival were all numerically higher in the ITT1225 and in its subgroups compared with the primary analysis of ITT850**
- **There are several key differences between the ITT1225 and ITT850 populations which help explain this reduction in *relative* benefit:**
  - The rate of subsequent immunotherapy in the docetaxel arm of the last 375 patients was twice that of the primary analysis in ITT850
  - There was higher rate of subsequent immunotherapy in the TC3 or IC3 patients within the docetaxel patients – patients who would be expected to respond well to CIT
  - There were fewer TC3 or IC3 patients in the TECENTRIQ arm for the last 375 patients than in the primary ITT850
  - Exploratory analyses - which were non-randomised and should be interpreted with caution – seem to indicate the likely impact of subsequent immunotherapy on survival of the docetaxel-treated patients in the last 375 enrolled patients.
- **When adjusting for treatment crossover, using either RPFST or AFT models, the HRs for overall survival decreased, indicating that subsequent non-protocol immunotherapy in the docetaxel arm may have confounded the OS HR for the primary endpoint in both the ITT850 and ITT1225**
- **In spite of high rate of subsequent immunotherapy there was still a clear OS benefit seen with TECENTRIQ in both ITT850 and ITT1225**

**Single technology appraisal**

**Atezolizumab for treating non-small-cell lung cancer after chemotherapy [ID970]**

Dear Stephanie and Tanith,

Following the meetings with NICE last week, we can now confirm an update to the atezolizumab PAS has been sent to the Department of Health. The new discount is [redacted]%, resulting in a net pack price of [redacted].

I have provided a set of updated results for the following populations, for consideration at the part 2b discussion on 21st February:

- All-comers
- PD-L1 positives (TC/IC 1/2/3)
- PD-L1 negatives (TC/IC 0)

Please let me know if you have any questions. We hope the updated analyses for all populations will support committee decision making, and we look forward to hearing the final decision from the committee.

Kind regards,

[redacted]

Health Economist
Roche Products Ltd

**All-comers:**

| | Total costs | Total QALYS | Inc. costs | Inc. QALYs | ICER |
|---|---|---|---|---|---|
| PAS price: Committee preferred scenario: 2-year stopping rule, 3-year treatment effect, include cost of testing in both arms, no treatment switching adjustment, company OS extrapolation: log-logistic | | | | | |
| Docetaxel | £20,512 | 0.71 | | | |
| Atezolizumab | [redacted] | 1.30 | [redacted] | 0.59 | [redacted] |

**PD-L1 positives:**

Cost utility analysis

| | Total costs | Total QALYS | Inc. costs | Inc. QALYs | ICER |
|---|---|---|---|---|---|
| PAS price: Committee preferred scenario: 2-year stopping rule, 3-year treatment effect, include cost of testing in both arms, no treatment switching adjustment, company OS extrapolation: log-logistic | | | | | |
| Pembrolizumab | £79,932 | 1.57 | | | [redacted] |
| Atezolizumab | [redacted] | 1.43 | [redacted] | -0.22 | [redacted] |

Cost minimisation analysis

| | | Atezolizumab | Pembrolizumab | Increment |
|---|---|---|---|---|
| Mean costs in PFS | Treatment cost | [redacted] | £48,133 | [redacted] |
| | Drug administration (including diagnostic test) | [redacted] | £2,657 | [redacted] |
| | Adverse events | [redacted] | £117 | [redacted] |
| | Supportive care costs | [redacted] | £10,661 | [redacted] |
| Mean costs in PD | Subsequent therapies | [redacted] | £3,749 | [redacted] |
| | Supportive care | [redacted] | £11,259 | [redacted] |
| | Terminal care | [redacted] | £3,356 | [redacted] |
| Total costs | | [redacted] | £79,932 | [redacted] |

**PD-L1 negatives:**

| | Total costs | Total QALYS | Inc. costs | Inc. QALYs | ICER |
|---|---|---|---|---|---|
| PAS price: Committee preferred scenario: 2-year stopping rule, 3-year treatment effect, include cost of testing in both arms, no treatment switching adjustment, company OS extrapolation: atezolizumab: log-logistic, docetaxel: log-normal | | | | | |
| Docetaxel | £21,180 | 0.77 | | | |
| Atezolizumab | [redacted] | 1.15 | [redacted] | 0.38 | [redacted] |

ID970 STA Atezolizumab Addendum 4

LIVERPOOL REVIEWS AND IMPLEMENTATION GROUP (LRiG)

# Atezolizumab for treating locally advanced or metastatic non-small cell lung cancer after chemotherapy [ID970]

Confidential until published

This report was commissioned by the NIHR HTA Programme as project number 16/56/11

Completed 19 January 2018

CONTAINS ACADEMIC AND COMMERCIAL IN CONFIDENCE DATA



UNIVERSITY OF LIVERPOOL | LIVERPOOL REVIEWS AND IMPLEMENTATION GROUP

A MEMBER OF THE RUSSELL GROUP

# 1 BACKGROUND

As part of the Single Technology Appraisal (STA) process, the company (Roche) has submitted additional information (January 2018 company submission [CS][1]) in response to the second Appraisal Consultation Document (ACD2[2]) issued by the National Institute for Health and Care Excellence (NICE) for the appraisal of atezolizumab for treating advanced or metastatic non-small cell lung cancer (NSCLC) after chemotherapy [ID970].

Within the company's original submission (February 2017 CS[3]), the main source of direct efficacy evidence used in the company model was data from the OAK trial[4,5] primary population. The OAK trial is an open-label, multicentre, randomised controlled trial (RCT) designed to investigate the efficacy and safety of atezolizumab versus docetaxel in patients with locally advanced or metastatic NSCLC whose disease has progressed during or following a platinum-containing regimen. The company carried out fractional polynomial (FP) indirect treatment comparisons (ITCs) to provide estimates of the effectiveness of atezolizumab versus nintedanib+docetaxel and atezolizumab versus pembrolizumab.

The Evidence Review Group (ERG) identified a number of weakness and areas of uncertainty relating to the evidence presented in the February 2017 CS.[3] These concerns were set out in the original ERG report[6] and, for information, are provided in Appendix 1.

The OAK trial data provided in the February 2017 CS[3] relate to the primary population (atezolizumab arm=425 patients, docetaxel arm=425 patients). Following the interim analysis of data from the POPLAR trial[7,8] (an open-label, multi-centre phase II RCT designed to investigate the efficacy and safety of treatment with atezolizumab versus docetaxel), the OAK trial population size was increased to ensure that at least 220 patients with programmed death-ligand 1 (PD-L1) tumour cell/ tumour-infiltrating immune cell (TC/IC) 3 (assuming a 20% prevalence) were enrolled. In total, 1225 patients were randomised (614 to the atezolizumab arm and 611 to the docetaxel arm). The primary population (n=850), plus the additional 375 patients, is known as the secondary population.

# 2 COST EFFECTIVENESS

The company considers (January 2018 CS[1]) that the data from the primary population (data cut-off date July 2016) are the appropriate data for decision making as these data were used in the pre-specified analysis (that provided sufficient power to test the co-primary end points), were the basis for regulatory approval, and are more robust because the results are less confounded by treatment switching compared with results generated from analyses of data from the secondary population (data cut-off date January 2017). The company has, therefore, continued to use data from the primary population in their economic model. This means that

the cost effectiveness results presented by the company in response to ACD2[2] have been developed using the same OAK trial effectiveness data that were used to generate the cost effectiveness results presented in the February 2017 CS.[3] The ERG also highlights that the only structural changes to the company model provided as part of the company response to ACD2[1,13] have been those required to facilitate a comparison of the cost effectiveness of treatment with atezolizumab versus pembrolizumab (an analysis that was not included in the February 2017 CS[3]). The ERG considers that that the changes made by the company to their model are technically correct.

## *2.1 The all-comers population*

The February 2017 CS[3] base case cost effectiveness results relate to the primary population of the OAK trial and are undifferentiated by tumour histology or level of PD-L1 expression.

Within the January 2018 CS,[1] the company has provided cost effectiveness results for the comparison of atezolizumab versus docetaxel in the all-comers population. The company's incremental cost effectiveness ratios (ICERs) are [redacted] per quality adjusted life year (QALY) gained when overall survival (OS) data have been adjusted for treatment switching and [redacted] per QALY gained when no adjustments for treatment switching have been made. The ERG, however, considers that docetaxel would only be prescribed to patients in the TC/IC 1/2/3 subgroup (54% of the all-comers population) if it was determined that immunotherapy was not an appropriate treatment. Pembrolizumab (TA428[9]) is recommended for the treatment of patients with PD-L1 positive NSCLC who have had at least one prior chemotherapy. The ERG, therefore, considers that the ICER per QALY gained for the comparison of atezolizumab versus docetaxel for the OAK trial all-comers population is not relevant to this appraisal.

The ERG highlights that nintedanib+docetaxel is also a treatment option for a subgroup of patients included in the OAK trial (patients with NSCLC of adenocarcinoma histology [**TA347**[10]]) and that, within the original ERG report:[6]

- the ERG's preferred ICER for the comparison of treatment with atezolizumab versus nintedanib+docetaxel (using list prices for both treatments) was greater than £1million per QALY gained
- the ERG expressed concerns that, when comparing the effectiveness of treatment with atezolizumab versus nintedanib+docetaxel, it might not be appropriate to consider atezolizumab as an End of Life treatment.

The ERG also highlights that there is uncertainty about the size of the population that currently receives treatment with nintedanib+docetaxel.

Company estimates of atezolizumab versus nintedanib+docetaxel, presented at the third AC meeting and generated using PAS prices can be found in Confidential Appendix 5.

## 2.2 TC/IC 0 subgroup

The company's ICER for the comparison of the cost effectiveness of atezolizumab versus docetaxel for the TC/IC 0 subgroup is [redacted] per QALY gained. The ERG highlights that the magnitude of this ICER per QALY gained (>£50,000) indicates that, even when calculated using the patient access scheme (PAS) price for atezolizumab and assuming adherence to NICE End of Life criteria,[11] atezolizumab is unlikely to be considered a cost effective option for this subgroup.

## 2.3 TC/IC 1/2/3 subgroup

The company's estimated ICER, for the TC/IC 1/2/3 subgroup, for the comparison of treatment with atezolizumab versus docetaxel is [redacted] per QALY gained. Within the January 2018 CS[1] (p10), the company states that, since the publication of NICE guidance in January 2017 (TA428[9]), pembrolizumab has become standard of care for patients with PD-L1 positive NSCLC who have received prior chemotherapy. The ERG considers that the ICER per QALY gained for the comparison of the cost effectiveness of atezolizumab versus docetaxel in this subgroup is, therefore, not relevant to the appraisal.

Within the December 2017 CS,[13] the company presented results from FP ITCs undertaken to compare the effectiveness of atezolizumab (TC/IC 1/2/3) versus pembrolizumab (tumour proportion score [TPS] ≥1%) using data from the OAK and KEYNOTE-010[12] trials. Analyses were undertaken with, and without, treatment switching adjustments having been made to docetaxel arm data. Results show, for both PFS and OS, that treatment with atezolizumab is non-inferior to pembrolizumab irrespective of adjusting for treatment switching. The ERG highlights that a range of input parameters could be used in the analyses and that it is difficult to identify the most appropriate combination of factors and, therefore, it is difficult to interpret results from the FP ITCs. In addition, as results from the company's FP ITCs show treatment with atezolizumab to be non-inferior to pembrolizumab (in terms of survival), the ERG was surprised to note that the company's QALY estimates for this comparison generally suggest that, over a patient lifetime, treatment with [redacted].

It is not currently possible to directly (or, with any confidence, indirectly) compare the effectiveness of atezolizumab versus pembrolizumab in patients whose tumours exhibit a level of PD-L1 expression. However, for completeness, the ERG has presented available comparable baseline characteristics, summary adverse event (AE) incidence data and survival results from the OAK and KEYNOTE-010 trials in Section 3 of this report.

Company estimates of atezolizumab versus pembrolizumab, presented at the third AC meeting and generated using PAS prices can be found in Confidential Appendix 5.

### 2.4 Other issues

The ERG highlights that:

- when compared with pembrolizumab, treatment with atezolizumab may not deliver an extension to life of ≥3 months (and, therefore, may not be considered an End of Life treatment)
- PAS prices are in place for atezolizumab, nintedanib, and pembrolizumab.

# 3 ATEZOLIZUMAB AND PEMBROLIZUMAB: COMPARATIVE INFORMATION

This section provides structured summaries to facilitate comparison between baseline characteristics and trial results of participants in the OAK trial (the TC/IC 1/2/3 subgroup) and KEYNOTE-010 (TPS ≥1%) trials. The KEYNOTE-010 trial data have been extracted from the ID840 (TA428[9]) CS and relate to two arms of that trial: the docetaxel arm and the pembrolizumab 2 mg/kg Q3W (every 3 weeks) arm. Tables facilitating comparison of baseline characteristics, main trial results and AEs are included in this section. In addition, OS and progression-free survival (PFS) Kaplan-Meier (K-M) data from the two trials are presented in graphs to allow comparison of survival over time.

### 3.1 Characteristics of patients enrolled in the OAK trial

The key baseline characteristics of patients included in the OAK and KEYNOTE-010 trials are provided in **Error! Reference source not found.**.

The ERG considers that the baseline characteristics of the OAK trial intention-to-treat (ITT) population are generally well balanced across the two treatment arms. In addition, clinical advice to the ERG is that the patients recruited to the OAK trial can be considered to be broadly representative of patients with advanced NSCLC, treated in the NHS, albeit slightly younger and fitter. The company states that the baseline characteristics of the TC/IC 1/2/3 subgroup are generally consistent with those of the primary population and generally balanced between arms. Demographic and baseline characteristics of the TC/IC 1/2/3 subgroup with a difference of ≥5% are shown in Table 2.

Table 1 OAK and KEYNOTE-010 trials: participant demographic and baseline characteristics

| | OAK trial primary population) | | KEYNOTE-010 trial | |
|---|---|---|---|---|
| | **Atezolizumab (1200 mg Q3W) N=425** | **Docetaxel (75 mg/m² Q3W) N=425** | **Pembrolizumab (2 mg/kg Q3W) N=339** | **Docetaxel (75 mg/m² Q3W) N=309** |
| Male n (%) | 261 (61) | 259 (61) | 212 (61.6) | 209 (60.9) |
| Mean months from initial diagnosis to randomisation (sd) | 21.04 (21.45) | 20.06 (23.0) | | |
| **Age** | | | | |
| Age, years, median (range) | 63.0 (33.0 to 82.0) | 64.0 (34.0 to 85.0) | 62.1 (29 to 82) | 61.6 (33.0 to 82.0) |
| <65 years, n (%) | 235 (55) | 218 (51) | 201 (58.4) | 209 (60.9) |
| ≥65 years, n (%) | 190 (45) | 207 (49) | 143 (41.6) | 134 (39.1) |
| **ECOG PS, n (%)** | | | | |
| 0 | 155 (36) | 160 (38) | 112 (32.6) | 116 (33.8) |
| 1 | 270 (64) | 265 (62) | 22.9 (66.6) | 224 (65.3) |
| **Histology** | | | | |
| Non-squamous | 313 (74) | 315 (74) | 240 (69.8) | 240 (70.0) |
| Squamous | 112 (26) | 110 (26) | 76 (22.1) | 66 (19.2) |
| **Current disease status (%)** | | | | |
| Locally advanced | 29 (7) | 19 (5) | 21 (6.1) | 22 (6.4) |
| Metastatic* | 396 (93) | 406 (95) | 315 (91.6) | 312 (91.0 |
| **Number of prior therapies n (%)** | | | | |
| 1 | 320 (75) | 320 (75) | 243 (70.6) | 235 (68.5) |
| 2 | 105 (25) | 105 (25) | 66 (19.2) | 75 (21.9) |
| **Smoking status n (%)** | | | | |
| Never | 84 (20) | 72 (17) | 63 (18.3) | 67 (19.5) |
| Current/previous | 341 (80) | 353 (83) | 279 (81.1) | 269 (78.4) |
| Missing | | | 2 (0.6) | 7 (2.0) |
| **Metastases** | | | | |
| Number of metastatic sites at enrolment, mean (sd) | 2.89 (1.43) | 2.97 (1.32) | | |
| **Confirmed metastases at enrolment n (%)** | | | | |
| Brain | 38 (9) | 47 (11) | 56 (16.3) | 48 (14.0) |
| **PD-L1 expression** | | | | |
| TC3 or IC3, n (%) | 72 (16.9) | 65 (15.3) | - | - |
| TC2/3 or IC2/3, n (%) | 129 (30.4) | 136 (32.0) | - | - |
| TC1/2/3 or IC1/2/3, n (%) | 241 (56.7) | 222 (52.2) | - | - |
| TPS 1-49% | - | - | 205 (59.6) | 191 (55.7%) |
| TPS ≥50% | - | - | 139 (40.4) | 152 (44.3) |

* KEYNOTE-010 trial: stage IIIb and IV
ECOG PS=Eastern Cooperative Oncology Group performance score; IC=immune cell; PD-L1=programmed death-ligand 1; sd=standard deviation; TC=tumour cell
Source: February 2017 CS, Table 24 and Table 26 and ID840 (TA428) CS, Table 17

Table 2 OAK trial TC/IC 1/2/3 subgroup (primary population): demographic and baseline characteristics with difference of ≥5% between treatment arms

| Baseline demographic characteristic | Atezolizumab (n=72) | Docetaxel (n=65) |
|---|---|---|
| [redacted] | [redacted] | [redacted] |
| [redacted] | [redacted] | [redacted] |
| [redacted] | [redacted] | [redacted] |

Source: OAK trial CSR, Table 17

## *3.2 Results from the OAK trial (TC/IC 1/2/3 subgroup) and the KEYNOTE-010 trial*

Survival results (OS, PFS) and response rates from the OAK (TC/IC 1/2/3 subgroup) and KEYNOTE-010 trials are shown in Table 3, with digitised K-M curves for OS and PFS shown in **Error! Reference source not found.** and **Error! Reference source not found.** respectively. The data seem to suggest better OS in the atezolizumab arm of the OAK trial TC/IC 1/2/3 subgroup) than in the pembrolizumab arm of the KEYNOTE-010 trial, with similar PFS. However, when interpreting these results, survival of patients in the docetaxel arms of the two trials should be taken into account, and the ERG highlights that, compared with results from the OAK trial, median PFS was higher, and median OS was lower, in the docetaxel arm of the KEYNOTE-010 trial.

Table 3 Results from the OAK and KEYNOTE-010 trials

| Endpoint | OAK trial (Primary population: TC/IC 1/2/3 subgroup) | | KEYNOTE-010 trial | |
|---|---|---|---|---|
| | Atezolizumab (1200 mg Q3W) [redacted] | Docetaxel (75 mg/m$^2$ Q3W) [redacted] | Pembrolizumab (2 mg/kg Q3W) N=339 | Docetaxel (75 mg/m$^2$ Q3W) N=309 |
| **PFS (BICR/IRC)** | | | | |
| Median, months (95% CI) | [redacted] | [redacted] | 3.9 (3.1 to 4.1) | 4.0 (3.1 to 4.2) |
| HR (95% CI) | [redacted] | | 0.88 (0.73 to 1.04) p=0.06758 | |
| PFS rate at 12 months (%) | | | 18% | 9% |
| **OS** | | | | |
| Median, months (95% CI) | [redacted] | [redacted] | 10.4 (7.4 to 11.9) | 8.5 (7.5 to 9.8) |
| HR (95% CI) | [redacted] | | 0.71 (0.58 to 0.88) p=0.00076 | |
| 12 month OS rate (%) | | | 43 | 35 |
| **ORR (BICR/IRC)** | | | | |
| Responders, n (%) (95%CI) | [redacted] | [redacted] | | |
| Confirmed ORR (95% CI) | | | 18.0% (14.1 to 22.5) | 9.3% (6.5 to 12.9) |
| **Time to response** | | | | |
| Median (range), days | | | 65 (38 to 217) | 65 (41 to 250) |
| Responders | [redacted] | [redacted] | | |
| **Response duration (BIRC/IRC)** | | | | |
| Median (range), days | | | NR (20+ to 610+) | 189 (43+ to 268+) |
| Median, months (95% CI) | [redacted] | [redacted] | | |
| % of responder ongoing among responder | | | 73% | 43% |

*stratified HR
HR=hazard ratio; ORR=objective response rate; OS=overall survival; PFS=progression-free survival;
Source: OAK trial CSR, Table 1 and ID840 (TA428) CS, Table 20

[redacted]

[redacted]

### 3.3 OAK trial OS by level of PD-L1 expression

The OS data from the OAK trial, for PD-L1 subgroups, were published in January 2017.[5] The ERG has reproduced these results for information (Table 4).

Table 4 OAK trial (primary population): OS results

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

CI=confidence interval; HR=hazard ratio; IC=immune cell; ITT=intention to treat; OS=overall survival; TC=tumour cell
Source: Rittmeyer[5]

### 3.4 Adverse events reported in the OAK and KEYNOTE-010 trials

The ERG highlights that comparison of summary AE incidences from the OAK and KEYNOTE-010 trials suggest that, in general, for the populations of interest, experience of AEs in both trials appears to be broadly similar, with the exception of the incidence of adverse events of special interest (AESI) in the docetaxel arms of the two trials and, but to a lesser extent, the incidence of AESIs in the intervention arms of the two trials.

Table 5 OAK and KEYNOTE-010 trials: summary of adverse events

| Adverse event type | OAK trial (safety evaluable population: TC/IC 1/2/3) | | KEYNOTE-010 trial (APaT population) | |
|---|---|---|---|---|
| | Atezolizumab (1200 mg Q3W) n=345 | Docetaxel (75 mg/m$^2$ Q3W) n=319 | Pembrolizumab (2 mg/kg Q3W) N=339 | Docetaxel (75 mg/m$^2$ Q3W) N=309 |
| One or more AE, n (%) | | | 331 (97.6) | 297 (96.1) |
| Treatment/drug related AE, n (%) | [redacted] | [redacted] | 215 (63.4) | 251 (81.2) |
| Grade 3 to 4 AE (%) | [redacted] | [redacted] | | |
| Grade 3 to 5 AE, n (%) | [redacted] | [redacted] | 158 (46.6) | 173 (56.0) |
| Grade 3 to 5 drug-related AE, n (%) | [redacted] | [redacted] | 43 (12.7) | 109 (35.3) |
| Treatment-related Grade 3 to 4 AEs, n (%) | [redacted] | [redacted] | | |
| Grade 5 AEs, n (%) | [redacted] | [redacted] | | |
| Treatment-related Grade 5 AEs, n (%) | [redacted] | [redacted] | | |
| SAE, n (%) | [redacted] | [redacted] | 115 (33.9) | 107 (34.6) |
| Treatment/drug-related SAE, n (%) | [redacted] | [redacted] | 32 (9.4) | 42 (13.6) |
| Death, n (%) | [redacted] | [redacted] | 17 (5.0) | 15 (4.9) |
| Death due to drug-related AE, n (%) | [redacted] | [redacted] | 3 (0.9) | 5 (1.6) |
| Discontinued due to AE, n (%) | [redacted] | [redacted] | 28 (8.3) | 42 (13.6) |
| Discontinued due to drug-related AE, n (%) | [redacted] | [redacted] | 15 (4.4) | 31 (10.0) |
| Discontinued due to SAE, n (%) | [redacted] | [redacted] | 24 (7.1) | 19 (6.1) |
| Discontinued due to drug-related SAE, n (%) | [redacted] | [redacted] | 11 (3.2) | 11 (3.6) |
| AESI, n (%) | [redacted] | [redacted] | 69 (20.4) | 13 (4.2) |
| Grade 3 to 4 AESI | [redacted] | [redacted] | | |
| Grade 3 to 5 AESI | | | 19 (5.6) | 4 (1.3) |

AE=adverse event; APaT=all patients as treated; AESI=adverse events of special interest; SAE=serious adverse event;
Source: OAK trial CSR, Table 90 and ID840 (TA428) CS, Table 53 and Table 57

## *3.5 Treatment costs*

The cost of treatment can be estimated taking into account time on treatment, treatment frequency and cost per dose.

As treatment with both atezolizumab and pembrolizumab is continued until disease progression or unacceptable toxicity, trial PFS K-M data act as a reasonable proxy for time on treatment. Data in **Error! Reference source not found.** suggest that time on treatment for patients treated with these drugs is likely to be similar. Moreover, the frequency with which

patients receive both drugs is the same (Q3W). However, atezolizumab is administered as a 1200 mg flat dose, whilst the pembrolizumab dose is 2 mg/kg of body weight. The list price cost of one dose of atezolizumab is £3,808 and the list price cost of one dose of pembrolizumab (estimated based on the mean weight of patients participating in the OAK trial [72kg]) is £3,787. However, PAS prices are in place for both drugs. Furthermore, treatment with pembrolizumab is only permitted for a period of 2 years; data from the OAK trial TC/IC 1/2/3 subgroup indicate that, at 128 weeks, 11.1% of that subgroup were still receiving atezolizumab. The actual lifetime cost differential between treatment with atezolizumab and treatment with pembrolizumab is, therefore, unclear.

# 4 OVERALL CONCLUSIONS

Within the February 2017 CS,[3] the company provided cost effectiveness estimates for the comparison of treatment with atezolizumab versus docetaxel for the primary population of the OAK trial. The ERG considers that this approach is inappropriate as there are a number of treatment options available for the population participating in the OAK trial, depending on tumour histology and level of PD-L1 expression.

The company's cost effectiveness estimate for the comparison of treatment with atezolizumab versus docetaxel (one of the options that is relevant for patients whose tumours demonstrate no level of PD-L1 expression), for the TC/IC 0 subgroup is [redacted] per QALY gained (calculated using the PAS price for atezolizumab).

There is no direct evidence available to facilitate a comparison of the effectiveness of atezolizumab versus pembrolizumab (one of the options that is relevant to patients whose tumours demonstrate a level of PD-L1 expression) and the ERG considers that results generated by the company's FP ITCs are difficult to interpret. Simple comparisons of baseline characteristics, incidence of AEs, PFS and OS results from the atezolizumab arm of the OAK trial (TC/IC 1/2/3 subgroup) and the pembrolizumab (2 mg/kg Q3W) arm of the KEYNOTE-010 trial suggest that treatment with atezolizumab and pembrolizumab may be similar. However, the ERG highlights that care needs to be taken when drawing conclusions as the median OS of the docetaxel arm of the KEYNOTE-010 trial is lower than that of the docetaxel arm of the OAK trial (primary population: TC/IC 1/2/3).

The ERG has estimated the cost per dose of treatment with pembrolizumab and compared this with the actual cost per dose of treatment with atezolizumab but considers that the lifetime cost differential between the two treatments is unclear.

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# 6 APPENDICES

## *6.1 Appendix 1*

### 6.1.1 Weaknesses and areas of uncertainty

Weaknesses and areas of uncertainty relating to the evidence presented in the February 2017 CS[3] were included in the original ERG report[6] and have been reproduced in this appendix.

**Clinical evidence**

- the company should have included pembrolizumab as a comparator
- only investigator-assessed PFS results are available from the OAK and POPLAR trials
- the ERG considers that the company should have included full subgroup analyses of effectiveness and cost effectiveness by levels of PD-L1 expression
- the PFS and OS HRs from OAK and POPLAR trial data were calculated using a pre-specified method that relies on an assumption that hazards are proportional. However, as demonstrated by the company, this assumption does not hold and therefore OS and PF HRs must be interpreted with caution
- the company approach to the ITC is influenced by a range of factors (e.g., comparators and population selected, type of FP model chosen and the use of FE or RE) which means that it is difficult to identify the most appropriate combination of factors to use to generate ITC results
- the FP ITC results are difficult to interpret
- the company's criteria for assessing the presence of heterogeneity in the ITC analyses are inappropriate
- clinical advice to the ERG is that AEs arising from treatment with atezolizumab and other immunotherapies in patients with NSCLC require careful monitoring by a specialist clinical team with the experience to provide early recognition and management of immunotherapy-related AEs.

**Cost effectiveness evidence**

- the ERG identified three model construction errors: incorrect application of discounting, absence of age-dependent utility decrements and incorrect use of a half-cycle correction to TTD data
- the company's approach to modelling of OS for patients treated with atezolizumab used a mixed cure-rate model; however, there is insufficient evidence for the application of a cure-rate and the value used for the cure-rate was not justified by the company the company's approach to modelling OS for patients treated with atezolizumab is implausible as it resulted in survival rates that, at some points, were higher than that of the UK general population
- the company assumed a lifetime duration of treatment effect for atezolizumab, an approach that has been criticised by a previous NICE Appraisal Committee when assessing an immunotherapy for the treatment of patients with advanced or metastatic NSCLC
- confidence in modelling OS for patients receiving docetaxel by adjusting the OS atezolizumab model by hazard rates generated by the company's ITC is limited by the

ERGs concerns relating to the company's FP ITC, including the fact that the FP ITC used to generate hazard rates involved inputs that are not relevant to this appraisal

- confidence in modelling OS for patients receiving nintedanib+docetaxel by adjusting the OS atezolizumab model by the hazard rates generated by the company's ITC is limited by concerns relating to identifying the most relevant FP ITC, including the fact that the FP ITC used to generate hazard rates involved inputs that are not relevant to this appraisal and that the FP ITC was not limited to patients with adenocarcinoma histology.