NICE National Institute for Health and Care Excellence

Single Technology Appraisal

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

Committee Papers

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

SINGLE TECHNOLOGY APPRAISAL

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

Contents:

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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 Thursday 24 August 2017 via NICE Docs.**

	Please read the checklist for submitting comments at the end of this form. We cannot accept forms that are not filled in correctly. The Appraisal Committee is interested in receiving comments on the following: • has all of the relevant evidence been taken into account? • are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence? • are the provisional recommendations sound and a suitable basis for guidance to the NHS? NICE is committed to promoting equality of opportunity, eliminating unlawful discrimination and fostering good relations between people with particular protected characteristics and others. Please let us know if you think that the preliminary recommendations may need changing in order to meet these aims. In particular, please tell us if the preliminary recommendations: • could have a different impact on people protected by the equality legislation than on the wider population, for example by making it more difficult in practice for a specific group to access the technology; • could have any adverse impact on people with a particular disability or disabilities. Please provide any relevant information or data you have regarding such impacts and how they could be avoided or reduced**.**
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**
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Atezolizumab for treating non-small-cell lung cancer after platinum-based chemotherapy [ID970]

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Comment number	Comments Insert each comment in a new row. Do not paste other tables into this table, because your comments could get lost – type directly into this table.
	Roche are disappointed with the provisional negative recommendation, although we do recognise the uncertainty presented to the committee through this appraisal. Based on our reading of the ACD, the key concerns underpinning the draft negative recommendation are uncertainty around the following defining points: • Network meta-analysis results, and impact on end of life criteria • Assumption regarding the duration of treatment effect • Assumption of a "cure" fraction for immunotherapy survival • Overall Survival (OS) extrapolation In addition to these, the lack of comparison to pembrolizumab has been highlighted as a drawback. Our full response is provided below and addresses in turn, each of the above mentioned key points underpinning the draft negative recommendation, and any additional analyses to support a reversal of this preliminary negative recommendation. In addition, Roche have submitted a new proposal to PASLU to support committee decision making in determining atezolizumab to be a cost-effective option for treatment of NSCLC after prior chemotherapy. Please note: all updated analyses include the errors identified by the ERG, however two adjustments had to be made after identifying errors in the ERG's approach when implementing: 1. C2: ERG implementation instructions only applied some age related disutilities to the atezolizumab arm 2. C3: ERG implementation instructions use administration costs in the drug costs column for the Nintedanib+Docetaxel comparator, and linked nintedanib treatment duration to the docetaxel treatment costs A detailed summary of the changes is provided in Appendix 8.
1	**Comparison to pembrolizumab** The ACD states: "*The committee was aware that NICE technology appraisal guidance now recommends pembrolizumab for treating PD-L1-positive NSCLC after chemotherapy. It heard from clinical experts that since publication of this guidance the use of pembrolizumab has been increasing*

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	and it can now be considered standard care for this population," … "*The committee discussed why pembrolizumab was excluded from the company's submission, and it was aware that both pembrolizumab and atezolizumab are monoclonal antibodies targeting PD-1. It considered the company's justification that pembrolizumab has a narrower marketing authorisation (PD-L1-expressing tumours with a tumour proportion score of 1% or more) than the marketing authorisation for atezolizumab, and that pembrolizumab may not yet be current clinical practice since publication in January 2017. The committee was disappointed that the company did not consider pembrolizumab as a comparator and would have preferred to see comparisons of atezolizumab with pembrolizumab in people whose tumours express PD-L1*." Firstly, as a point of clarification: atezolizumab targets the ligand PD-L1 while pembrolizumab targets the protein, PD-1. While this means they ultimately target the same immune checkpoint, there are mechanistic differences between the two approaches in terms of which other co-inhibitory interactions that they blockade. We are concerned that the rationale for why pembrolizumab was excluded from the company submission has not been fully and accurately reflected. • At the committee meeting, the clinical expert referred to the challenges being experienced in pathology labs to enable treatment with pembrolizumab in the second line setting. Since its recommendation, PD-L1 testing had not yet become ingrained in clinical practice, thus it has been unable to become standard of care in NSCLC patients whose tumours express PD-L1. However, there was acknowledgment this was now changing as a result of the recent recommendation of pembrolizumab in the first line setting. • The marketing authorisation is narrower for pembrolizumab, but moreover, a comparison of PD-L1 expressing patients is not appropriate due to the differing diagnostic tests: ○ As highlighted in our response to clarification questions, PD-L1 expression in OAK and POPLAR was assessed in a central laboratory using the Ventana PD-L1 (SP142) immunohistochemistry (IHC) assay. The SP142 assay stratified PD-L1 expression on both tumour cells (TCs) and tumour-infiltrating immune cells (ICs). TC1/2/3 or IC1/2/3 was defined as PD-L1 expression on 1% or more of TCs or ICs, TC2/3 or IC2/3 was defined as PD-L1 expression on 5% of these cells; TC3 was defined as PD-L1 expression on 50% or more of TCs and IC3 was defined as 10% or more of ICs; and TC0 as PD-L1 expression on less than 1% of TCs and IC0 on less than 1% of ICs (see Table 13 from company submission). PD-L1 expression in the

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	pembrolizumab KEYNOTE-010 clinical trial was assessed in a central laboratory using the Dako 22C3 IHC assay (Herbst et al., 2016). The 22C3 assay stratified PD-L1 expression on TCs only using a tumour proportion score (TPS). Tumours staining for PD-L1 with ≥1% were considered expressers (TPS ≥1%), with a further analysis of those expressing 50% or greater (TPS ≥50%). Tumours with <1% cells for PD-L1 staining were considered non-expressers (TPS <1%). Only people whose tumours expressed PD-L1 (based on a TPS of ≥1%) were eligible for randomisation to the study. Given these differences, it is not appropriate to compare atezolizumab PD-L1 expressers to pembrolizumab PD-L1 expressers, as the patient populations identified with these two different assays are not equivalent. Nevertheless, as provided in response to clarification questions, the NMA results demonstrate that in their licensed populations, pembrolizumab and atezolizumab are equivalent in efficacy. As such, in response to this ACD, Roche have provided a cost minimisation analysis of these populations to facilitate committee decision making. Please refer to Appendix 1 of this response for the summary and results of this analysis. As detailed in the response to clarification questions, this is a conservative approach: by comparing non-equivalent populations, there is a risk the relative clinical benefits of pembrolizumab are overestimated. By demonstrating that atezolizumab in an unselected population (i.e. including patients who could be considered most resistant to a PD-1/PD-L1 checkpoint inhibitors) performs as well as pembrolizumab in a population where low and negative expressers are excluded, there is high degree of confidence that if the two drugs could be compared in genuinely matched populations, atezolizumab would at least match the performance of pembrolizumab.
2	**Network meta-analysis results** The ACD states: "*The committee was aware that the ERG had requested estimates of difference in overall survival using a reduced network of studies that contained only the comparators that were relevant to the scope, to reduce 'noise' in the analyses*" … "*The committee also heard from the ERG that it preferred a random effects model rather than the company's fixed effects model because it captures the uncertainty in the expected difference of overall survival better than the fixed effects model*" … "*The committee agreed to proceed with ERG's preferred network and noted the degree of uncertainty associated with all the indirect analyses*." As a result, the overall survival estimate for atezolizumab compared with nintedanib plus docetaxel was considered uncertain.

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	Whilst Roche's position remains that the extended network better reflects the comparative effectiveness, and can provide more data for better network connectivity and reduction of uncertainty; we accept the updated committee preference of a reduced network of 3-4 studies. However, as depicted in literature [(Dias S et al., 2011),(Dias et al., 2011), (Borenstein et al., 2007)], it is not appropriate to utilise random effects on a small, reduced network as the estimated distribution of the between-studies variance will be poorly identified and likely include values that are implausibly high. Thus, the reduced network is acceptable, but should be analysed under fixed effects to obtain any meaningful insights. Alternatively, if the committee have a preference for the random effects, the extended network should be used. Given the new comparison to pembrolizumab being conducted, the NMA has been re-run on a new reduced network consisting of: atezolizumab, docetaxel, pembrolizumab (PD-L1 positive), and nintedanib + docetaxel (adenocarcinoma). Details are provided in Appendix 2, along with an output summary of all the reduced network, fixed effects results. Importantly, this network does not compare equivalent populations. Roche originally submitted a like-with-like comparison of the total populations for atezolizumab and nintedanib + docetaxel comparison. However, in light of committee preferences, the current updated network utilises all licensed populations. As a result, by comparing non-equivalent populations, there is a risk the relative clinical benefits of nintedanib + docetaxel, and pembrolizumab are overestimated, hence results are considered significantly conservative to atezolizumab. Despite this, what remains consistent across all estimations is that the point estimate mean overall survival benefit of atezolizumab is greater than 3 months versus nintedanib plus docetaxel in the adenocarcinoma population. The mean estimate not only acts as the anchor of the analysis (with 95% confidence intervals incorporated as part of the sensitivity analysis), but also demonstrates the end of life criteria for atezolizumab versus nintedanib + docetaxel is met. This is further supported by the 8.94 months mean OS difference as predicted by the economic model. It should further be noted that because of the minority group of patients who experience very extended remissions on immunotherapies like atezolizumab, mean survival is a better measure of the survival gain across the population than the median. As part of the response to ACD, Roche have provided a new set of results incorporating key updates explored in the below sections. In these results, the new reduced network using fixed effects is used

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	as the base case, with an adjustment for crossover analysis explored as a scenario. See Appendix 4-7 for details. In considering any comparison to docetaxel + nintedanib, it is essential to highlight that nintedanib + docetaxel use is extremely low in clinical practice. Roche has heard from several expert lung clinicians that this regimen is only used in a very small minority of second-line adenocarcinoma patients. As an example, feedback from a leading clinical oncologist at [redacted] (one of the largest centres treating NSCLC) is that just 7 patients have been treated since December 2015, thus the real-world significance of this as a comparator is very limited. Whilst the comparison is presented for the committee, feedback from clinical experts indicates caution should be exercised when assessing the ICER and rather the docetaxel and pembrolizumab comparators should carry more weight for decision making purposes in this appraisal.
3	**Assumption regarding the duration of treatment effect** The ACD states: "*The committee considered that there is no evidence to support a substantial continued benefit of atezolizumab after stopping treatment and the size of this effect and its duration is unknown for NSCLC. The committee concluded that although it considered the company's preferred scenario of a lifetime treatment effect to be implausible, it had not been presented with any evidence on which it could agree a single clinically plausible scenario"* Duration of treatment effect is an area of uncertainty for new immunotherapies, and has arisen in all NSCLC immunotherapy appraisals to date (TA447, TA428, ID900, ID811). We appreciate the committee acknowledging the lack of evidence for a single clinically plausible scenario. Roche firmly believes the ERG preferred 3 year treatment benefit cap is arbitrary and clinically inappropriate. In response to this ACD, Roche have provided a range of scenarios exploring different treatment effect durations; however, questions of clinical plausibility remain. Therefore, in addition to these scenarios, Roche has also developed a methodology where a waning effect is imposed on the treatment effect of atezolizumab between 5 years (chosen as the point where the clinical expert in the appraisal meeting highlighted there is a change in immunotherapy effect in melanoma) and the time horizon of the model: 25 years. Between these two periods, treatment has a linearly decreasing effect. In the absence of evidence to support a single clinically plausible scenario, this alternative scenario is also presented. Nevertheless, it is still subject to a number of assumptions and therefore should be interpreted with caution.

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	As demonstrated in the results accompanying this response to ACD (see Appendix 4-7), atezolizumab is cost effective in all duration of treatment effect scenarios.
4	**Assumption of a "cure" fraction for immunotherapy survival** The ACD states "*The committee agreed that the use of the cure rate model and the cure rate applied had not been sufficiently justified and the long-term effect of immunotherapy on NSCLC was largely unknown. The committee concluded that the company's cure rate of 2% was not sufficiently supported by evidence."* The rationale for the cure fraction methodology was two-fold: firstly, as has been demonstrated in trial results to date, there are a proportion of patients who experience long term, sustained response to immunotherapies, i.e. their cancer-related mortality risk decreases over time. The mixed-cure model is a method to account for this. Secondly, by utilising a mixed-cure model, background mortality is incorporated in to the survival function which ensures survival for atezolizumab never crosses mortality of the general population. Thus, Roche maintains that a mixed cure methodology is appropriate for immunotherapies, and this patient population. However Roche appreciates the committee's preference not to proceed with this methodology, in favour of a simpler approach. The cure rate applied is a second, separate consideration. As detailed in the submission, to obtain the cure fraction, Roche explored clinical and real world evidence, overall survival estimates from other appraisals, and importantly, clinical validation. Since then, data from the OAK trial has been analysed further, exploring the proportion of patients with durable, sustained, complete responses, which further supports a 2% cure fraction. However, as the committee highlighted, the true long term effect of immunotherapy on NSCLC is largely unknown, beyond the 5-year OS data published by BMS at AACR in April this year which showed a 5-year OS of 16% (Brahmer J et al, 2017, Velcheti, 2017). Therefore, Roche appreciates the uncertainty of the 2% cure fraction, and the committee's preference not to proceed with this. In the following section, Roche follows on from this point to a more encompassing extrapolation consideration for overall survival.
5	**Overall Survival (OS) extrapolation** The ACD states: "*The committee considered that it was unclear how the company had arrived at the choice of a log-logistic model. It heard from the clinical experts that there is considerable uncertainty around the long-term survival benefit for patients with NSCLC after prior therapy before*

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	atezolizumab. The ERG explained that the log-logistic distribution was not robust and this is more important than the statistical fit of the model to the data. The ERGs preferred method was to use the Kaplan–Meier curve up to 19 months and then extrapolate using an exponential model, which was the best fit visually for the trial data after 19 months" … "*The committee concluded that using Kaplan–Meier data up to 83 weeks followed by extrapolation using the exponential model was a more appropriate visual fit and was more clinically plausible."* Roche challenge the appropriateness of this conclusion. The summary of our position, which precedes our detailed justification, is as follows: • Roche's submission clearly described how the log-logistic model was selected, and maintain that it is robust choice that also accurately reflects the long term survival tails that are being witnessed with immunotherapies • The ERG and committee-preferred survival extrapolation is both inappropriate, unjustified and unrepresentative of data available for both docetaxel and atezolizumab survival, as well as the PD-1 inhibitors nivolumab and pembrolizumab which act on the same immune checkpoint as atezolizumab and have shown similar clinical characteristics • Roche propose an alternative scenario which better reflects the 3 and 5 year data that has recently become available for immunotherapies within this indication. In combination with the updated PAS, and scenario where OAK results are adjusted for treatment switching, this updated extrapolation demonstrates atezolizumab as a cost-effective option for the treatment of NSCLC after prior chemotherapy. ***Log-logistic model selection justification*** As discussed in our company submission, the approach to select the most appropriate parametric distribution for overall survival (OS) was consistent with the methodology employed for time to treatment discontinuation (TTD) and progression free survival (PFS). Firstly, the Exponential, Weibull, Log Normal, Log Logistic, Gamma and Gompertz parametric models were fitted to the OAK data to determine the best statistical fit based on AIC and BIC statistics (see Table 58 from company submission). This indicated that the Log Logistic model was the best fitting extrapolation to the entire OAK data-set available. Secondly, the curves were assessed for visual fit. Again, the log logistic curve fit the data well, visually. Finally, the full extrapolated curve, and survival outputs were validated with clinical experts at an advisory board.

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	The ERG have not provided any evidence to support their statement that "the log-logistic distribution [is] not robust", and whilst there is uncertainty around the long-term survival benefit, clinical experts also highlighted "immunotherapies might be able to create a long-term durable response for a proportion of patients with lung cancer". In this response, Roche have provided 3-year atezolizumab OS data from the POPLAR trial, together with 3- and 5-year data from two similar immunotherapies, the PD-1 inhibitors nivolumab and pembrolizumab (3-year pembrolizumab OS data from the KEYNOTE-001 trial, and 3 and 5-year nivolumab OS data from the CA209-003 trial, see Appendix 3). In addition, Roche have provided two sets of duration of response data from the OAK trial: one from the primary ITT population, and an update conducted more recently. In the primary analysis, median duration of response for atezolizumab was 16.3 months, with the upper bound not estimable given the ongoing response of patients. In the update conducted recently, this figure has increased to XX months (95% CI: XX, XX); demonstrating again, responses are still ongoing (see Table 18 and Table 19 in Appendix 3). These data further validate the clinical expert opinion sought by Roche and demonstrate that a proportion of patients treated with immunotherapy achieve a sustained, durable response which translates into elevated long term overall survival. This supports the need for a distribution that recognises the tail of overall survival, as the Log Logistic does. ***Committee-preferred extrapolation is inappropriate*** The extrapolation the ERG opted for, and committee subsequently supported has not only been demonstrated as inappropriate given the proportional hazards assumption of the OAK trial has not been met, but results in consistently low OS estimates for both treatment arms. Roche utilised registry data and expert opinion to determine the most plausible OS estimates. However the alternative distribution chosen as the preferred base case by the committee was not validated with any additional published data, and importantly, was not validated with clinical experts. Roche have provided a table in Appendix 3 (see Table 16), summarising the outputs of the committee preferred overall survival extrapolation and the company base case extrapolation for docetaxel, as compared with published and unpublished clinical trial landmarks and real world data from the NLCA registry for patients with stage IV NSCLC. This comparison demonstrates that regardless of treatment arm, the committee-preferred extrapolation underestimates survival of patients. In the same Appendix (see Table 17**Error! Reference source not found.**), the same comparison is made for atezolizumab. Whilst it is evident the committee-preferred extrapolation significantly

	underestimates survival, upon recent availability of POPLAR 3-year landmark analysis, the company base case is also shown to overestimate survival. Thus, there is a need for an alternative scenario which better reflects the evidence available for both treatment arms. ***Alternative scenario proposed*** Roche appreciates the committee is only able to make a decision based on the scenarios provided to them. Thus Roche proposes providing a new base case as part of this response to ACD, which provides an alternative scenario between the committee-preferred base case, and the company base case, improving on both of the scenarios through a better match to the clinical and real world evidence available for docetaxel, atezolizumab and the other immunotherapies (nivolumab and pembrolizumab). As discussed in the company submission and above, the Log Logistic curve is the best statistical and visual fit to the entire OAK data set, and has been validated with clinical experts as a robust and representative assumption of the expected survival of patients on immunotherapies. However, the Gamma curve was the second best fitting, and also provides a small tail of long term survivors. The committee preference is to make use of the Kaplain Meier (KM) data and add a parametric distribution for the tail of the data. Thus, Roche explored two options: the KM+Gamma tail and the KM+Log Logistic tail. Table 20 and Table 21 in Appendix 3 compare the outcomes of the modelled data with the clinical and real world evidence available for both immunotherapies and docetaxel. As demonstrated, the KM+Log Logistic was the much better fit to the data, but still significantly underestimates survival of atezolizumab when compared with the 5-year nivolumab overall survival data. Hence, this curve could be considered a conservative estimate. The resulting curve has been validated for clinical plausibility by mapping against the age adjusted background mortality curve. Within the time horizon of the economic model (25 years) the two curves do not cross: i.e. atezolizumab patients always have mortality rates that are greater than the mortality rates of the UK general population of the same age. In addition, Roche have provided full cost effectiveness results adjusting for treatment switching in the OAK trial. As detailed in the original submission, by not adjusting for treatment switching, Roche were taking a conservative estimate of the overall survival benefit of atezolizumab, and thus the cost effectiveness. This is in contrast with the approach taken by other appraisals, including pembrolizumab (National Institute for Health and Care Excellence, 2016). However, Roche believe it is now imperative to demonstrate the cost effectiveness results of atezolizumab with this treatment

	switching adjustment for transparency and clarity purposes for the committee. Whilst these are provided as a scenario analysis, Roche believes these firmly demonstrate atezolizumab as a cost effective use of NHS resources, and the committee should consider these results as a robust and accurate reflection of the benefit of atezolizumab. Full cost effectiveness base case results are provided in Appendix 4 and 5. All further scenario analyses, including treatment effect capping, treatment effect waning, and importantly, adjustment for treatment switching can be found in Appendix 6 and 7.
6	**Conclusion** As discussed above, the new analyses provided in response to ACD has resulted in a new set of base case results. Further details can be found in Appendix 4-7, but a summary is also provided here: ***Cost Minimisation versus pembrolizumab*** At list price, atezolizumab is more costly than pembrolizumab. However, as both products have a PAS in place this is not the relevant comparison. At the updated PAS price, atezolizumab is less costly than pembrolizumab. The difference in total cost is further emphasised when utilising the MSD dosing assumptions or assuming equivalent duration of treatment between products (with the difference in costs decreasing by £5,000 and £6,000 respectively at list price). However, the pembrolizumab PAS is unknown, therefore this analysis could not be completed incorporating this discount. ***Updated survival extrapolation*** By utilising an updated NMA, and an updated survival curve that more accurately reflects the data available for docetaxel, atezolizumab, and other immunotherapies, the ICER at list price increases to £91,142 versus docetaxel, and £92,587 versus nintedanib + docetaxel in the adenocarcinoma population. At the updated PAS level, the ICERs reduce to [redacted] versus docetaxel and [redacted] versus nintedanib + docetaxel. Further, when adjusting for treatment switching experienced in the OAK clinical trial, these ICERs further reduce to £83,049 and £75,751 at list price, respectively; and [redacted] and [redacted] respectively. Caution should be exercised when assessing the relevance of the nintedanib + docetaxel ICER. Nintedanib is associated with an unknown level of discount, but more importantly, clinical use of this

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	product is minimal. Thus, feedback from clinical experts indicates the docetaxel and pembrolizumab comparators should carry more weight for decision making purposes in this appraisal.

Insert extra rows as needed

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- Use this comment form and submit it as a Word document (not a PDF).
- Complete the disclosure about links with, or funding from, the tobacco industry.
- Combine all comments from your organisation into 1 response. We cannot accept more than 1 set of comments from each organisation.
- Do not paste other tables into this table – type directly into the table.
- Please underline all confidential information, and separately highlight information that is submitted under 'commercial in confidence' in turquoise and all information submitted under 'academic in confidence' in yellow. If confidential information is submitted, please also send a 2nd version of your comment with that information replaced with the following text: 'academic / commercial in confidence information removed'. See the Guide to the processes of technology appraisal (section 3.1.23 to 3.1.29) for more information.
- Do not include medical information about yourself or another person from which you or the person could be identified.
- Do not use abbreviations Do not include attachments such as research articles, letters or leaflets. For copyright reasons, we will have to return comments forms that have attachments without reading them. You can resubmit your comments form without attachments, it must send it by the deadline.
- If you have received agreement from NICE to submit additional evidence with your comments on the appraisal consultation document, please submit these separately.

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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 Insert each comment in a new row. Do not paste other tables into this table, because your comments could get lost – type directly into this table.
General	The BTOG-NCRI-ACP-RCP-RCR is grateful for the opportunity to respond to the above consultation. We have liaised with our experts and would like to make the following comments.
1	The recommendation 'Atezolizumab is not recommended, within its CHMP opinion, for treating locally advanced or metastatic non-small-cell lung cancer in adults after chemotherapy (and targeted treatment if they have an epidermal growth factor receptor [EGFR] or anaplastic lymphoma kinase [ALK]-positive tumour)' has been affected to a substanstial degree by the uncertainty around the long term survival benefit of atezolizumab or 'tail of the survival curve'. The ERG proposed that the company model overestimated survival benefit therefore used another method in their economic modelling with substantially different outcomes. Although there is relatively little data to guide the committee with regard to long term survival of NSCLC patients receiving immunotherapy there is some evidence which demonstrates a potentially significant improvement in 3 and 5 year overall survival. At ASCO June 2017 mature overall survival data from the KEYNOTE-001 was presented which demonstrated that in 449 previously treated patients who received pembrolizumab (median follow up 34.5 months) 3 year OS was 19% (29.7% in those with PDL-1 expression >50). Similar data was presented by Dr J Brahmer at the AACR meeting earlier in the year where an 18% 3 year overall survival was shown in patients who had received Nivolumab. The 5 year survival in this presentation was also good at 16% (although numbers were unsurprisingly small at this time point). In the ERG's model the estimated 3 and 5 year survival figures appear to be lower than this

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	(approximately 14% and 4%, taken from the slide 'ERG remodelled OS atezolizumab vs docetaxel of the ERG presentation). It therefore appears likely that the ERG model underestimates the long-term survival benefit of PD-1/PD-L1 blockade.
2	The ACD suggests that the benefit of Atezolizumab is less significant compared to Docetaxel plus Nintedanib from indirect comparisons. Whilst this is possible, the number of patients who actually receive this combination treatment is small. In the Greater Manchester and Cheshire Cancer Network (population 3.4 million), pharmacy data suggests that 13 patients have received Docetaxel and Nintedanib in the past 20 months. An audit is currently underway using the SACT database which will provide nationwide figures, but data is not yet available.

Insert extra rows as needed

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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:	[**Yvonne Summers**]

Comment number	Comments Insert each comment in a new row. Do not paste other tables into this table, because your comments could get lost – type directly into this table.
1	The recommendation "Atezolizumab is not recommended, within its CHMP opinion, for treating locally advanced or metastatic non-small-cell lung cancer in adults after chemotherapy (and targeted treatment if they have an epidermal growth factor receptor [EGFR] or anaplastic lymphoma kinase [ALK]-positive tumour)" has been affected to a substanstial degree by the uncertainty around the long term survival benefit of atezolizumab or "tail of the survival curve". The ERG proposed that the company model overestimated survival benefit therefore used another method in their economic modelling with substantially different outcomes. Although there is relatively little data to guide the committee with regard to long term survival of NSCLC patients receiving immunotherapy there is some evidence which demonstrates a potentially significant improvement in 3 and 5 year overall survival. At ASCO June 2017 mature overall survival data from the KEYNOTE-001 was presented which demonstrated that in 449 previously treated patients who received pembrolizumab (median follow up 34.5 months) 3 year OS was 19% (29.7% in those with PDL-1 expression >50). Similar data was presented by Dr J Brahmer at the AACR meeting earlier in the year where an 18% 3 year overall survival was shown in patients who had received Nivolumab. The 5 year survival in this presentation was also good at 16% (although numbers were unsurprisingly small at this time point). In the ERG's model the estimated 3 and 5 year survival figures appear to be lower than this (approximately 14% and 4%, taken from the slide "ERG remodelled OS atezolizumab vs docetaxel of the ERG presentation). It therefore appears likely that the ERG model underestimates the long-term survival benefit of PD-

Please return via NICE DOCS.

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

Consultation on the appraisal consultation document – deadline for comments **5pm on Thursday 24 August 2017 via NICE Docs.**

	1/PD-L1 blockade.
2	The ACD suggests that the benefit of Atezolizumab is less significant compared to Docetaxel plus Nintedanib from indirect comparisons. Whilst this is possible, the number of patients who actually receive this combination treatment is small. In the Greater Manchester and Cheshire Cancer Network (population 3.4 million), pharmacy data suggests that 13 patients have received Docetaxel and Nintedanib in the past 20 months. An audit is currently underway using the SACT database which will provide nationwide figures, but data is not yet available.

Insert extra rows as needed

Appendix 1: Cost minimisation analysis

As part of the clarification questions response, Roche provided indirect treatment comparison (ITC) results for a reduced network of comparators (atezolizumab 1200mg, docetaxel 75mg/m2, pembrolizumab 2mg). Figure 1 is from the ITC of atezolizumab in its licensed indication (all-comers), versus pembrolizumab in its licensed indication (PD-L1 positive). As detailed in the main body of this ACD response, it is not appropriate to compare atezolizumab PD-L1 expressers to pembrolizumab PD-L1 expressers, as the patient populations identified with these two different assays are not equivalent. Therefore a comparison of the licensed indications has been conducted. As demonstrated below, atezolizumab and pembrolizumab in their licensed populations are equivalent in efficacy.

Since, an update to the ITC for a new reduced network of all comparators included in the response to ACD (atezolizumab, docetaxel, nintedanib+docetaxel adenocarcinoma, and pembrolizumab PD-L1+) has been conducted, and further validates the clinical equivalence (Figure 2). Therefore a cost-minimisation analysis is the most appropriate methodology to employ for the comparison of these two products.

Figure 1: OS reduced network result (Weibull FE): atezolizumab, docetaxel and pembrolizumab

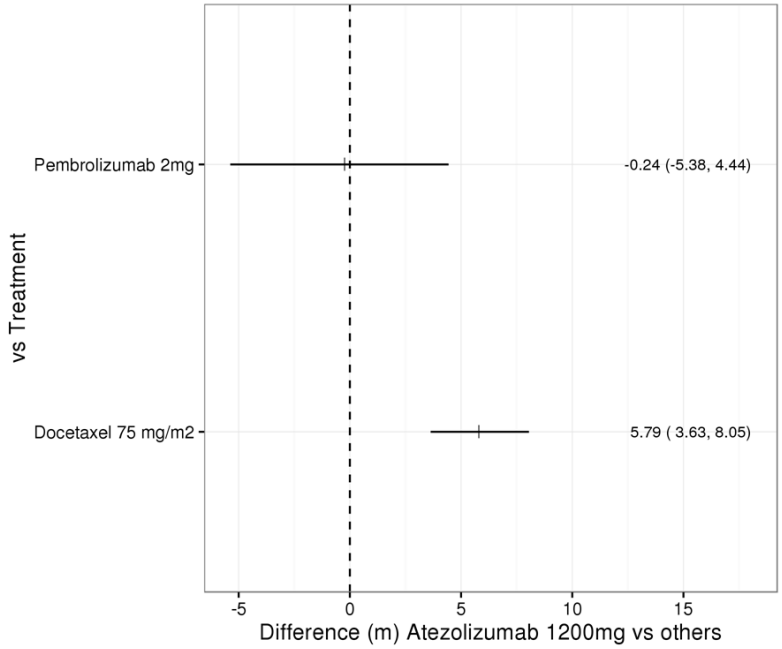
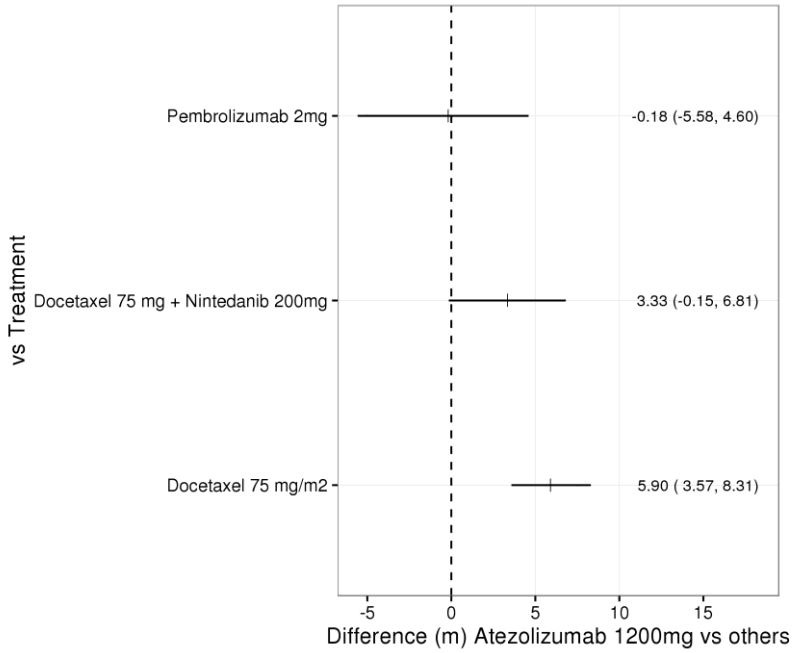


Figure 2: OS reduced network result (Weibull FE): atezolizumab, docetaxel, nintedanib+docetaxel and pembrolizumab



To conduct the cost minimisation analysis, the originally submitted cost utility analysis model was adapted to incorporate pembrolizumab costs, and remove quality of life data.

As TTD data for pembrolizumab is unavailable, PFS curves are utilised to determine treatment duration and supportive care costs.

However, as detailed in the SmPC (European Medicines Agency, 2015), some patients can continue treatment beyond progression if they remain clinically stable. As such, this assumption should be deemed a conservative approach: reducing the treatment costs associated with pembrolizumab. As the median treatment duration of KEYNOTE-010 was comparable to that of the OAK trial (3.5 months (Herbst et al.) versus 3.4 months (Rittmeyer et al., 2016) respectively), a scenario is incorporated where TTD for pembrolizumab is considered equivalent to atezolizumab.

With the exception of the additions below, all other inputs and assumptions remain consistent with those detailed in the original company submission.

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 1 and Table 2. 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 1: Drug acquisition costs

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 weight from patients recruited from European sites in the OAK clinical trial, which also corresponded with the average weight across the OAK trial (72kg), was used to estimate the distribution of the number of vials required for patients treated with pembrolizumab. 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, the average number of pembrolizumab vials required per patient per cycle was 3.00, resulting in a total drug cost per patient per administration of £3,945.00 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 2: Drug cost per treatment cycle

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	£3,945.00
Pembrolizumab (list price); KEYNOTE-010 average weight assumption *Scenario analysis*	Please refer to Table 3	3.39 x 50mg vial Q3W	IV; no vial sharing	£4,453.13

Table 3: MSD 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 4).

Table 4: 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

Adverse event unit costs and resource use

As detailed in the original company submission, all grade ≥3 treatment related AEs with an incidence of ≥2% in either the docetaxel or atezolizumab arms of the OAK trial (primary population ITT who received any dose) are included in the base case analyses. To remain consistent with this methodology, OAK and KEYNOTE-010 grade ≥3 treatment related AEs were reanalysed to incorporate any grade ≥3 treatment related AEs with an incidence of ≥2% in either the atezolizumab or pembrolizumab treatment arms (Herbst RS, 2015). No adverse events with an incidence of ≥2% were identified in either treatment arm; therefore these costs were excluded from the analysis.

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 5). This cost is incorporated in to the economic model as a single upfront cost for pembrolizumab only.

Table 5: 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.

Base-case results (list price)

At list price, atezolizumab is more costly than pembrolizumab in all scenarios. However, the difference in costs is considerably driven by the TTD and dosing scenarios utilised.

Table 6: Base-case cost minimisation results: disaggregated costs (list price)

		Atezolizumab	Pembrolizumab	Increment	% absolute increment
Mean costs in PFS/On treatment	Treatment cost	£46,438	£37,367	£9,071	72.19%
	Diagnostic cost	£0	£338	-£338	2.69%
	Drug administration	£2,426	£1,884	£542	4.31%
	Adverse events	£0	£0	£0	0.00%
	Supportive care	£9,919	£8,226	£1,693	13.47%
Total costs in PFS/On treatment		£58,784	£47,815	£10,969	92.66%
Mean costs in PD/Off treatment	Supportive care	£9,022	£9,924	-£903	7.18%
	Subsequent therapy cost	£3,289	£3,308	-£20	0.16%
Total costs in PD/Off treatment		£12,310	£13,233	-£923	7.34%
Total costs		£71,094	£61,048	£10,046	100.00%

Table 7: Dosing scenario analysis cost minimisation results: disaggregated costs (list price)

		Atezolizumab	Pembrolizumab	Increment	% absolute increment
Mean costs in PFS/On treatment	Treatment cost	£46,438	£42,180	£4,258	54.92%
	Diagnostic cost	£0	£338	-£338	4.35%
	Drug administration	£2,426	£1,884	£542	6.99%
	Adverse events	£0	£0	£0	0.00%
	Supportive care	£9,919	£8,226	£1,693	21.84%
Total costs in PFS/On treatment		£58,784	£52,628	£6,156	88.10%
Mean costs in PD/Off treatment	Supportive care	£9,022	£9,924	-£903	11.64%
	Subsequent therapy cost	£3,289	£3,308	-£20	0.25%
Total costs in PD/Off treatment		£12,310	£13,233	-£923	11.90%
Total costs		£71,094	£65,861	£5,233	100.00%

Table 8: TTD scenario analysis cost minimisation results: disaggregated costs (list price)

		Atezolizumab	Pembrolizumab	Increment	% absolute increment
Mean costs in PFS/On treatment	Treatment cost	£46,438	£42,957	£3,482	52.00%
	Diagnostic cost	£0	£338	-£338	5.04%
	Drug administration	£2,426	£2,166	£260	3.88%
	Adverse events	£0	£0	£0	0.00%
	Supportive care	£9,919	£8,226	£1,693	25.29%
Total costs in PFS/On treatment		£58,784	£53,686	£5,097	86.22%
Mean costs in PD/Off treatment	Supportive care	£9,022	£9,924	-£903	13.49%
	Subsequent therapy cost	£3,289	£3,308	-£20	0.29%
Total costs in PD/Off treatment		£12,310	£13,233	-£923	13.78%
Total costs		£71,094	£66,919	£4,175	100.00%

Base-case results (updated PAS)

An update to the currently approved PAS has been submitted to the Department of Health and is currently under assessment. The scheme is in the form of a simple discount, and offers a [redacted] reduction on the list price of atezolizumab. If accepted, this would reduce the cost of atezolizumab from a list price of £3807.69 to a net price of [redacted] per vial (1,200mg).

At the updated PAS level for atezolizumab, atezolizumab is less costly than pembrolizumab all scenarios. However, pembrolizumab has a confidential PAS in place, thus these results should be interpreted with caution.

Table 9: Base-case cost minimisation results: disaggregated costs (updated PAS)

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

Table 10: Scenario analysis cost minimisation results: disaggregated costs (updated PAS)

		Atezolizumab	Pembrolizumab	Increment	% absolute increment
Mean costs in PFS/On treatment	Treatment cost	[redacted]	£42,180	[redacted]	[redacted]
	Diagnostic cost	£0	£338	-£338	[redacted]
	Drug administration	£2,426	£1,884	£542	[redacted]
	Adverse events	£0	£0	£0	[redacted]
	Supportive care	£9,919	£8,226	£1,693	[redacted]
Total costs in PFS/On treatment		[redacted]	£52,628	[redacted]	[redacted]
Mean costs in PD/Off treatment	Supportive care	£9,022	£9,924	-£903	[redacted]
	Subsequent therapy cost	£3,289	£3,308	-£20	[redacted]
Total costs in PD/Off treatment		£12,310	£13,233	-£923	[redacted]
Total costs		[redacted]	£65,861	[redacted]	100%

Table 11: TTD scenario analysis cost minimisation results: disaggregated costs (updated PAS)

		Atezolizumab	Pembrolizumab	Increment	% absolute increment
Mean costs	Treatment cost	[redacted]	£42,957	[redacted]	[redacted]

in PFS/On treatment	Diagnostic cost	£0	£338	-£338	[redacted]
	Drug administration	£2,426	£2,166	£260	[redacted]
	Adverse events	£0	£0	£0	[redacted]
	Supportive care	£9,919	£8,226	£1,693	[redacted]
Total costs in PFS/On treatment		[redacted]	£53,686	[redacted]	[redacted]
Mean costs in PD/Off treatment	Supportive care	£9,022	£9,924	-£903	[redacted]
	Subsequent therapy cost	£3,289	£3,308	-£20	[redacted]
Total costs in PD/Off treatment		£12,310	£13,233	-£923	[redacted]
Total costs		[redacted]	£66,919	[redacted]	100.00%

Appendix 2: NMA outputs

Updated restricted network: atezolizumab, docetaxel, pembrolizumab (PD-L1+), nintedanib + docetaxel (adenocarcinoma)

Given committee preference for a reduced network, an update to the ITC was conducted, incorporating the pembrolizumab PD-L1-positive population. ITC methodology remains consistent with the initial company submission, therefore only results are presented. As explained above, a fixed effects model is used due to the small nature of the reduced network, and better fit by DIC statistics (Dias S et al., 2011).

For each endpoint, a forest plot of the relative difference in expected survival (in months) for atezolizumab versus competing interventions is provided. The plots represent the summary measure by a vertical mark (point estimate). The associated credible intervals are the lateral tips of the point estimates. A dashed vertical line of no effect is also included at 0 for no difference in expected survival. In addition to the graphical representation of the results, all pairwise comparisons are presented in separate tables (cross-tabulations).

Progression Free Survival Time-To-Event: fixed effects 1st order p1=0 (Weibull), 2.5 year time horizon

Atezolizumab showed (statistically significant) favourable results for atezolizumab versus docetaxel, and comparable results to the other competing interventions: See Figure 3 and Table 12. For the cross-tabulation of all pairwise treatment comparisons, cells highlighted in green showed statistically significant better results, cells in orange show comparable results. The resulting hazard ratios over time are shown in Figure 4.

Figure 3: Forest-plot of atezolizumab vs intervention of expected PFS difference (months)

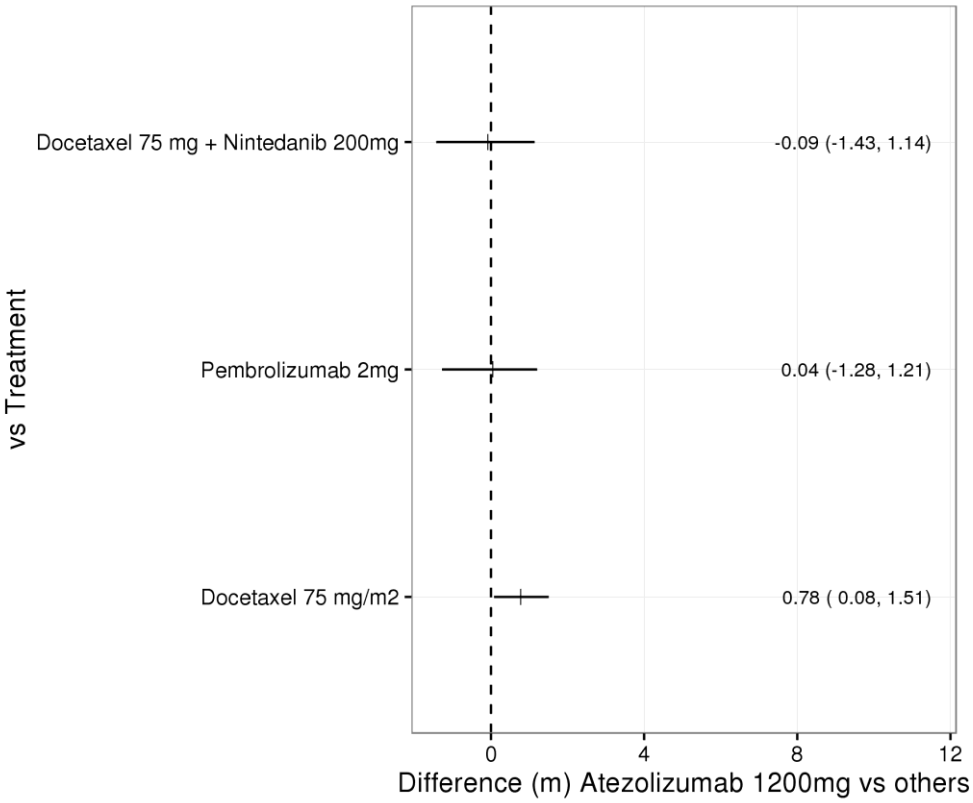
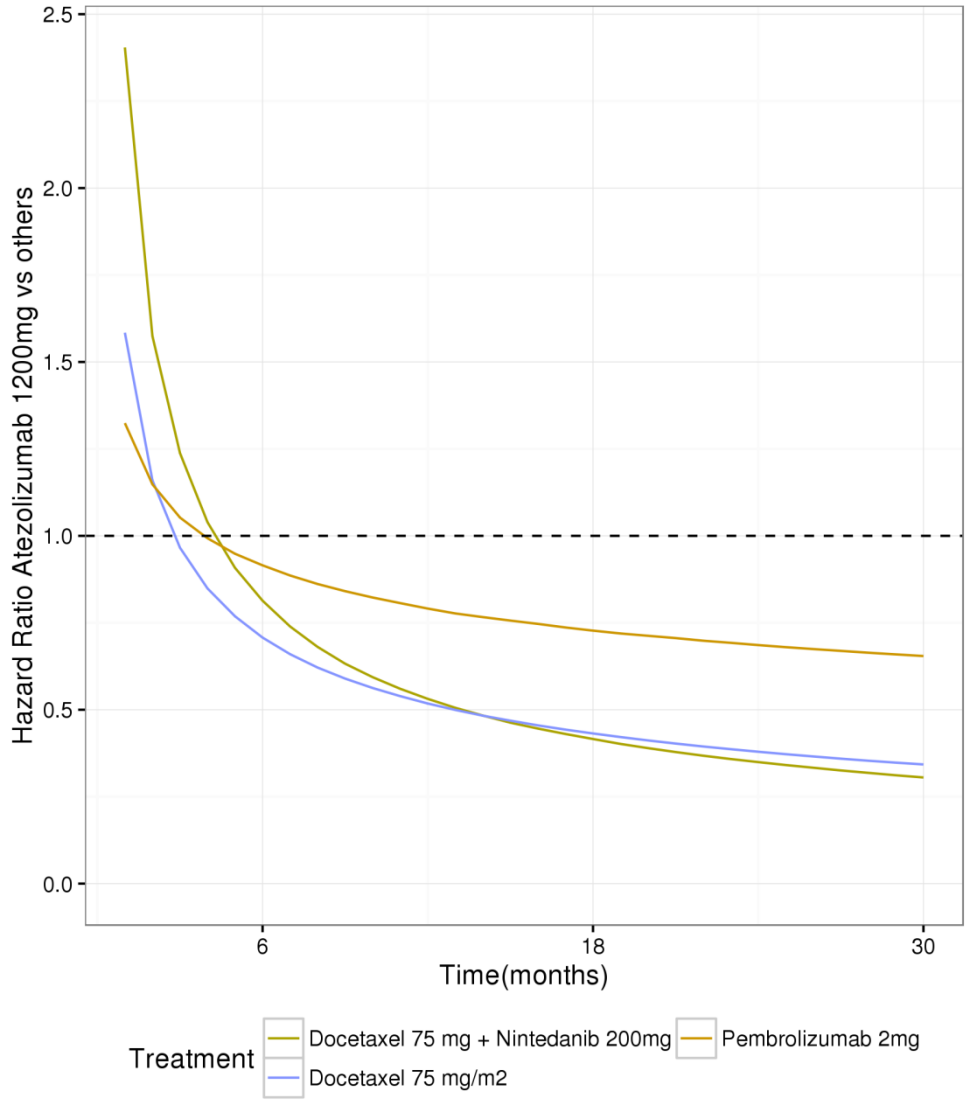


Table 12: Cross-tabulations of expected PFS difference (months) and 95% CIs

	Docetaxel 75 mg/m2	Docetaxel 75 mg + Nintedanib 200mg	Pembrolizumab 2mg
Atezolizumab 1200mg	0.78 (0.08, 1.51)	-0.09 (-1.43, 1.14)	0.04 (-1.28, 1.21)

Figure 4: PFS hazard ratios over time; atezolizumab 1200mg vs comparators



Overall Survival Time-To-Event: fixed effects 1st order p1=0 (Weibull), 5 year time horizon

Atezolizumab showed (statistically significant) favourable expected overall survival time (measured in months) compared to docetaxel, and numerically favourable (but not statistically significant) expected overall survival time compared to nintedanib+docetaxel adenocarcinoma population. OS results were comparable versus pembrolizumab (Figure 5 and Table 13): Cells highlighted in green show statistically significant better results, cells in orange show non-statistically significant results. The resulting hazard ratios over time are shown in Figure 6.

Figure 5: Forest-plot of atezolizumab vs intervention of expected OS difference (months)

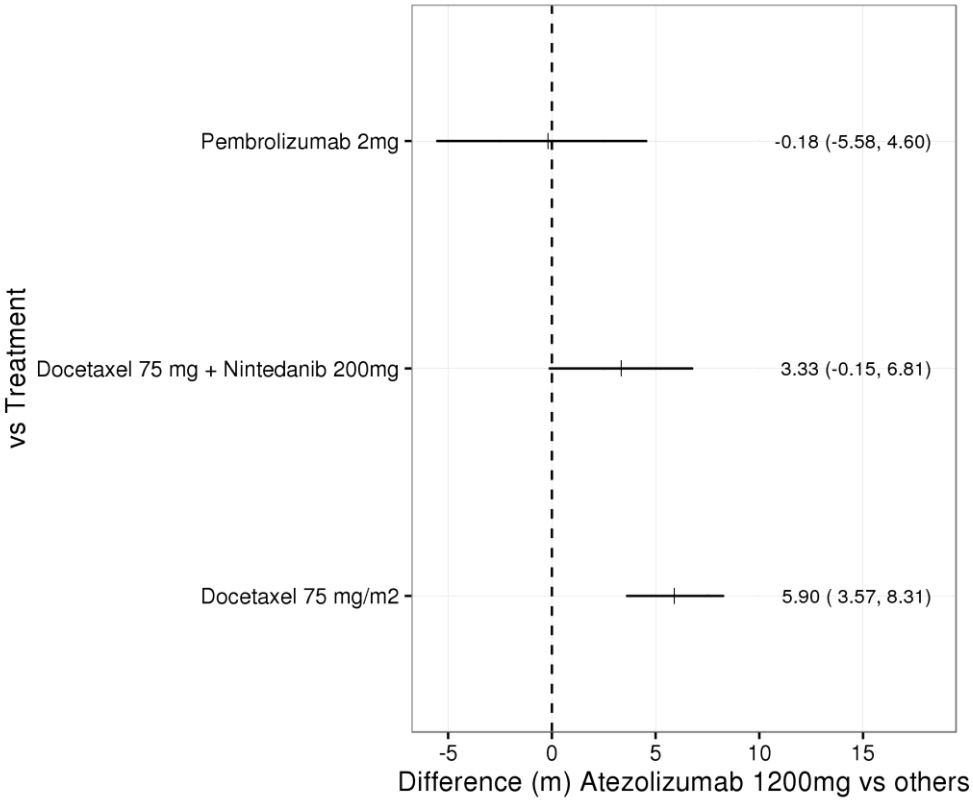
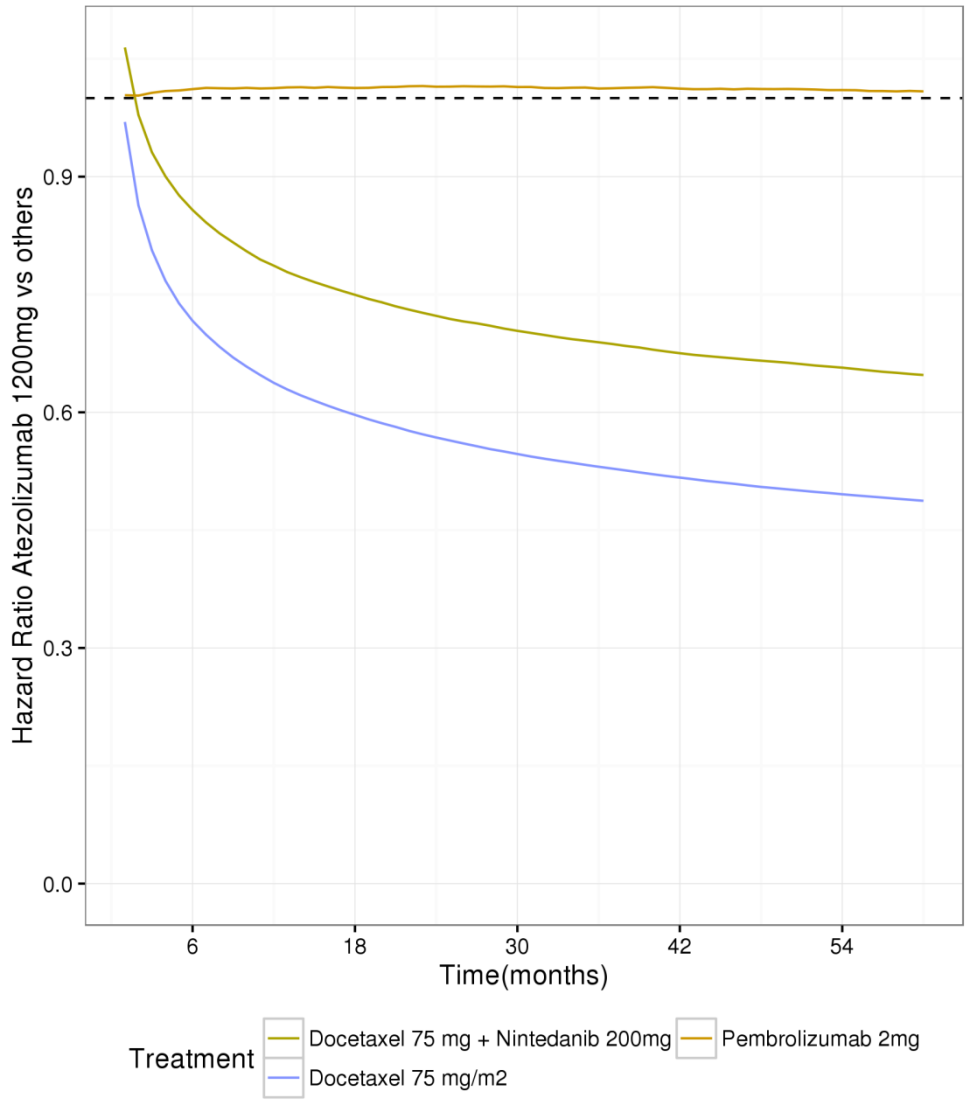


Table 13: Cross-tabulations of expected OS difference (months) and 95% CIs

	Docetaxel 75 mg/m2	Docetaxel 75 mg + Nintedanib 200mg	Pembrolizumab 2mg
Atezolizumab 1200mg	5.90 (3.57, 8.31)	3.33 (-0.15, 6.81)	-0.18 (-5.58, 4.60)

Figure 6: OS hazard ratios over time; atezolizumab 1200mg vs comparators



Overall Survival Time-To-Event (with treatment-switching adjustment: fixed effects 1st order p1=0 (Weibull), 5 year time horizon

Atezolizumab showed (statistically significant) favourable expected overall survival time (measured in months) compared to docetaxel and nintedanib + docetaxel in adenocarcinoma patients, and comparable results versus pembrolizumab (Figure 7 and Table 14): Cells highlighted in green showed statistically significant better results, cells in orange show comparable results. The resulting hazard ratios over time are shown in Figure 8.

Figure 7: Forest-plot of atezolizumab vs intervention of expected OS with switch adj difference (months)

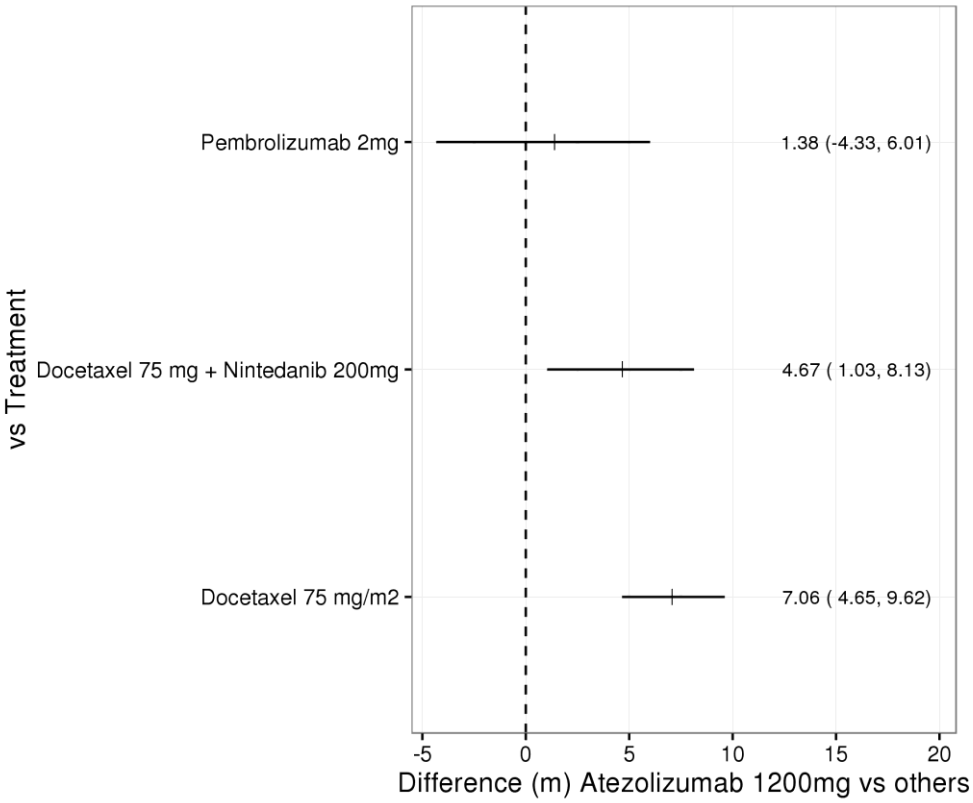


Table 14: Cross-tabulations of expected OS with switch adj difference (months) and 95% CIs

	Docetaxel 75 mg/m2	Docetaxel 75 mg + Nintedanib 200mg	Pembrolizumab 2mg
Atezolizumab 1200mg	7.06 (4.65, 9.62)	4.67 (1.03, 8.13)	1.38 (-4.33, 6.01)

Figure 8: OS with switch adj hazard ratios over time; Atezolizumab 1200mg vs comparators

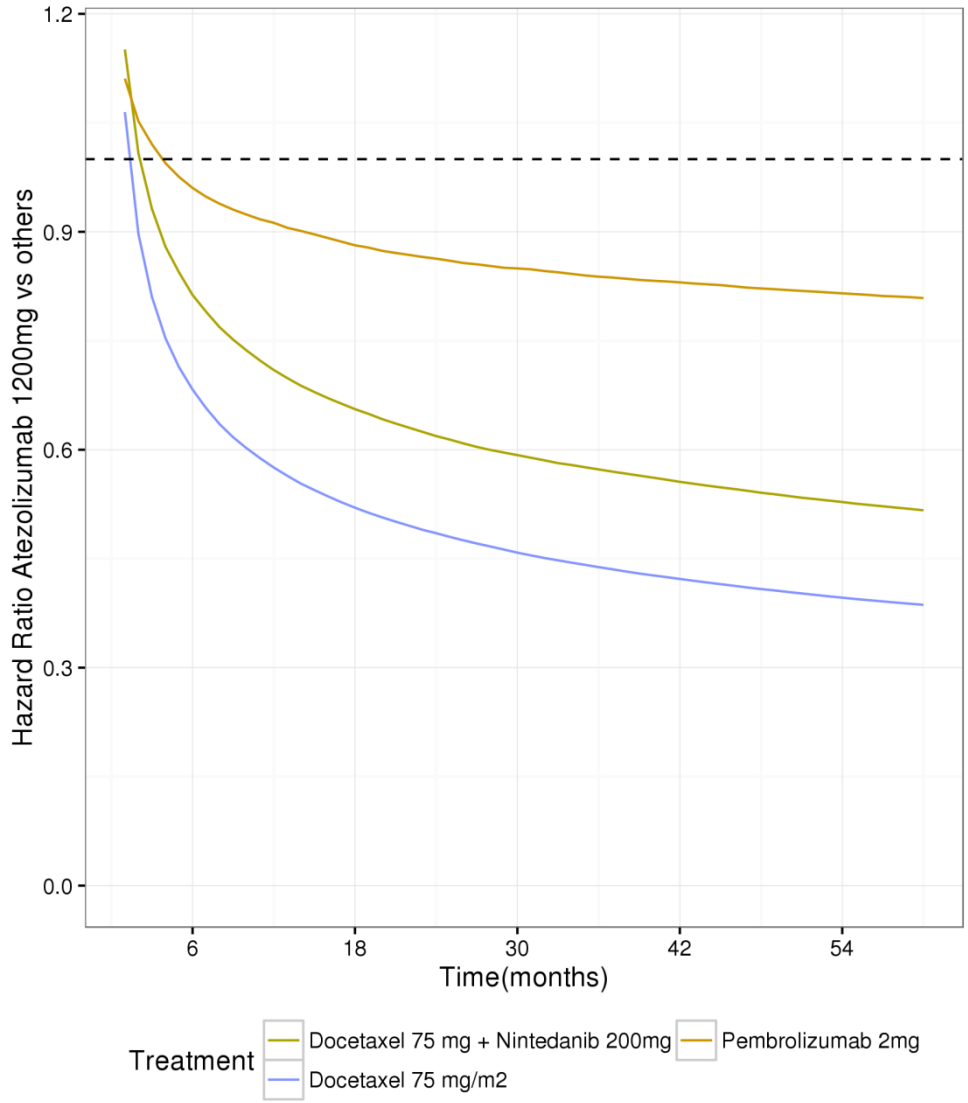


Table 15: Summary of outputs across restricted networks

Network	Population	Chosen model	OS difference: atezolizumab vs. nintedanib+docetaxel
Restricted	N+D: adenocarcinoma Atezo: all-comers	Fixed effects	3.33 (-0.16, 6.74)
New restricted	N+D: adenocarcinoma Atezo: all-comers Pembro: PD-L1+	Fixed effects	3.33 (-0.15, 6.81)
New restricted (adjusted for cross-over)	N+D: adenocarcinoma Atezo: all-comers Pembro: PD-L1+	Fixed effects	4.67 (1.03, 8.13)

Appendix 3: Overall Survival Extrapolation

Table 16: Comparison of modelled, observed, and real world data: docetaxel

Data source	2 year OS	3 year OS	5 year OS
Company preferred OS: 2% mixed cure methodology	19%	9%	2%
ERG and committee preferred OS: KM+exponential	17%	7%	1%
POPLAR (F. Hoffmann-La Roche Ltd, 2017b)	[redacted]	[redacted]	-
KEYNOTE-010 [TPS ≥1%] (Herbst RS, 2015)	15%	-	
Checkmate-017 [Squamous histology] (Barlesi F et al., 2016)	8%	-	-
Checkmate-057 [Non-squamous histology] (Barlesi F et al., 2016)	16%	-	-
NCLA (OS stage IIIB/IV; PS0-1 with chemotherapy) (Beckett P et al., 2013)	20%	13%	7%
NCLA (OS stage IV) (Beckett P et al., 2013)	7%	4%	3%

Table 17: 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	5 year OS
Company preferred OS: 2% mixed cure methodology	32%	21%	12%
ERG and committee preferred OS: KM+exponential	29%	16%	4%
POPLAR (F. Hoffmann-La Roche Ltd, 2017b)	[redacted]	[redacted]	-
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%	-
KEYNOTE-010	30%	-	-

(TPS ≥1%) [TPS ≥1%] (Herbst RS, 2015)			
Checkmate-017 [Squamous histology] (Barlesi F et al., 2016)	23%	-	-
Checkmate-057 [Non-squamous histology] (Barlesi F et al., 2016)	29%	-	-

Table 18: OAK, duration of response in the ITT population

	Atezolizumab n=58	**Docetaxel n=57**
Patients without event, n (%)	30 (51.7)	10 (17.5)
Median duration of response, months (95% CI)	16.3 (10.0, NE)	6.2 (4.9, 7.6)
Unstratified HR (95% CI)	0.34 (0.21, 0.55)	

CI, confidence interval; HR, hazard ratio; NE, not estimated
Source: (F. Hoffmann-La Roche Ltd, 2016, Rittmeyer et al., 2016)

Table 19: OAK, duration of response in the secondary population

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

CI, confidence interval; HR, hazard ratio; NE, not estimated
Source: (F. Hoffmann-La Roche Ltd, 2017a)

Table 20: New company base case: Comparison of modelled, observed, and real world data: docetaxel

Data source	**2 year OS**	**3 year OS**	**5 year OS**
New company base case OS: KM+log logistic	16%	7%	2%
KM+Gamma	16%	6%	1%
POPLAR (F. Hoffmann-La Roche Ltd, 2017b)	[redacted]	[redacted]	-
KEYNOTE-010 [TPS ≥1%] (Herbst RS, 2015)	15%	-	
Checkmate-017 [Squamous histology] (Barlesi F et al., 2016)	8%	-	-

Checkmate-057 [Non-squamous histology] (Barlesi F et al., 2016)	16%	-	-
NCLA (OS stage IIIB/IV; PS0-1 with chemotherapy) (Beckett P et al., 2013)	20%	13%	7%
NCLA (OS stage IV) (Beckett P et al., 2013)	7%	4%	3%

Table 21: New company base case: 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	5 year OS
New company base case OS: KM+log logistic	30%	19%	10%
KM+Gamma	30%	17%	6%
POPLAR (F. Hoffmann-La Roche Ltd, 2017b)	[redacted]	[redacted]	-
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%	-
KEYNOTE-010 (TPS ≥1%) [TPS ≥1%] (Herbst RS, 2015)	30%	-	-
Checkmate-017 [Squamous histology] (Barlesi F et al., 2016)	23%	-	-
Checkmate-057 [Non-squamous histology] (Barlesi F et al., 2016)	29%	-	-

Appendix 4: Results utilising updated survival extrapolation (list price)

Base Case Results

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 £38,261 at list price.

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

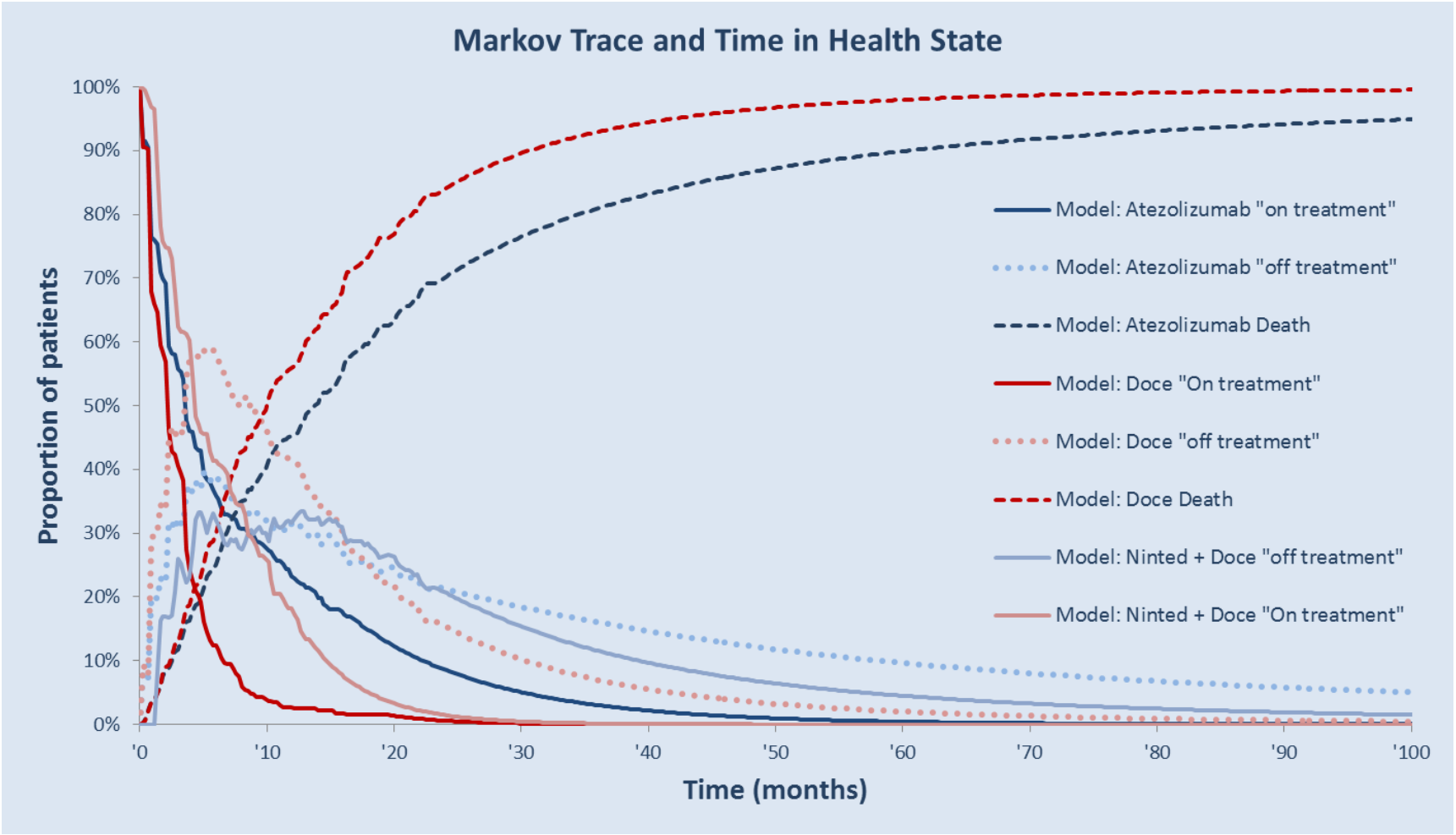
However, nintedanib is associated with a PAS, at an unknown level of discount; therefore the analysis could not be conducted at the with-PAS price level.

See Table 22 for a summary of the base case results.

Table 22: Updated base case results (list price)

				Versus Docetaxel				Versus N+D			
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)
Docetaxel	£20,181	1.17	0.71	-	-	-	-	-	-	-	-
Nintedanib + Docetaxel	£38,261	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

Figure 9: Markov trace: on/off treatment: combined results for all comparators



PFS used as a proxy for nintedanib plus docetaxel “on treatment”

The QALY gain disaggregated by health states allows exploration of which health state is driving QALY gain. Table 23 and Table 24 show the results for the comparison to docetaxel and nintedanib (plus docetaxel), respectively.

In all comparators, the majority of incremental QALY gain for atezolizumab is achieved when patients are in the "off treatment" health state. These results are as expected, given the substantial survival gain anticipated with immunotherapy treatments compared with PFS gains (see Section 4.13 of company submission).

Table 23: Summary of QALY gain by health state: comparison to docetaxel

Health state	QALYs: Atezolizumab	QALYs: Docetaxel	Increment	% absolute increment QALYs
On treatment	0.48	0.19	0.28	47.69%
Off treatment	0.83	0.52	0.31	51.85%
Adverse events	0.00	0.00	0.00	0.46%
Total	1.31	0.71	0.60	100.00%

Note: numbers may not sum due to rounding

Table 24: Summary of QALY gain by health state: comparison to nintedanib + docetaxel

Health state	QALYs: Atezolizumab	QALYs: Nintedanib + docetaxel	Increment	% absolute increment QALYs
On treatment	0.48	0.39	0.09	22.09%
Off treatment	0.83	0.54	0.29	73.24%
Adverse events	0.00	-0.02	0.02	4.68%
Total	1.31	0.91	0.39	100.00%

Note: numbers may not sum due to rounding
PFS used as a proxy for nintedanib (plus docetaxel) "on treatment"

A breakdown of the difference in costs can be found below. Cost is disaggregated by health state and resource use for all comparators.

Table 25: Disaggregated costs: comparison to docetaxel

		Atezolizumab	Docetaxel	Increment	% absolute increment
Mean costs in PFS/On treatment	Treatment cost	£46,438	£135	£46,303	82.43%
	Drug administration	£2,426	£781	£1,645	2.93%
	Adverse events	£111	£793	-£682	1.21%
	Supportive care	£9,919	£6,856	£3,063	5.45%
Total costs in PFS/On treatment		£58,895	£8,565	£50,330	92.02%

Mean costs in PD/Off treatment	Supportive care	£9,022	£4,719	£4,303	7.66%
	Subsequent therapy cost	£3,289	£3,335	-£46	0.08%
Total costs in PD/Off treatment		£12,310	£8,054	£4,256	7.74%
Terminal care cost		£3,430	£3,562	-£132	0.23%
Total costs		£74,636	£19,941	£54,695	100%

Note: numbers may not sum due to rounding

Table 26: Disaggregated costs: comparison to nintedanib + docetaxel

		Atezolizumab	Nintedanib + Docetaxel	Increment	% absolute increment
Mean costs in PFS/On treatment	Treatment cost	£46,438	£14,709	£31,729	80.92%
	Drug administration	£2,426	£1,050	£1,376	3.51%
	Adverse events	£111	£1,385	-£1,274	3.25%
	Supportive care	£9,919	£8,178	£1,741	4.44%
Total costs in PFS/On treatment		£58,895	£17,796	£41,099	92.12%
Mean costs in PD/Off treatment	£9,022	£9,022	£6,076	£2,946	7.51%
	£3,289	£3,289	£3,315	-£27	0.07%
Total costs in PD/Off treatment		£12,310	£9,391	£2,919	7.58%
Terminal care cost		£3,430	£3,547	-£117	0.3%
Total costs		£74,636	£38,261	£36,375	100%

Note: numbers may not sum due to rounding

Probabilistic Sensitivity Analysis

To assess the uncertainty surrounding the variables included in the cost-effectiveness model, a probabilistic sensitivity analysis (PSA) was undertaken using 1,000 samples. The mean values, distributions around the means, and sources used to estimate the parameters are detailed in section 5.6 of the company submission.

Results of the PSA compared to deterministic results are presented in Table 27. The scatterplot in Figure 10 shows the iterations and the cost effectiveness acceptability curve is shown in Figure 11.

Table 27: PSA results compared to base-case (list price)

	Costs		QALYs		ICERs (vs. docetaxel)		ICERs (vs. N+D)	
	Base case	PSA	Base case	PSA	Base case	PSA	Base case	PSA
Docetaxel	£20,181	£20,976	0.71	0.71	-	-	-	-
Nintedanib + docetaxel	£38,261	£39,752	0.91	0.94	£88,367	£83,166	-	-
Atezolizumab	£74,636	£75,749	1.31	1.31	£91,142	£92,382	£92,587	£98,050

Figure 10: Scatterplot of PSA results for cost effectiveness plane

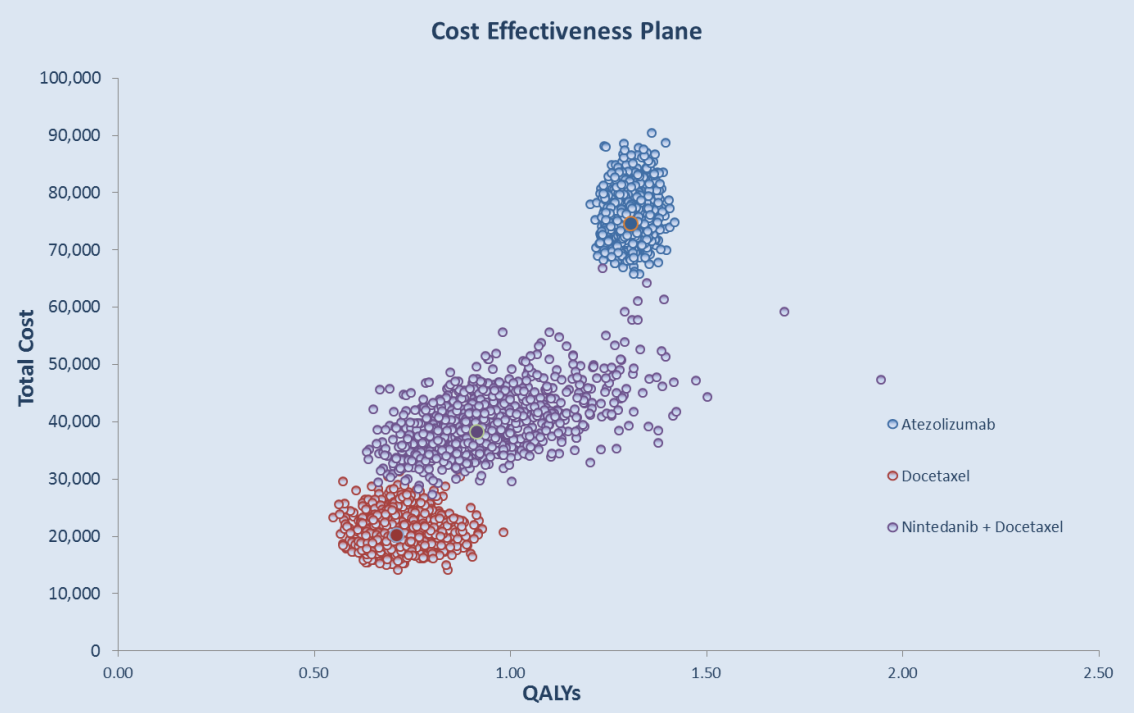
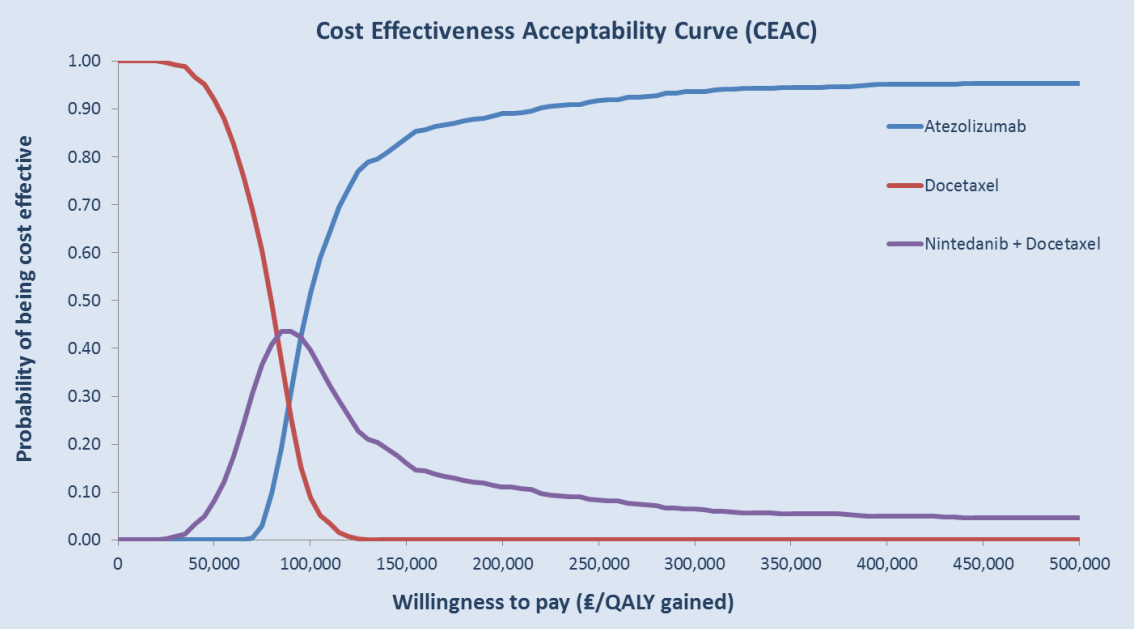


Figure 11: Cost-effectiveness acceptability curve



Univariate Sensitivity Analysis

The parameters included in the univariate analysis are consistent with the parameters tested in the original company submission, with the exception of removal of drug costs, as requested by NICE. The parameter values used in the analyses which had the greatest impact on the results can be found in Table 28 below. Generally, the base case value of

parameters were varied across a +/- 50% range. Results of the analyses using atezolizumab list price are displayed in Figure 12 and Figure 13.

Table 28: Parameter values for univariate sensitivity analysis

Parameter	Base case value	Lower value	Higher value
Discount effects	3.5%	1.5%	6%
Discount costs	3.5%	1.5%	6%
Supportive costs, on treatment, atezolizumab	£282.96	-50%	+50%
Supportive costs, off treatment, atezolizumab	£128.25	-50%	+50%
Supportive costs, on treatment, docetaxel	£282.96	-50%	+50%
Supportive costs, off treatment, docetaxel	£128.25	-50%	+50%
Supportive costs, on treatment, nintedanib+docetaxel	£282.96	-50%	+50%
Supportive costs, off treatment, nintedanib+docetaxel	£128.25	-50%	+50%
Weekly AE cost, docetaxel	£75.87	-50%	+50%
Weekly AE cost, nintedanib+docetaxel	£47.93	-50%	+50%
Admin cost, docetaxel	£198.94	-50%	+50%
Admin cost, atezolizumab	£198.94	-50%	+50%
Terminal care cost	3679.37	-50%	+50%

Figure 12: Comparison to docetaxel univariate sensitivity analysis (list price)

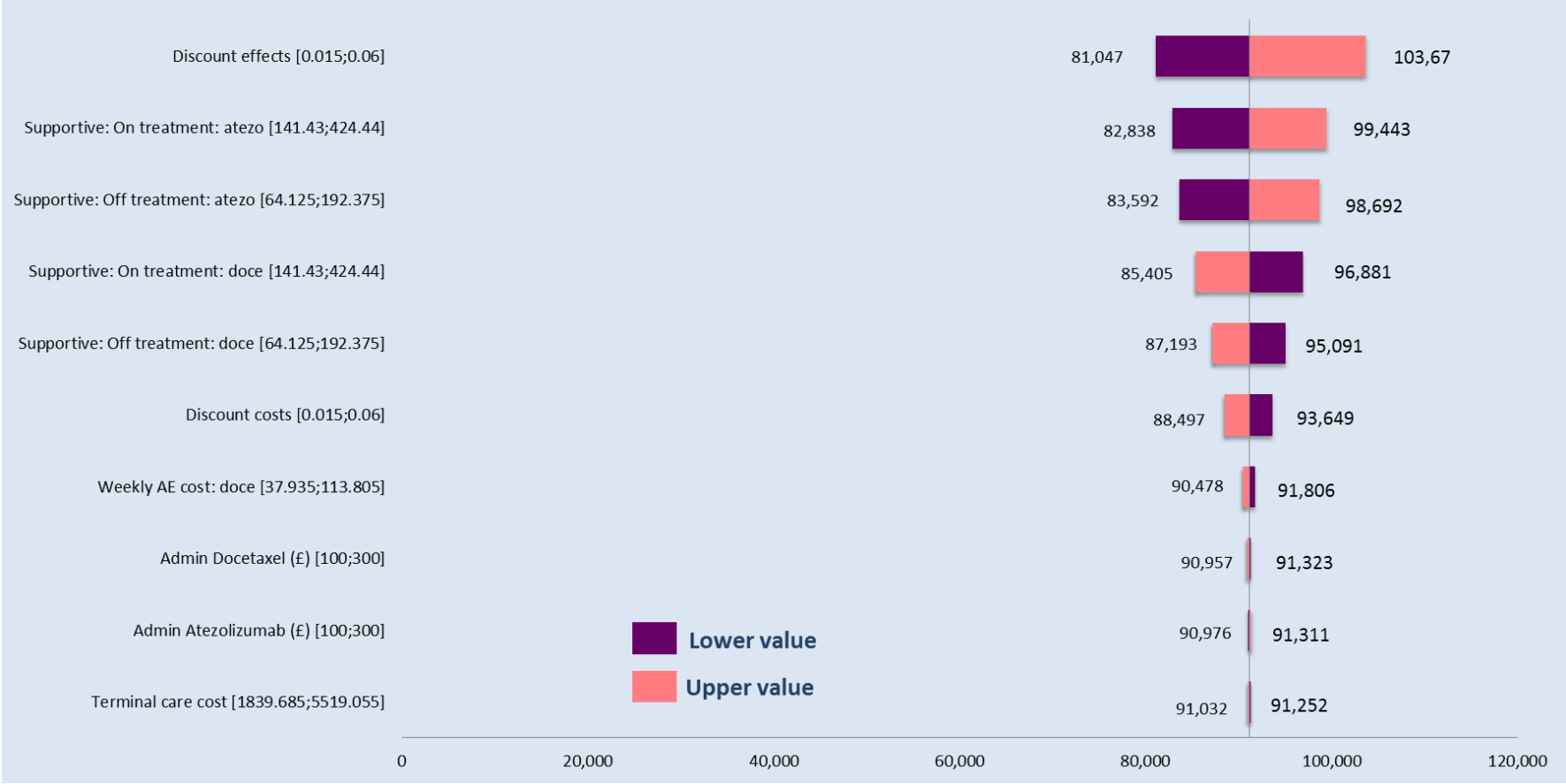
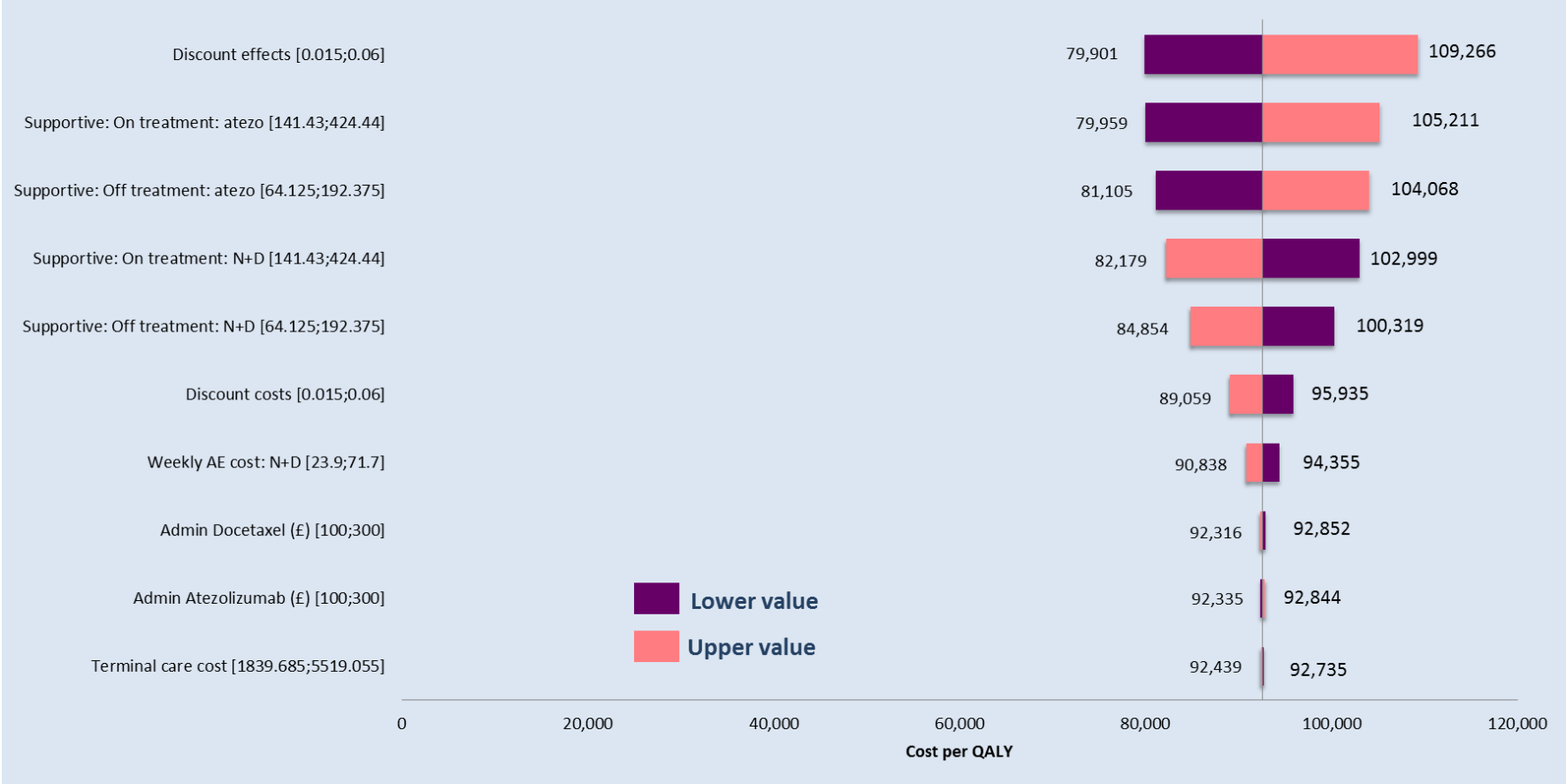


Figure 13: Comparison to nintedanib + docetaxel univariate sensitivity analysis (list price)



Appendix 5: Results utilising updated survival extrapolation (updated PAS)

An update to the currently approved PAS has been submitted to the Department of Health and is currently under assessment. The scheme is in the form of a simple discount, and offers a [redacted] reduction on the list price of atezolizumab. If accepted, this would reduce the cost of atezolizumab from a list price of £3807.69 to a net price of [redacted] per vial (1,200mg).

Base Case Results

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]. 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 £38,261 at list price.

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

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 29 for a summary of the base case results.

Table 29: Updated base case results (updated PAS price)

				Versus Docetaxel				Versus N+D			
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)
Docetaxel	£20,181	1.17	0.71	-	-	-	-	-	-	-	-
Nintedanib + Docetaxel	£38,261	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]

The Markov trace, and QALY gain disaggregated by health states remains consistent with Appendix 4 and 5.

The disaggregated costs by health state and resource use for all comparators can be found below.

Table 30: Disaggregated costs: comparison to docetaxel (updated PAS price)

		Atezolizumab	Docetaxel	Increment	% absolute increment
Mean costs in PFS/On treatment	Treatment cost	[redacted]	£135	[redacted]	[redacted]
	Drug administration	£2,426	£781	£1,645	[redacted]
	Adverse events	£111	£793	-£682	[redacted]
	Supportive care	£9,919	£6,856	£3,063	[redacted]
Total costs in PFS/On treatment		[redacted]	£8,565	[redacted]	[redacted]
Mean costs in PD/Off treatment	Supportive care	£9,022	£4,719	£4,303	[redacted]
	Subsequent therapy cost	£3,289	£3,335	-£46	[redacted]
Total costs in PD/Off treatment		£12,310	£8,054	£4,256	[redacted]
Terminal care cost		£3,430	£3,562	-£132	[redacted]
Total costs		[redacted]	£19,941	[redacted]	100%

Note: numbers may not sum due to rounding

Table 31: Disaggregated costs: comparison to nintedanib + docetaxel (updated PAS price)

		Atezolizumab	Nintedanib + Docetaxel	Increment	% absolute increment
Mean costs in PFS/On treatment	Treatment cost	[redacted]	£14,709	[redacted]	[redacted]
	Drug administration	£2,426	£1,050	£1,376	[redacted]
	Adverse events	£111	£1,385	-£1,274	[redacted]
	Supportive care	£9,919	£8,178	£1,741	[redacted]
Total costs in PFS/On treatment		[redacted]	£17,796	[redacted]	[redacted]
Mean costs in PD/Off treatment	Supportive care	£9,022	£6,076	[redacted]	[redacted]
	Subsequent therapy cost	£3,289	£3,315	[redacted]	[redacted]
Total costs in PD/Off treatment		£12,310	£9,391	£2,919	[redacted]
Terminal care cost		£3,430	£3,547	-£117	[redacted]
Total costs		[redacted]	£38,261	[redacted]	**100%**

Note: numbers may not sum due to rounding

Probabilistic Sensitivity Analysis

To assess the uncertainty surrounding the variables included in the cost-effectiveness model, a probabilistic sensitivity analysis (PSA) was undertaken using 1,000 samples. The mean values, distributions around the means, and sources used to estimate the parameters are detailed in section 5.6 of the company submission.

Results of the PSA compared to deterministic results are presented in Table 32. The scatterplot in Figure 14 shows the iterations and the cost effectiveness acceptability curve is shown in Figure 15.

Table 32: PSA results compared to base-case (updated PAS)

	Costs		QALYs		ICERs (vs. docetaxel)		ICERs (vs. N+D)	
	Base case	PSA	Base case	PSA	Base case	PSA	Base case	PSA
Docetaxel	£20,181	£21,116	0.71	0.71	-	-	-	-
Nintedanib + docetaxel	£38,261	£39,901	0.91	0.94	£88,367	£82,909	-	-
Atezolizumab	[redacted]	[redacted]	1.31	1.31	[redacted]	[redacted]	[redacted]	[redacted]

Figure 14: Scatterplot of PSA results for cost effectiveness plane (updated PAS price)

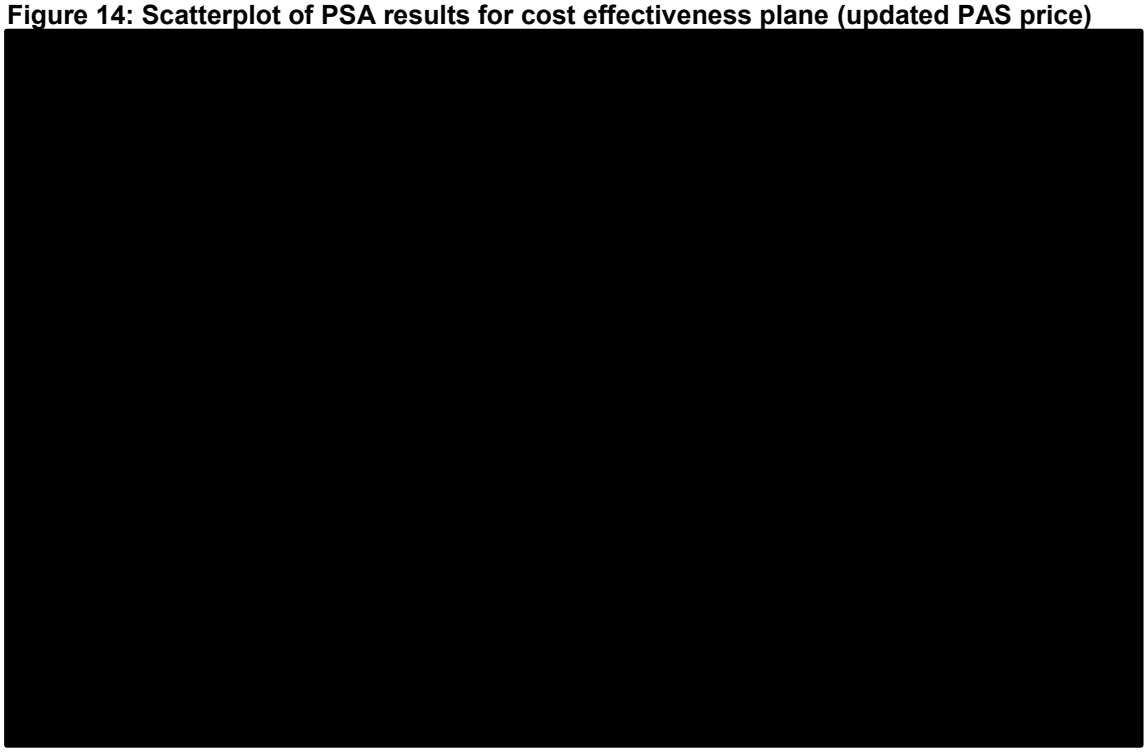


Figure 15: Cost-effectiveness acceptability curve (updated PAS price)

Univariate Sensitivity Analysis

The parameters included in the univariate analysis are consistent with the parameters tested in the original company submission, and in Appendix 4. For further details of the parameter values used in the analyses which had the greatest impact on the results, see Table 28 in

Appendix 4. Results of the analyses using atezolizumab updated PAS price are displayed in Figure 16 and Figure 17.

Figure 16: Comparison to docetaxel univariate sensitivity analysis (updated PAS)

Figure 17: Comparison to nintedanib + docetaxel univariate sensitivity analysis (updated PAS)

Appendix 6: Scenario analyses (list price)

Scenario analyses have been conducted to assess uncertainty around structural assumptions of the model. Without-PAS results are shown below. With-PAS results are reported in the following appendix. The following alternative scenarios were tested as part of the sensitivity analysis to assess uncertainty in committee preferences:

- OS adjusted for treatment switching
- Duration of treatment effect:
    - Waning effect: 5-25 years
    - Capped at 5 years
    - Capped at 10 years
    - Capped at 15 years
    - Capped at 20 years

Adjustment for treatment switching

As explained in our initial submission, whilst crossover from the docetaxel arm to the atezolizumab arm was not permitted for the primary population in OAK, 5% of patients randomised to atezolizumab, and 17% of patients in the docetaxel arm, went on to receive subsequent cancer immunotherapies, predominantly nivolumab (Table 33).

As such, the OS treatment effect estimate of the docetaxel arm was assessed to determine if adjustment was required to correct for any bias induced by treatment switch.

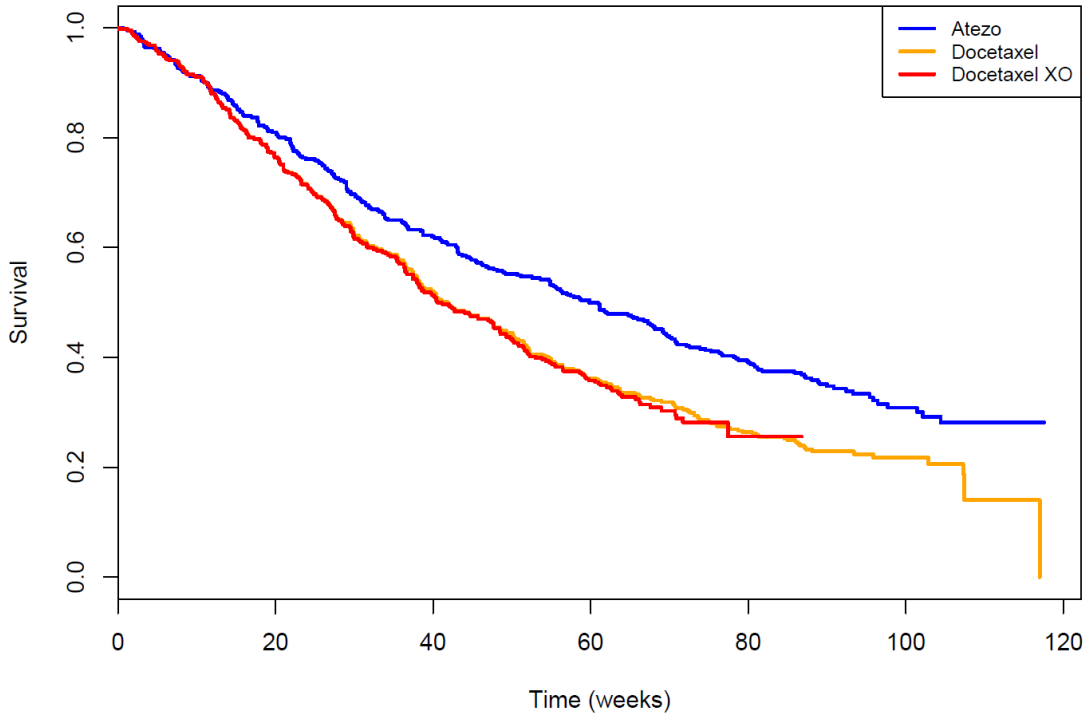
Similar to the pembrolizumab appraisal (National Institute for Health and Care Excellence, 2016), and in-line with the NICE DSU guidance (Latimer, 2014), the Rank Preserving Structural Failure Time (RPSFT) method was used to assess the impact of treatment switching on OS estimates.

The KM estimates of treatment switch adjusted OS in OAK can be seen in Figure 18. In the company submission, the decision was taken not to adjust for treatment switching, and to provide a conservative estimate of the clinical effectiveness, and ICER for atezolizumab versus docetaxel. However, Roche now feels it is imperative to demonstrate to the committee the true effect of atezolizumab in the treatment switching adjustment analysis. Whilst this is only presented as a scenario analysis, other appraisals have used this analysis as their base case, therefore we urge the committee to reflect on these results as a robust and accurate reflection of the benefit of atezolizumab.

Table 33: Subsequent therapies in OAK

Treatment, %	Atezolizumab n=425	Docetaxel n=425
Any non-protocol therapy	206 (48.5)	192 (45.2)
Chemotherapy	176 (41.4)	131 (30.8)
Targeted therapy	63 (14.8)	66 (15.5)
Immunotherapy	19 (4.5)	73 (17.2)
Nivolumab	16 (3.8)	58 (13.6)

Figure 18: KM estimates of crossover (RPSFT) adjusted OS in OAK (ITT primary population; 7 Jul 2016 data cut)



Base Case Results (list price)

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. In contrast, docetaxel provides a QALY gain of 0.64, and a life-year gain of 1.07, at a total cost of £19,536; and nintedanib (plus docetaxel) provides a QALY gain of 0.81, and a life-year gain of 1.31, at a total cost of £37,265 at list price.

As such, the atezolizumab resulting ICER versus docetaxel is £83,049, and versus nintedanib (plus docetaxel) is £75,751.

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 34 for a summary of the base case results accounting for treatment switching.

Table 34: Treatment-switch adjustment scenario: base case results (list price)

				Versus Docetaxel				Versus N+D			
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)
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

Duration of treatment effect

Table 35 provides a summary of ICER results for the different duration of treatment effect scenarios.

Table 36 provides a summary of ICER results for the different duration of treatment effect scenarios where OS has been adjusted for cross-over to subsequent immunotherapies, as described above.

Table 35: Duration of treatment effect scenarios (list price)

Scenario	ICER vs. Docetaxel	ICER vs. Nintedanib+Docetaxel
Lifetime	£91,142	£92,587
Waning effect: 5-25 years	£91,207	£92,664
5 years	£91,689	£93,208
10 years	£91,213	£92,673
15 years	£91,155	£92,603
20 years	£91,144	£92,589

Table 36: Duration of treatment effect scenarios: adjusted for cross-over (list price)

Scenario	ICER vs. Docetaxel	ICER vs. Nintedanib+Docetaxel
Lifetime	£83,049	£75,751
Waning effect: 5-25 years	£83,105	£75,812
5 years	£83,532	£76,253
10 years	£83,109	£75,818
15 years	£83,059	£75,763
20 years	£83,050	£75,752

Appendix 7: Scenario analyses (updated PAS)

Adjustment for crossover: base case results

Base Case Results (updated PAS)

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]. In contrast, docetaxel provides a QALY gain of 0.64, and a life-year gain of 1.07, at a total cost of £19,536; and nintedanib (plus docetaxel) provides a QALY gain of 0.81, and a life-year gain of 1.31, at a total cost of £37,265 at list price.

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

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 37 for a summary of the base case results accounting for treatment switching.

Table 37: Treatment-switch adjustment scenario: base case results (updated PAS)

				Versus Docetaxel				Versus N+D			
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)
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]

Duration of treatment effect

Table 38: Duration of treatment effect scenarios (updated PAS)

Scenario	ICER vs. Docetaxel	ICER vs. Nintedanib+Docetaxel
Lifetime	[redacted]	[redacted]
Waning effect: 5-25 years	[redacted]	[redacted]
5 years	[redacted]	[redacted]
10 years	[redacted]	[redacted]
15 years	[redacted]	[redacted]
20 years	[redacted]	[redacted]

Table 39: Duration of treatment effect scenarios: adjusted for cross-over (updated PAS)

Scenario	ICER vs. Docetaxel	ICER vs. Nintedanib+Docetaxel
Lifetime	[redacted]	[redacted]
Waning effect: 5-25 years	[redacted]	[redacted]
5 years	[redacted]	[redacted]
10 years	[redacted]	[redacted]
15 years	[redacted]	[redacted]
20 years	[redacted]	[redacted]

Appendix 8: Corrections to ERG implementation of errors

ERG section 6 results table revision	ERG implementation instructions	Roche comments, and implementation employed
C2 Age related utility decrement	In Sheet 'Atezo' Set formula in cell CM118 =IF(util_optn=4,((BB118*u_Pre5On-0.02)+BC118*(u_Pre15On-0.02)+BD118*(u_Pre30On-0.02)+BE118*(u_Post30On-0.02))*(BV118*AV118),IF(util_optn=1,BV118*AV118*(**u_pfs_new-0.02**),AW118*(**u_pfs_new-0.02**))) Copy cell CM118 to CM119:CM586 Set formula in cell CM587 =IF(util_optn=4,((BB587*u_Pre5On-0.07)+BC587*(u_Pre15On-0.07)+BD587*(u_Pre30On-0.07)+BE587*(u_Post30On-0.07))*(BV587*AV587),IF(util_optn=1,BV587*AV587*(**u_pfs_new-0.07**),AW587*(**u_pfs_new-0.07**))) Copy cell CM587 to CM588:CM1578 Set formula in cell CO118 =IF(util_optn=4,(BB118*(u_Pre5Off-0.02)+BC118*(u_Pre15Off-0.02)+BD118*(u_Pre30Off-0.02)+BE118*(u_Post30Off-0.02))*(AY118-BV118*AV118),IF(util_optn=1,(AY118-BV118*AV118)*(**u_prog-0.02**),AX118*(**u_prog-0.02**))) Copy cell CO118 to CO119:CO586 Set formula in cell CO587 =IF(util_optn=4,(BB587*(u_Pre5Off-0.07)+BC587*(u_Pre15Off-0.07)+BD587*(u_Pre30Off-0.07)+BE587*(u_Post30Off-0.07))*(AY587-BV587*AV587),IF(util_optn=1,(AY587-BV587*AV587)*(**u_prog-0.07**),AX587*(**u_prog-0.07**))) Copy cell CO587 to CO588:CO1578 In Sheet 'Doce'	Utility decrement at latter end of equation only implemented for atezo: see in bold. In Sheet 'Atezo' Set formula in cell CM118 =IF(util_optn=4,((BB118*u_Pre5On-0.02)+BC118*(u_Pre15On-0.02)+BD118*(u_Pre30On-0.02)+BE118*(u_Post30On-0.02))*(BV118*AV118),IF(util_optn=1,BV118*AV118*(**u_pfs_new-0.02**),AW118*(**u_pfs_new-0.02**))) Copy cell CM118 to CM119:CM586 Set formula in cell CM587 =IF(util_optn=4,((BB587*u_Pre5On-0.07)+BC587*(u_Pre15On-0.07)+BD587*(u_Pre30On-0.07)+BE587*(u_Post30On-0.07))*(BV587*AV587),IF(util_optn=1,BV587*AV587*(**u_pfs_new-0.07**),AW587*(**u_pfs_new-0.07**))) Copy cell CM587 to CM588:CM1578 Set formula in cell CO118 =IF(util_optn=4,(BB118*(u_Pre5Off-0.02)+BC118*(u_Pre15Off-0.02)+BD118*(u_Pre30Off-0.02)+BE118*(u_Post30Off-0.02))*(AY118-BV118*AV118),IF(util_optn=1,(AY118-BV118*AV118)*(**u_prog-0.02**),AX118*(**u_prog-0.02**))) Copy cell CO118 to CO119:CO586 Set formula in cell CO587 =IF(util_optn=4,(BB587*(u_Pre5Off-0.07)+BC587*(u_Pre15Off-0.07)+BD587*(u_Pre30Off-0.07)+BE587*(u_Post30Off-0.07))*(AY587-

	Set formula in cell CJ118 =IF(util_optn=4,(AZ118*(u_Pre5On-0.02)+BA118*(u_Pre15On-0.02)+BB118*(u_Pre30On-0.02)+BC118*(u_Post30On-0.02))*(BT118*AT118),IF(util_optn=1,BT118*AT118***u_pfs_com**,AU118***u_pfs_com**)) Copy cell CJ118 to CJ119:CJ586 Set formula in cell CJ587 = IF(util_optn=4,(AZ587*(u_Pre5On-0.07)+BA587*(u_Pre15On-0.07)+BB587*(u_Pre30On-0.07)+BC587*(u_Post30On-0.07))*(BT587*AT587),IF(util_optn=1,BT587*AT587***u_pfs_com**,AU587***u_pfs_com**)) Copy cell CJ587 to CJ588:CJ1578 Set formula in cell CL118 =IF(util_optn=4,(AZ118*(u_Pre5Off-0.02)+BA118*(u_Pre15Off-0.02)+BB118*(u_Pre30Off-0.02)+BC118*(u_Post30Off-0.02))*(AW118-BT118*AT118),IF(util_optn=1,(AW118-BT118*AT118)***u_prog**,AV118***u_prog**)) Copy cell CL118 to CL119:CL586 Set formula in cell CL587 =IF(util_optn=4,(AZ587*(u_Pre5Off-0.07)+BA587*(u_Pre15Off-0.07)+BB587*(u_Pre30Off-0.07)+BC587*(u_Post30Off-0.07))*(AW587-BT587*AT587),IF(util_optn=1,(AW587-BT587*AT587)***u_prog**,AV587***u_prog**)) Copy cell CL587 to CL588:CL1578 In Sheet 'Ninted + Doce – ITC' Set formula in cell AR118 =IF(util_optn=4,(U118*(u_Pre5On-0.02)+V118*(u_Pre15On-0.02)+W118*(u_Pre30On-0.02)+X118*(u_Post30On-0.02))*P118,P118***u_pfs_com3**) Copy cell AR118 to AR119:AR586 Set formula in cell AR587 =IF(util_optn=4,(U587*(u_Pre5On-0.07)+V587*(u_Pre15On-0.07)+W587*(u_Pre30On-0.07)+X587*(u_Post30On-0.07))*P587,P587***u_pfs_com3**) Copy cell AR587 to AR588:AR1578 Set formula in cell AT118 =IF(util_optn=4,(U118*(u_Pre5Off-0.02)+V118*(u_Pre15Off-0.02)+W118*(u_Pre30Off-0.02)+X118*(u_Post30Off-0.02))*Q118,Q118***u_prog**)	BV587*AV587),IF(util_optn=1,(AY587-BV587*AV587)*(**u_prog-0.07**),AX587*(**u_prog-0.07**))) Copy cell CO587 to CO588:CO1578 In Sheet 'Doce' Set formula in cell CJ118 =IF(util_optn=4,(AZ118*(u_Pre5On-0.02)+BA118*(u_Pre15On-0.02)+BB118*(u_Pre30On-0.02)+BC118*(u_Post30On-0.02))*(BT118*AT118),IF(util_optn=1,BT118*AT118*(**u_pfs_com-0.02)**,AU118*(**u_pfs_com-0.02)**)) Copy cell CJ118 to CJ119:CJ586 Set formula in cell CJ587 = IF(util_optn=4,(AZ587*(u_Pre5On-0.07)+BA587*(u_Pre15On-0.07)+BB587*(u_Pre30On-0.07)+BC587*(u_Post30On-0.07))*(BT587*AT587),IF(util_optn=1,BT587*AT587*(**u_pfs_com-0.07)**,AU587*(**u_pfs_com-0.07)**)) Copy cell CJ587 to CJ588:CJ1578 Set formula in cell CL118 =IF(util_optn=4,(AZ118*(u_Pre5Off-0.02)+BA118*(u_Pre15Off-0.02)+BB118*(u_Pre30Off-0.02)+BC118*(u_Post30Off-0.02))*(AW118-BT118*AT118),IF(util_optn=1,(AW118-BT118*AT118)*(**u_prog-0.02)**,AV118*(**u_prog-0.02)**)) Copy cell CL118 to CL119:CL586 Set formula in cell CL587 =IF(util_optn=4,(AZ587*(u_Pre5Off-0.07)+BA587*(u_Pre15Off-0.07)+BB587*(u_Pre30Off-0.07)+BC587*(u_Post30Off-0.07))*(AW587-BT587*AT587),IF(util_optn=1,(AW587-BT587*AT587)*(**u_prog-0.07)**,AV587*(**u_prog-0.07)**)) Copy cell CL587 to CL588:CL1578 In Sheet 'Ninted + Doce – ITC'

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C3 ToT half cycle correction	In Sheet 'Atezo' Set formula in cell BV13 = BU13 Copy cell BV13 to BV14:BV1578 In Sheet 'Doce'' Set formula in cell BT13 = BS13 Copy cell BT13 to BT14:BT1578 In Sheet 'Ninted + Doce – ITC'	Administration cost implemented in drug cost column for nintedanib+docetaxel; and equation links treatment duration of nintedanib to the treatment cap of docetaxel: see in bold. In Sheet 'Atezo' Set formula in cell BV13 = BU13 Copy cell BV13 to BV14:BV1578 In Sheet 'Doce'' Set formula in cell BT13 = BS13

	Set formula in cell Z13 = Y13 Copy cell Z13 to Z14:Z1578 Set formula in cell AB13= IF(MOD(F13,(1/cyc2wk))=0,1,0)*Y13*AA13*IF(F13=0,c_adm1_com3,c_adm_com3) Copy cell AB13 to AB14:AB1578 Set formula in cell AD13= **IF(F13<doc_cap,**IF(MOD(F13,(1/cyc2wk))=0,1,0)*Y13*AA13*IF(F13=0,**c_adm1_com,c_adm_com),0)** Copy cell AD13 to AD14:AD1578	Copy cell BT13 to BT14:BT1578 <u>In Sheet 'Ninted + Doce – ITC'</u> Set formula in cell Z13 = Y13 Copy cell Z13 to Z14:Z1578 Set formula in cell AB13= IF(MOD(F13,(1/cyc2wk))=0,1,0)*Y13*AA13*IF(F13=0,c_adm1_com3,c_adm_com3) Copy cell AB13 to AB14:AB1578 Set formula in cell AD13= =IF(MOD(F13,(1/cyc2wk))=0,1,0)* Y13*AA13*IF(F13<load_com3a*(1/cyc2wk),c_com3a_1st,c_com3a) Copy cell AD13 to AD14:AD1578

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Email sent to company for clarification – prepared by NICE

29/08/2017

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Dear Jessica & colleagues,

Thank-you for the ACD comments and new evidence received on Thursday 24 August 2017. The NICE team and the ERG are now working to review the ACD consultation comments and are briefing the committee before the meeting on 13 September 2017.

We note that your consultation response may not fully address the issue of PD-L1 subgroups highlighted in the ACD: *'…in practice there does appear to be a correlation between PD-L1 expression levels and the degree of clinical benefit gained. The committee concluded that it was disappointed that the company did not present all relevant results by PD-L1 subgroup.'*

However, the NICE team note that Roche have not responded fully to the ACD or provided any cost-effectiveness analysis for subgroups of people with PD-L1 positive, or PD-L1 negative tumours. To assist the committee in its decision-making, and potentially add weight to your argument that atezolizumab should be recommended for use for all patients irrespective of PD-L1 status, we ask that you provide clinical and cost-effectiveness estimates separately for populations who are PD-L1 positive and PD-L1 negative, in addition to those for the full population regardless of PD-L1 status. Please provide this for all relevant comparators (docetaxel, docetaxel and nintedanib, and pembroliumab). The committee wish to see these subgroup analyses,

so we request that you provide these in order to best brief committee and allow decision-making at the meeting.

We would be grateful if you could also clarify the data analysis date for the results presented in Table 19 p31 of your response to the ACD ('OAK, duration of response in the secondary population'), was this from the most recent data cut of the OAK trial or the previous data cut? And was this adjusted for cross-over?

Additionally the draft SPC you sent us was with your company submission in February 2017, and therefore before the CHMP opinion was granted, please provide an updated draft summary of product characteristics and draft EPAR, highlighting any data, comments or changes regarding PD-L1 expression in the most recent document.

Finally as per the NICE guide to the process of technology appraisal section 3.7.29 *"The new evidence must be presented as a separate appendix to the comments on the ACD"* please can I remind you to split your 'ACD response' from the 'new evidence'. I recognise that you have submitted two responses, one including the 'current PAS' and one including an 'updated PAS' but it is imperative that both responses are split correctly. At the same time, please can you provide a redacted version of all four documents? This will ensure we are readily prepared to include the correct version with the guidance document in the committee papers following the meeting. If appropriate, please supply an updated checklist of confidentiality as well.

Please upload your updated responses to NICE Docs https://appraisals.nice.org.uk/request/31494 by **3pm on Thursday 31 September 2017.**

The ERG have highlighted a potential issue with the models. I will be sending a separate email with regards to this.

If you have any questions, please do not hesitate to get in touch.

Kind regards,

Stephanie

Stephanie Yates | Technology Appraisals Project Manager (Committee C) | National Institute for Health and Care Excellence | Phone 0161 870 3248

Email sent to company for clarification – prepared by NICE

29/08/2017

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Kind regards,

Stephanie

Stephanie Yates | Technology Appraisals Project Manager (Committee C) | National Institute for Health and Care Excellence | Phone 0161 870 3248

Email in response to clarification – prepared by Roche

From: Purchase, Jessica [mailto:jessica.purchase@roche.com]
Sent: 31 August 2017 18:29
To: Stephanie Yates <Stephanie.Yates@nice.org.uk>
Cc: Cain, Denzyl <denzyl.cain@roche.com>; Matt Hodgson <matt.hodgson@roche.com>
Subject: Re: ID970 atezolizumab: Response to ACD

Dear Stephanie,

Thank you for your email dated 29th August.

I have just uploaded a number of documents to NICE docs including:

- Most recent draft SmPC with a singular comment where wording on PD-L1 has been adapted (The CHMP has not yet provided Roche with a copy of the EPAR)
- ACIC marked consultation document, and accompanying new evidence appendices (updated PAS only)
- Redacted consultation document, and accompanying new evidence appendices (updated PAS only)
- Updated confidentiality checklist
- New versions of the economic models

Please note, we did not have any issues with the economic models on our side. However, I've changed the files to .XLSB format in the hope this fixes the issues being experienced by the ERG.

You will also note only the updated PAS versions of documents have been provided. This is because the discount has now been approved, and we are in the process of informing PASLU.

As per your question on Table 19 of the response, this is from the most recent data cut, and has not been adjusted for crossover, no.

Regarding the request for subgroups by PDL1 status, I regret to inform you that, as we informed NICE some 4 weeks ago, we will not be providing this evidence.

As highlighted in the ACD, whilst there is some correlation between PD-L1 expression and response, clinical experts confirmed "that PD-L1 is not a perfect biomarker and therapies such as atezolizumab have shown benefit in people with PD-L1-positive and negative tumours". Indeed, for overall survival - the central driver of clinical and cost effectiveness – the benefit over docetaxel chemotherapy is essentially the same in the lowest expressors (tumour cell [TC] and immune cells [IC] both <1%) and those with higher levels of expression. In the pivotal OAK study there is a 25% reduction in the risk of death (HR 0.75) for the 379 patients with TC/IC expression<1% compared with 26% reduction (HR 0.74) in the 463 patients with higher levels of expression. Indeed, one of the key advantages of atezolizumab over other immunotherapies where biomarker selection is required is that it extends the benefits of immunotherapy to all patients regardless of PD-L1 status or the availability of tissue for PD-L1 testing, it obviates treatment delays whilst testing is

undertaken and reduces the resources expended by the NHS in procuring tissue samples, testing and reporting them.

Further slicing of the data will not add weight to our argument that atezolizumab should be recommended for use for all patients irrespective of PD-L1 status, and increases the chance of assessment being made on an improperly powered PD-L1 negative subgroup, rather than on the full evidence base of a positive, well-powered phase 3 clinical study. Rather, the updated analyses provided in response to the ACD in the all-comers population should be utilised as the best representation of cost effectiveness across all patients.

It is pertinent to point out that Roche have discounted significantly to ensure all patients who can benefit from treatment have the opportunity to access atezolizumab, and maintain equality in treatment options for all patients. The discount offered factors in the degree of benefit offered by the drug and the number of patients needing treatment. We hope NICE will consider the complete dataset available to them to appraise atezolizumab as a cost effective option for all patients.

Kind regards,

Jessica

From: [redacted]
Sent: 31 August 2017 18:29
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Cc: [redacted]
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Kind regards,

[redacted]

ID970 STA Atezolizumab Addendum 1

LIVERPOOL REVIEWS AND IMPLEMENTATION GROUP (LRiG)

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

ERG response to ACD consultation responses

Confidential until published

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

Completed 6 September 2017

DOES NOT CONTAINS CONFIDENTIAL DATA

UNIVERSITY OF LIVERPOOL | LIVERPOOL REVIEWS AND IMPLEMENTATION GROUP

A MEMBER OF THE RUSSELL GROUP

1 INTRODUCTION

The National Institute for Health and Care Excellence (NICE) invited Roche Products Limited (the company), who is the marketing authorisation holder for atezolizumab, to submit evidence for the clinical and cost effectiveness of atezolizumab for the treatment of locally advanced or metastatic non-small cell lung cancer (NSCLC) after chemotherapy in accordance with the Institute's Single Technology Appraisal (STA) process. The Liverpool Reviews and Implementation Group (LRiG) at the University of Liverpool was commissioned to act as the Evidence Review Group (ERG) for this appraisal. The first Appraisal Committee (AC) meeting was held in June 2014 and the AC submitted its recommendations to NICE in the form of an Appraisal Consultation Document (ACD). NICE invited consultees, commentators and the public to comment on the ACD. This document contains the ERG's critique of, and comments on, responses received during the consultation process. A confidential appendix (Confidential Appendix 3) contains results from the company's economic analyses which have been generated using the updated patient access scheme (PAS) discount for atezolizumab and the PAS discounts for nintedanib and prembrolizumab

2 CLINICAL ISSUES

2.1 Recently reported trial results

Currently, there are no long-term overall survival (OS) data from previously treated patients with locally advanced or metastatic NSCLC treated with atezolizumab as data from the OAK[1,2] and POPLAR trials[3,4] of atezolizumab are not mature and Kaplan-Meier (K-M) data from these trials are only available up to 27 months. In responses to the ACD, the point was made that *'there is relatively little data to guide the committee with regard to long term survival of NSCLC patients receiving immunotherapy'* and evidence that demonstrates a potentially significant improvement in 3- and 5-year OS for patients receiving two different immunotherapies was highlighted. The results highlighted by the ACD respondents are reproduced in Box 1.

Box 1 Information provided by respondents to the ACD

Pembrolizumab

At ASCO June 2017 mature overall survival data from the KEYNOTE-001 were presented which demonstrate that in 449 previously treated patients who received pembrolizumab (median follow up 34.5 months) 3-year OS was 19% (29.7% in those with PD-L1 expression >50).

Nivolumab

Data were presented by Dr J Brahmer at the AACR meeting earlier in the year where an 18% 3 year overall survival was shown in patients who had received Nivolumab. The 5-year survival in this presentation was also good at 16% (although numbers were unsurprisingly small at this time point).

AACR=American Association for Cancer Research; ACD=appraisal consultation document; ASCO=American Society of Clinical Oncology; OS=overall survival; PD-L1=programmed death-ligand 1

The ERG agrees with the respondents that the quoted results presented for pembrolizumab and nivolumab appear promising. However, the ERG considers that this information should not be used as the basis for justifying any projection of life-time survival (model time horizon is 25-years) for patients treated with atezolizumab as:

- evidence is only available for a maximum of 5 years, i.e. there is still **no** evidence for the remaining 80% (20 years) of the model time horizon
- as the company has highlighted in the response to the ACD, atezolizumab targets the ligand PD-L1 while pembrolizumab targets the protein, PD-1. While this means that all drugs ultimately target the same immune checkpoint, there are mechanistic differences between the two approaches in terms of which other co-inhibitory interactions they blockade. The ERG is, therefore, unclear whether it is reasonable to assume that treatment with atezolizumab is as equally effective as either pembrolizumab or nivolumab
- evidence from the KEYNOTE-001 trial[5] is difficult to interpret within the context of this STA as:
    - this is a Phase I, randomised, parallel assignment, open label trial that only considers pembrolizumab
    - it is not clear whether results presented at the conference relate to patients who have baseline characteristics that are similar to those of patients recruited to the OAK and POPLAR trials
- evidence from the CA209-003 trial[6] is difficult to interpret within the context of this STA:
    - this is a Phase I dose-escalation cohort expansion trial that only considers nivolumab
    - recruited patients were heavily pre-treated (1 to 5 prior systemic regimens)
    - results relate to patients who received three different doses of nivolumab (1, 3, or 10 mg/kg every 2 weeks in 8-week cycles for up to 96 weeks); the recommended dose of nivolumab is 3mg/kg nivolumab every 2 weeks
    - OS from the time of first dose was an exploratory objective.

In addition, the ERG questions whether evidence relating to nivolumab should be considered relevant to this appraisal as, within the ERG report (submitted to NICE in April 2017) the

ERG agreed with the company that nivolumab was not a relevant comparator. The rationale being that, at the time the company submission was sent to NICE, nivolumab had not been recommended by NICE as a treatment for the population under consideration in this appraisal. The ERG, however, highlights that currently (September 2017), as well as at the time of submitting the original ERG report to NICE (April 2017), two STAs considering the use of nivolumab for the treatment of locally advanced or metastatic NSCLC are on-going, one for patients with squamous disease (ID811)[7] and the other for patients with non-squamous disease (ID900)[8]. The fact that these appraisals are on-going means that nivolumab cannot be considered a standard of care and is, therefore, still not a relevant comparator.

2.2 Updated network meta-analysis

Within the ERG report (dated 27 April 2017), the ERG raised several concerns regarding the indirect treatment comparison (ITC) presented within the company submission (CS). In summary, the ERG did not support the ITC approach taken by the company as:

- the main network included comparators that were not listed in the final scope issued by NICE[9]
- when considering the relative efficacy of atezolizumab versus nintedanib+docetaxel, the company compared effectiveness relating to the whole LUME-Lung 1 trial population, rather than considering the relevant population, i.e. the narrower population for which nintedanib+docetaxel is licensed (patients with adenocarcinoma)
- the company did not convincingly justify the exclusion of pembrolizumab from the ITC network of comparators relevant to this appraisal
- the ERG did not agree with the company's use of the deviance information criterion (DIC) statistic (a measure of model fit) for assessing the presence of heterogeneity in the analyses.

Due to ERG concerns regarding potential heterogeneity in the ITC, during the clarification process, the ERG asked the company to provide results from random-effects (RE) models so that these could be compared with the fixed-effects (FE) results presented in the company submission. The ERG's request for RE results was made for methodological completeness, rather than due to any preference for RE results from the analyses carried out by the company. The ERG emphasises that a range of factors may influence the results of the company's ITC (including choice of comparators and population selected, type of fractional polynomial [FP] model chosen and the use of FE or RE). This means that it is difficult to identify the most appropriate combination of factors to use to generate ITC results and, therefore, to determine which is the 'best' model to use.

The company has presented the results from an updated ITC from a network of atezolizumab, docetaxel, nintedanib+docetaxel and pembrolizumab (Figure 1).

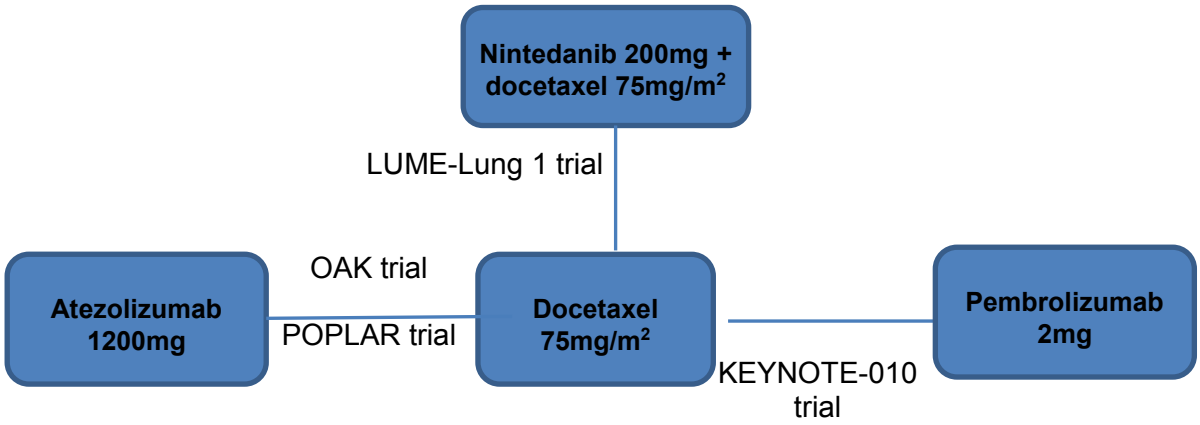

Figure 1 Updated network plots for ITCs of OS and PFS

The updated ITC relates to the whole population of the OAK[1,2] and POPLAR[3,4] trials, to the adenocarcinoma subgroup of the LUME-LUNG 1 trial[10] and to the PD-L1-positive population of the KEYNOTE-010 trial.[11] The methodology employed to carry out the updated ITC is consistent with that used by the company to undertake their original ITC (see Section 4.6.2 of the ERG report for a summary) and results are presented in Table 1 from the company's 'best-fitting' FE Weibull model with a time horizon of 5 years for OS and 2.5 years for progression-free survival (PFS).

Table 1 Expected survival differences for updated NMA of atezolizumab, docetaxel, nintedanib+docetaxel and pembrolizumab

Expected survival difference in months (95% CrI)			
Outcome	**Atezolizumab vs docetaxel*** **	**Atezolizumab vs pembrolizumab*** **	**Atezolizumab vs nintedanib+docetaxel*** **
OS (using original ITC methods)*	5.70 (3.57 to 8.31)	-0.18 (-5.58 to 4.60)	3.33 (-0.15 to 6.81)
OS (treatment switching adjustment)**	7.06 (4.65 to 9.62)	1.38 (-4.33 to 6.01)	4.67 (1.03 to 8.13)
PFS (original ITC methods)*	0.78 (0.08 to 1.57)	0.04 (-1.28 to 1.21)	-0.09 (-1.43 to 1.14)

CrI=credible interval; FE=fixed effects; FP=fractional polynomial; PFS=progression-free survival; OS=overall survival; NMA=network meta-analysis
*Results came from the 'best fitting' Weibull FE FP model
** ITC results with adjustment for treatment switching in the OAK trial via the Rank Preserving Structural Failure Time method
*** The updated ITC relates to the whole population of the OAK[1,2] and POPLAR[3,4] trials, to the adenocarcinoma subgroup of the LUME-LUNG 1[5] trial and to the PD-L1-positive population of the KEYNOTE-010 trial[6]
Source: Company response to the ACD, adapted from Table 12, Table 13, Table 14

In line with the results presented in Section 4.6.3 and Section 4.6.4 of the ERG report, results from the company's updated ITC show a statistically significant difference in favour of atezolizumab compared to docetaxel in terms of both OS and PFS, but no statistically significant difference in expected survival between atezolizumab and pembrolizumab, or between atezolizumab and nintedanib+docetaxel, for either OS or PFS.

The company's original ITC did not include any adjustment to account for the fact that 5% of patients randomised to receive atezolizumab and 17% of patients in the docetaxel arm of the OAK trial received subsequent cancer immunotherapies, predominantly nivolumab (see Table 28 of the company submission). The company states that the decision not to adjust for treatment switching was taken to provide a conservative estimate of clinical (OS) and cost effective benefit resulting from treatment with atezolizumab compared with docetaxel. However, the company now considers that the true effect of atezolizumab should be demonstrated via a 'treatment-switching' adjustment scenario analysis.

The company adjusted the OS estimate in the OAK trial using the Rank Preserving Structural Failure Time (RPSFT) method, according to NICE DSU guidance for treatment-switching analyses.[12] The ERG notes that the adjustment that the company makes is for subsequent (non-trial) therapies rather than for cross-over trial therapies; the RPSFT method is intended for adjust for the effects of cross-over trial therapies.

The results in Table 1 show a statistically significant OS difference in favour of atezolizumab compared to docetaxel, and also for atezolizumab compared to nintedanib+docetaxel. The adjusted analysis shows no statistically significant difference in expected OS between atezolizumab and pembrolizumab.

The ERG has the following concerns regarding the updated ITC:

- The ERG notes that non-equivalent populations are compared within this ITC. Therefore, the results presented in Table 1 should be interpreted with caution.
- The company states that a FE model has been used due to the small size of the reduced network. The ERG acknowledges that RE models can be difficult to fit to small networks but emphasises that the FE and RE results presented in Section 4.6.3 of the ERG report suggest potential statistical heterogeneity within the networks and that this impacts on the precision, and therefore the reliability, of the ITC estimates.
- The company presents an additional ITC that includes an adjustment to the OS estimate for subsequent therapies that participants received during the OAK trial. However, the RPSFT method used for this adjusted analysis is intended for cross-over trial therapies rather than for subsequent non-trial therapies. Therefore, the ERG is unsure if the RPSFT method is valid for this additional ITC.

- The ERG emphasises that a range of factors influence the results from the company's ITC (including comparators in the network, choice of FP model, FE or RE and adjustment for subsequent therapies). It is therefore difficult to identify the most appropriate combination of factors to use to generate ITC results and, therefore, to determine which is the 'best' model to use.

3 COST EFFECTIVENESS ISSUES

3.1 Summary of the original company model and the ERG amendments

In the CS, the company presented an economic model for atezolizumab compared to docetaxel or nintedanib+docetaxel. In the final scope issued by NICE[9] for the appraisal of atezolizumab, pembrolizumab had been identified as a comparator, but the company had not included pembrolizumab in their economic analysis. The ERG considered that pembrolizumab was an appropriate comparator and should have been included in the analysis.

The company model included in the CS was constructed based on OAK trial OS data from patients receiving atezolizumab and, for patients receiving docetaxel and nintedanib+docetaxel, results from the company's NMA (the updated NMA is described in Section 2.2 of this report). Utilities, which were based on time to death, were drawn from the OAK trial and the treatment costs of atezolizumab were based upon time to treatment discontinuation (TTD) for patients receiving atezolizumab in the OAK trial. The company's basecase analysis, using list prices for all treatments, generated an incremental cost effectiveness ratio (ICER) of £72,356 per quality adjusted life year (QALY) gained for atezolizumab versus docetaxel, and £56,076 for atezolizumab versus nintedanib+docetaxel.

In their review of the CS, the ERG considered that there were three errors in the company model that needed to be corrected if the model was to produce accurate cost effectiveness results that reflected the underlying assumptions of the company base-case analysis. These errors were:

- incorrect application of discounting
- absence of age-dependent utility decrements
- incorrect use of a half-cycle correction to TTD data.

The ERG considered that the company's approach to modelling OS generated overly optimistic survival gains when atezolizumab was compared with docetaxel and when atezolizumab was compared with nintedanib+docetaxel.

To model the OS of patients treated with atezolizumab, the company used a mixed cure-rate model: OS for 98% of the population was represented by a log-logistic distribution fitted to

OAK trial OS K-M data and survival for the remaining 2% of the population was assumed to be the same as that of the general age-matched population.

The ERG identified three issues with this approach:

- use of the log-logistic function produced an implausibly long survival tail with mortality rates that are, at some points, lower than the mortality rates of the general population of the same age
- there is insufficient evidence to support the application of a cure-rate
- the value for the cure-rate used by the company was not justified in the company submission.

During the clarification process, the ERG asked the company to indirectly compare atezolizumab versus nintedanib+docetaxel in the adenocarcinoma population only, the population for whom nintedanib is licensed. However, the company did not provide these results. Instead, the company provided the results of atezolizumab (total population, OAK and POPLAR trials) versus nintedanib+docetaxel (adenocarcinoma population, LUME-Lung 1 trial). This comparison showed no statistically significant difference in OS and so the ERG concluded that there was no justification for modelling a differential OS for atezolizumab and nintedanib+docetaxel.

The ERG also had concerns relating to the company's assumption that treatment with atezolizumab has a lifetime protective effect. This assumption was criticised by a previous NICE AC[13] when considering the use of an immunotherapy for treating patients with previously treated advanced or metastatic NSCLC.

The ERG considered that OS for atezolizumab and docetaxel could be more accurately modelled by using K-M data from the OAK trial until constant hazards could be observed and then fitting exponential extrapolations after the point robust K-M data were available. The ERG also limited the duration of treatment effect of atezolizumab to be approximately 3 years.

The ERG considers that there is no statistically significant difference in OS between atezolizumab and nintedanib+docetaxel in the adenocarcinoma population. The ERG modelled OS for atezolizumab as described above for the comparison of atezolizumab and docetaxel and assumed that the OS for nintedanib+docetaxel was identical to that for atezolizumab.

Application of the ERG model amendments results in an ICER for the comparison of treatment with atezolizumab versus docetaxel of £170,497 per QALY gained when assuming an approximately 3 year duration of treatment effect. Compared to nintedanib+docetaxel, the

ERG estimated that the ICER for atezolizumab would be £1,170,793 per QALY gained when assuming an approximately 3 year duration of treatment effect for both treatments.

3.2 Company response to the ACD

3.2.1 Corrections to ERG amendments to company model

In their response to the ACD, the company highlighted what they consider to be two errors in the ERG's corrections to their model relating. These related to age-dependent utility and to the half-cycle correction employed for nintedanib+docetaxel.

The utility formula error highlighted by the company resulted in decrements for age that apply to atezolizumab only when utilities are based upon progression status. However, in both the company basecase analysis and ERG preferred scenario, time to death utilities were used and, in this case, the ERG formula applies age-related decrements equally to all treatments in the model. As such, the company's correction does not affect either the ICERs of the corrected company base case or the ERG preferred scenarios presented in the ERG report submitted for consideration at the first AC meeting.

The company's suggested correction to the half-cycle adjustment would lead to stopping treatment with nintedanib after six cycles, as is the case for docetaxel. However, in clinical practice, whilst clinical advice to the ERG is that docetaxel is commonly limited to a maximum of six cycles, nintedanib continues to be administered until disease progression, as is the case in the ERG corrected model. As such, the ERG does not consider that the correction suggested by the company is required.

3.2.2 Amended overall survival projections

In their response to the ACD, the company has considered the views of the ERG and the AC on the company's approach to modelling OS for patients receiving atezolizumab. The company has now suggested an alternative extrapolation that differs from the approach described in the CS and from the approach favoured by the ERG and members of the AC. The company has provided a rationale for their new preferred approach to OS modelling for atezolizumab which can be summarised as follows:

- long-term survival data from trials considering other immunotherapies can inform the long-term survival of patients who have been treated with atezolizumab
- clinical opinion, that the company reported in the CS, about potential 5-year survival for atezolizumab and considered uninformative by the ERG and the AC should be reconsidered
- the log-logistic distribution for OS extrapolation is appropriate and the ERG preferred extrapolation was unjustified

- the mixed cure-rate model used in the analyses presented in the CS should be replaced by a model that demonstrates waning of efficacy of atezolizumab over time
- the analysis presented in the CS did not include an adjustment for treatment switching.

New information on survival data

The additional OS information presented in the company response to the ACD is discussed in Section 2.1. In summary, the ERG does not consider the additional information should be used to inform long-term OS projections because:

- the information is on treatments that were not originally considered by the company to be relevant comparators to atezolizumab
- information comes from trials that do not have an alternative drug as a comparator
- in the case of pembrolizumab, information is on a treatment indicated for a different population to that considered in the company model
- ultimately the information presented still only represents, at best, 20% of the time horizon over which the company project OS for atezolizumab.

Clinical opinion

In the ERG report (p105), the ERG stated:

> *"To assess the clinical plausibility of any projection, the company explored potential 5-year survival rates for patients treated with atezolizumab by eliciting opinions from clinicians. In the CS (p161), the company states that unanimous clinical opinion is that a value of 10% for the 5-year OS rate of patients receiving immunotherapy "…would not be implausible". The company did not provide any context to explain how this number was elicited from clinicians. The ERG considers that the phrase "…would not be implausible" should not be interpreted as 'likely'."*

In their response to the ACD, the company provides no additional information on how the value of 10% was obtained from clinicians. The ERG considers that extrapolation of survival based upon clinical opinion of what may be plausible (as opposed to 'likely') for a treatment that is in its infancy in terms of long-term outcomes is not robust, even if the process for gathering this information was robust. With no information on how the views of clinicians were gathered (e.g., methods, the questions posed, numbers, and who were asked), the ERG considers that the value obtained should not be included in any extrapolation of OS for atezolizumab.

Log-logistic distribution for extrapolation and the ERG extrapolation being unjustified

In the ERG critique of the CS, the ERG expressed concern that the log-logistic distribution produced a long survival tail and that the use of this distribution, therefore needed to be

justified. The ERG considers that the information presented on long-term survival, both in the CS and in the company response to the ACD, does not sufficiently justify the predicted atezolizumab 5-year survival rate or the long tail predicted by the log-logistic extrapolation. This conclusion applies both to the model that formed part of the CS and to the model provided in the company response to the ACD.

In the ERG report, the ERG's extrapolation method was fully justified over four pages (ERG report pp105-109). In summary, the ERG's preferred extrapolation relies only upon the OAK trial data and not on any speculation about plausible long-term survival rates. The ERG presented evidence in their report (pp17-109) that cumulative hazards had become linear for both the atezolizumab and docetaxel arms in the OAK trial after week 56. As such, an exponential extrapolation could be applied from week 56 for both treatment arms. The evidence supporting the decision to apply a different exponential curve for each treatment arm was limited, but because there appeared to be some separation in OS between the atezolizumab arms and the docetaxel arms, different exponential curves were fitted by the ERG to the atezolizumab and docetaxel arms.

Waning of treatment

The company has replaced the original mixed cure-rate model with a model that assumes a waning of treatment effect over time. In the ERG report, the ERG described how it had amended the company model to limit the duration of treatment effect of atezolizumab to 3 years, which was in line with TA428 (Pembrolizumab for treating PD-L1 positive NSCLC after chemotherapy). As the likelihood, effect, or indeed mechanism, of waning is unknown, this approach at least produced consistency between submissions for immunotherapy treatments in patients with NSCLC. By introducing a waning function into the model, the company has replaced one source of speculation (the cure rate) with another (a long-term deterioration in treatment effect).

Treatment switching

In the CS the company stated that whilst 17% of docetaxel patients in the OAK trial had switched to atezolizumab, "crossover was considered to only make a marginal impact, hence was excluded from the economic model" (company submission, p166). In their response to the ACD, whilst still recognising the minimal impact of treatment switching, the company has undertaken an analysis of treatment switching and included the results in an updated economic model. Without access to the patient level data on treatment switching from the OAK trial, the ERG is not able to comment on whether the methods used to adjust OS have been applied correctly. However, referring to the original position of the company (i.e., only a small

percentage of patients crossed over and there is only a small period of time during which OS data that could potentially be affected by crossover), it is unlikely that adjusting for crossover materially impacts on the projected OS curves for docetaxel.

To explore this issue further, the ERG examined the updated company model OS results for patients receiving docetaxel. Whilst there are other model changes that the company has made in its response to the ACD that would affect the OS of patients receiving docetaxel, the updated company model estimates mean OS for docetaxel to be 1.17 years compared to 1.188 years in the original company model. This suggests that any adjustment for crossover has a minor effect on OS for docetaxel and, as such, the ERG has not amended the preferred extrapolation for treatment switching. In any case, in the ERG preferred extrapolation, the predicted OS extrapolation for docetaxel was already more pessimistic (docetaxel, mean life expectancy=1.3 years) than the updated company extrapolation.

Overall survival – summary

The ERG commends the company for their attempts to exhaust all potential avenues currently available to provide information on the potential long-term survival of patients receiving atezolizumab. However, the ERG considers the direct evidence base for long-term survival for atezolizumab has not changed since the CS and the indirect evidence presented in the company response to the ACD is not robust enough to move beyond the ERG preferred approach of simply extrapolating from the available trial data.

3.2.3 Cost minimisation analysis (atezolizumab versus pembrolizumab)

In their response to the ACD, reflecting the opinion of the ERG and the AC that pembrolizumab is an appropriate comparator for atezolizumab, the company has undertaken a cost minimisation analysis of atezolizumab versus pembrolizumab. The company undertook this analysis as results from the company's NMA suggest that atezolizumab and pembrolizumab are equally effective. The results of this analysis are presented in the company response to the ACD together with substantial caveats from the company that the analysis is not robust. The ERG agrees that the analysis is not robust as the populations of the trials included in the NMA are not the same and the confidence intervals around the OS hazard ratio between the two treatments are wide.

Even if the trials of atezolizumab and pembrolizumab were comparable, as the company points out in their response to the ACD, the mechanisms of action of the treatments are different. This means that even if treatment effects are equal over 2 years, as suggested by the company NMA, the different mechanisms of action highlighted by the company would be

cast doubt over whether efficacy would remain equivalent over the following 23 year model time horizon.

The ERG commends the company for attempting to include pembrolizumab as a comparator but considers the cost-minimisation results presented in the company response to the ACD of limited value to decision makers.

3.3 End of life considerations

The company response did not refer to the NICE end of life criteria and no information presented by the company changed the ERG's original end of life assessment. For information, the ERG has provided a summary of the end of life section (Section 7) of the ERG report.

The NICE end of life criteria, and the data presented by the company to show that these have been met, are presented in Table 2.

Table 2 End of life criteria

NICE End of Life criteria	Data presented by the company
The treatment is indicated for patients with a short life expectancy, normally less than 24 months	The company considers this criterion to be met and quotes values from Beckett 2013[14] that show median survival for patients with Stage IIIb and Stage IV NSCLC is 7.5 months and 3.4 months, respectively (CS, Section 3.4)
There is sufficient evidence to indicate that the treatment offers an extension to life, normally of at least an additional 3 months, compared with current NHS treatment	The company considers this criterion to be met and quotes data (CS, Figure 8) from the OAK trial that show that treatment with atezolizumab is associated with a statistically significant improvement in OS compared with docetaxel in the ITT population (HR 0.73, 95% CI: 0.62 to 0.87). The company also highlights that results from the OAK trial (CS, Section 4.7) show that median OS in the ITT population is 9.6 months (95% CI: 8.6 to 11.2) in the docetaxel arm and 13.8 months (95% CI: 11.8 to 15.7) in the atezolizumab arm

CI=confidence interval; CS=company submission; HR=hazard ratio; ITT=intention to treat; NSCLC=non-small cell lung cancer; OS=overall survival

Short life expectancy

The ERG agrees with the company that patients with advanced or metastatic NSCLC have a life expectancy of less than 24 months, although the survival estimates quoted by the company relate to all patients with Stage IIIb and Stage IV NSCLC and the population being considered in this appraisal is restricted to patients who have progressed after prior chemotherapy. However, as the K-M data from the OAK trial suggest that median life expectancy for patients receiving docetaxel is 9.6 months, the NICE end of life criterion for short life expectancy criteria is met.

Extension to life

An examination of the ERG's remodelled OS suggests that treatment with atezolizumab generates a mean survival gain of 4.7 months compared to docetaxel. This suggests that, when the whole trial population is considered, patient life expectancy is extended by more than 3 months when treatment with atezolizumab is compared with docetaxel. However, when treatment with atezolizumab is compared with nintedanib+docetaxel, the size of the survival gain is uncertain.

The company provided evidence during the clarification process that suggests there is no statistically significant difference in OS for atezolizumab (total population) compared to nintedanib+docetaxel (adenocarcinoma patients only). If there is no statistically significant difference in OS, then, for the adenocarcinoma population, atezolizumab does not offer an extension to life of at least 3 months and so does not meet the NICE end of life criterion for life extension.

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ID970 STA Atezolizumab Addendum 2

LIVERPOOL REVIEWS AND IMPLEMENTATION GROUP (LRiG)

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

ERG response to ACD consultation responses

Confidential until published

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UNIVERSITY OF LIVERPOOL | LIVERPOOL REVIEWS AND IMPLEMENTATION GROUP

A MEMBER OF THE RUSSELL GROUP

1 INTRODUCTION

The National Institute for Health and Care Excellence (NICE) invited Roche Products Limited (the company), who is the marketing authorisation holder for atezolizumab, to submit evidence for the clinical and cost effectiveness of atezolizumab for the treatment of locally advanced or metastatic non-small cell lung cancer (NSCLC) after chemotherapy in accordance with the Institute's Single Technology Appraisal (STA) process. The first Appraisal Committee (AC) meeting was held in June 2014 and the AC submitted its recommendations to NICE in the form of an Appraisal Consultation Document (ACD). NICE invited consultees, commentators and the public to comment on the ACD. The ERG's response to points raised during the consultation process may be found in a separate addendum (Addendum 1) and a confidential appendix (Confidential Appendix 3). This document contains results from additional analyses, requested by NICE, to be presented at the second AC meeting (13 September 2017).

2 ADDITIONAL ANALYSES

The Evidence Review Group (ERG) was asked by NICE to carry out the R4 analysis using the patient access scheme (PAS) price for atezolizumab and the list price for nintedanib. The ERG was also asked to explore potential alternatives to overall survival (OS) modelling for nintedanib+docetaxel as well as R4. The ERG highlights that there is no statistically significant evidence showing that OS for atezolizumab is different to OS for nintedanib+docetaxel for the adenocarcinoma population for which nintedanib is indicated. In response to the request from NICE, the ERG has generated results from two approaches to modelling OS for nintedanib+docetaxel, noting that neither approach is robust and so findings should be treated with caution.

First, the nintedanib+docetaxel OS curve is modelled using the company fractional polynomial (FP) indirect treatment comparison (ITC) time dependent hazard ratios (HRs) for nintedanib+docetaxel applied to the ERG preferred OS for atezolizumab, with a 5-year duration of treatment effect for nintedanib+docetaxel that was applied in the same way as for atezolizumab (R5). This change resulted in an incremental quality adjusted life year (QALY) gain for atezolizumab of 0.175 compared to nintedanib+docetaxel with an incremental cost effectiveness ratio (ICER) of [redacted] per QALY gained (using the atezolizumab PAS discount and the nintedanib list price).

A second approach (R6) takes the OS HR for nintedanib+docetaxel compared to docetaxel from the LUME-Lung 1 trial (0.83) and applies it to the ERG remodelled docetaxel OS curve.

Hazards in LUME-Lung 1 were not proportional, rendering such an approach statistically unsound. In combination with the ERG preferred OS for atezolizumab, the QALY gain for atezolizumab over nintedanib+docetaxel falls from 0.65 in the company base case to 0.148, resulting in an ICER for atezolizumab compared to nintedanib+docetaxel of [redacted] per QALY gained (using the atezolizumab PAS discount and the nintedanib list price).

Table 1 Cost effectiveness results for atezolizumab vs nintedanib+docetaxel with ERG revisions to company's base case (PAS price for atezolizumab and list price for nintedanib)

Model scenario & ERG revisions	Atezolizumab			Nintedanib + docetaxel			Incremental			ICER £/QALY	ICER Change
	Cost	QALYs	Life years	Cost	QALYs	Life years	Cost	QALYs	Life years		
R4) ERG corrected original base case with ERG preferred OS for atezolizumab and assumed equal to OS for nintedanib+docetaxel, and treatment duration effect for both set to 5 years	[redacted]	0.988	1.527	£39,313	0.961	1.527	[redacted]	0.027	0.000	[redacted]	[redacted]
R5) ERG preferred OS for atezolizumab, FP ITC for nintedanib+docetaxel OS and treatment duration effect for both set to 5 years	[redacted]	0.988	1.527	£37,582	0.813	1.306	[redacted]	0.175	0.221	[redacted]	[redacted]
R6) ERG preferred OS for atezolizumab, LUME Lung 1 HR for nintedanib+docetaxel OS and treatment duration effect for both set to 5 years	[redacted]	0.988	1.527	£37,847	0.840	1.347	[redacted]	0.148	0.180	[redacted]	[redacted]

FP=fractional polynomial; ITC=indirect treatment comparison; ICER=incremental cost effectiveness ratio; OS=overall survival; PAS=patient access scheme; QALY=quality adjusted life year

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

From: Yvonne Summers

Sent: 12 September 2017 20:22

To: Stephanie Yates <Stephanie.Yates@nice.org.uk>

Cc: Summers Yvonne (RBV) NHS Christie Tr

Subject: RE: Clinical expert attendance: 13 September 2017: Atezolizumab for treating non-small-cell lung cancer after platinum-based chemotherapy [ID970]

Hi Stephanie,

Apologies for the late delay in responding. I am only just back from ESMO. However, there was some data presented at ESMO which directly relates to your questions:

Gadeel presented data from 400 patients treated on OAK, from which tissue was available for further analysis they had PDL1 analysis with the Ventana SP142 for the trial but then had the Dako 22C3 test carried out.

The population tested was about half of those who went into the trial (due to tissue availability). They were similar in baseline characteristics to the ITT population, however, there was 9% EGFR mutation positive rate in the population for whom DAKO results are available compared to 12% in the overall population. The median overall survival was 7.7 mo vs 14.1 mo for Docetaxel vs atezolizumab compared to 9.6 vs 13.8 in the ITT population.

218 of the 400 patients were negative to one or other or both of the tests (52% which seems to be a high rate of negatives). 77% of the population who were negative with SP142 were negative by 22C3. HR was 0.55 for the SP142 and 0.61 for 22C3 and for the group negative with both HR 0.63. The OS outcomes for SP142 high (TC3 or IC3, n=73) versus 22C3 high (TPS >50%, n=100 were similar at HR 0.37 and 0.49 respectively.

There was no breakdown by histology.

In summary the results show benefit for all the subgroups and there is some concordance between negative by SP142 and 22C3, but the subpopulations are not exactly the same.

In response to your specific questions:

- Would you consider the populations above to be non-equivalent from a clinical point of view? The patients in each sub group are probably different but there is likely to be a substantial overlap. From a clinical point of view the OS outcomes are similar in the negative and high groups presented.

-

- Is PD-L1 testing in the NHS currently carried out using the Dako IHC 22C3 test providing only TPS for pembrolizumab treatment decisions? The NHS testing is predominantly Dako 22C3 (due to pembrolizumab being available in the 1st line setting and second line) but given the data above most clinicians would be fairly happy using the DAKO antibody to make treatment decisions in the second line setting (for other PD-1 PD-L1 antibodies) ie I don't think it would be necessary for path labs to test for both.

Kind regards,

Yvonne

Yvonne Summers FRCP, PhD

Consultant Medical Oncologist

UHSM & The Christie NHS Foundation Trust

From: National Institute for Health and Care Excellence [mailto:stephanie.yates@nice.org.uk]

Sent: 05 September 2017 16:44

To: Yvonne Summers

Subject: RE: Clinical expert attendance: 13 September 2017: Atezolizumab for treating non-small-cell lung cancer after platinum-based chemotherapy [ID970]

Dear Yvonne,

Thanks for your quick response confirming that you are unavailable for the next committee meeting.

As you unfortunately can't attend, the NICE team would be grateful if you could let us have an answer to the following query about equivalence of PD-L1 positive populations which has arisen for this topic.

The company has provided a comparison of atezolizumab in its licensed indication (all-comers) with pembrolizumab in its licensed indication (PD-L1 positive), but they note that that different assays were used in the ATEZ and PEMB trials (Ventana SP142 IHC assay, and Dako 22C3 IHC assay respectively) and these stratified patients differently:

- Ventana stratified PD-L1 expression on both tumour cells (TCs) and tumour-infiltrating immune cells (ICs), whereas

- Dako stratified PD-L1 expression on tumour cells only using a tumour proportion score (TPS)

For this reason, the company argue that it's not appropriate to compare atezolizumab PD-L1 expressers to pembrolizumab PD-L1 expressers, as the patient populations identified with these two different assays are not equivalent. From our reading, it seems that many of the PD-L1 assays have disparate positivity cut-off points and scoring systems which complicate the standardisation of clinical decision-making.

- Would you consider the populations above to be non-equivalent from a clinical point of view?

- Is PD-L1 testing in the NHS currently carried out using the Dako IHC 22C3 test providing only TPS for pembrolizumab treatment decisions?

If you could please send your feedback by 12 noon on Friday 8 September, that would be most helpful.

Many thanks in advance for any help you can provide,

Kind regards,

Steph