NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

SINGLE TECHNOLOGY APPRAISAL

Atezolizumab in combination for treating advanced non-squamous non-small-cell lung cancer [ID1210]

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

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

2. **Consultee and commentator comments on the Appraisal Consultation Document** from:
   - Roche (company)

   A no comment response was received from the Department of Health and Social Care.

   Comments on the Appraisal Consultation Document from experts:
   There were no comments received from patient or clinical experts/through the NICE website consultation

   Comments on the Appraisal Consultation Document received through the NICE website
   There were no comments received through the NICE website consultation

3. **Evidence Review Group critique of company response** – prepared by Southampton Health Technology Assessments Centre
   - Post-consultation ERG addendum
   - Post-consultation ERG exploratory analysis addendum

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

Appraisal title

Single Technology Appraisal

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

Type of stakeholder:

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

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

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

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

Please note: Comments received in the course of consultations carried out by NICE are published in the interests of openness and transparency, and to promote understanding of how recommendations are developed. The comments are published as a record of the submissions that NICE has received, and are not endorsed by NICE, its officers or advisory committees.

Comment number	Type of stakeholder	Organisation name	Stakeholder comment Please insert each new comment in a new row	NICE Response Please respond to each comment
1	Consultee (company)	Roche Products Ltd	Relevance of ITT analysis versus subgroup-specific analyses Before providing our responses to the statements and conclusions in the ACD for the EGFR- or ALK-positive subgroup, we want to highlight that we believe the primary focus of the NICE committee should not be on the subgroup-specific analyses. Rather, the NICE committee should be focusing on the ITT-level comparison of Atezo+Bev+CP versus pemetrexed plus platinum plus pemetrexed maintenance. The ITT comparison is a much more robust and appropriate analysis to inform NICE's decision-making, based on the fact that the ITT population: (i) provides larger patient numbers and greater statistical power in study IMPower 150, (ii) provides a more robust NMA to derive relative effect estimates versus pemetrexed-based chemotherapy, without relying on subgroup-specific assumptions and (iii) reflects the marketing authorisation for the atezolizumab combination in this indication. The ITT analysis demonstrates that the atezolizumab combination is a clinically- and cost-effective treatment option compared to pemetrexed-based chemotherapy for patients with untreated metastatic non-squamous NSCLC. Atezo+Bev+CP should therefore be recommended as an additional treatment option for untreated metastatic non-squamous NSCLC patients who do not have routine access to a cancer immunotherapy (i.e. patients with low/negative PD-L1 expression and patients with EGFR/ALK+ NSCLC). The subgroup-specific analyses and economic model results should be seen as complementary and supportive in nature; they provide additional evidence to explicitly demonstrate the clinical- and cost-effectiveness of Atezo+Bev+CP in these subgroups.	Thank you for your comment. The FAD recommends atezolizumab plus bevacizumab, carboplatin and paclitaxel for treating untreated metastatic non-squamous non-small-cell lung cancer (NSCLC) or for previously treated (with targeted therapy) epidermal growth factor receptor (EGFR)-positive or anaplastic lymphoma kinase (ALK)-positive NSCLC in adults.
2	Consultee (company)	Roche Products Ltd	**EGFR- or ALK-positive metastatic non-squamous NSCLC population** **<u>Size of population and grouping of EGFR- and ALK-positive patients</u>** The ACD states in Section 3.9 *"The committee concluded that the EGFR- or ALK-positive NSCLC subgroup in IMpower150 was small, there was no biological reason for combining the groups and the survival data were immature. These factors substantially add to the uncertainty about survival."* Whilst we acknowledge that the EGFR- or ALK-positive NSCLC subgroup in IMpower150 is small, the numbers in the study (~8% EGFR-positive and ~3% ALK-positive) are aligned with mutation	Thank you for your comment. During the appraisal, the committee considered the available data for the EGFR- or ALK-positive NSCLC subgroup, the views of the clinical experts about grouping people with

Comment number	Type of stakeholder	Organisation name	Stakeholder comment Please insert each new comment in a new row	NICE Response Please respond to each comment
			rates seen in UK clinical practice (1). We also consider that it is realistic for these patients to be combined, as both are NSCLC adenocarcinomas with driver mutations, and these patients have similar clinical characteristics such as younger age and being predominantly non-smokers (2). Importantly, combining these two subgroups provides additional statistical power, reduces uncertainty and therefore is a more robust basis for decision-making, compared to assessing EGFR- and ALK-positive patients separately. In addition, the grouped EGFR/ALK positive patient population represents patients with an unmet need for a CIT option following targeted therapies. Therefore, grouping these patients is reasonable, appropriate and very relevant from a reimbursement perspective as well. More importantly however, we do not believe that the primary focus of the NICE committee should be the subgroup-specific analyses. Rather, the NICE committee should be focusing on the ITT-level comparison of Atezo+Bev+CP versus pemetrexed plus platinum plus pemetrexed maintenance. The ITT comparison is a much more robust and appropriate analysis to inform NICE's decision-making (see comment 1 for more details). This is also consistent with previous NICE appraisals of atezolizumab and pembrolizumab in previously treated NSCLC (3) (4), where despite the fact that EGFR/ALK positive patients were included in the ITT study population and in the NICE recommendation, no economic analyses specific to the EGFR/ALK positive subgroup were used or requested to inform decision-making. In terms of efficacy in patients with EGFR/ALK positive non-squamous NSCLC, study IMpower 150 demonstrated that the Atezo+Bev+CP combination showed a clinically and statistically significant reduction in death of 46% for these patients (HR=0.54, CI: 0.29,1.03). This is clinically important as the only remaining option for these patients after targeted therapies is chemotherapy alone, which yields sub-standard results. Importantly, study IMpower 150 also showed that the atezolizumab combination demonstrates a clinical benefit in the EGFR- and ALK- positive patient populations independently, with the point estimates for the OS HR being [redacted] (see Figure **1** below). The forest plot in Figure **1** also demonstrates that the uncertainty in the estimates increases when smaller subgroups of patients are being assessed, therefore justifying the approach of combining EGFR and ALK positive patients to reduce uncertainty in the efficacy estimates.	EGFR- or ALK-positive NSCLC into 1 subgroup and the company response to ACD consultation. The committee did not agree that the further justification provided by the company at consultation resolved the uncertainty about this combined subgroup (see section 3.9 of the FAD). However, the committee concluded that consideration of the ITT population is more appropriate for decision making (see section 3.16 of the FAD).

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			Figure 1: [redacted] Notably, the clinical significance of the efficacy results, as well as the unmet need in the EGFR/ALK positive population were recognised by the MHRA which awarded an EAMS for the atezolizumab combination in this population in December 2018, and also by the EMA which has included the EGFR/ALK positive population in their positive CHMP opinion for the Atezo+Bev+CP combination. **<u>Survival data for EGFR- and ALK-positive patients</u>** In Section 3.9 the ACD also states that survival data are immature for the EGFR/ALK positive population. Whilst we acknowledge that this is true, we would like to point out that the ACD does not recognise or mention the fact that we have used the most conservative approach when extrapolating these data, and model long-term OS in our evidence submission for this subgroup. This conservative approach aimed to ensure that the long-term OS estimates for EGFR/ALK positive patients are as credible, relevant and appropriate as possible for NICE's decision-making. Please see more details on our approach to the long-term survival estimates for the EGFR- and ALK-positive subgroup in comment 3. It should also be noted that the median follow-up in the EGFR/ALK positive subgroup is similar to the ITT population of the study; 18.6 months for the EGFR/ALK positive patients and 19.7 months for the ITT population.	Thank you for your comments. During the appraisal, the committee understood that a conservative approach was taken when extrapolating the overall survival for the EGFR- or ALK-positive NSCLC subgroup and were aware of the limitations of the data for this subgroup. The committee accepted that there are limitations and concluded that consideration of the ITT population is more appropriate for decision making (see section 3.16 of the FAD).
3	Consultee (company)	Roche Products Ltd	**Extrapolating overall survival data in EGFR- or ALK-positive population** The ACD states in Section 3.16 *"The committee agreed that the long-term overall survival estimates from the company's model were too high and not credible. But, a difference of around 8% to 10% between the long-term overall survival estimates for people who had atezolizumab with bevacizumab, carboplatin and paclitaxel and people who had pemetrexed plus carboplatin or cisplatin and pemetrexed maintenance was plausible. The committee concluded that the company's estimates of long-term overall survival for people with EGFR- or ALK-positive NSCLC were too high and not credible. It accepted that atezolizumab plus bevacizumab, carboplatin and paclitaxel increased overall survival but by how much was uncertain."*	Thank you for your comments. During the appraisal, the committee understood that a conservative approach was taken when extrapolating the overall survival for the EGFR- or ALK-positive NSCLC

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			We would like to note that the ACD does not acknowledge the fact that in the company model, when extrapolating the OS data for the EGFR/ALK positive population, we have used one of the most conservative parametric models, in order to provide long-term OS estimates in our evidence submission for this subgroup that are as credible as possible. Other parametric extrapolations (Log-logistic, General Gamma) provide a much higher 5-year OS for Atezo+Bev+CP, ranging from 35%-42%. It should therefore be acknowledged that we made every possible effort to use the most conservative OS extrapolation for this subgroup, and produce long-term OS estimates that are relevant and appropriate as a basis for decision-making. In addition, in the ERG approach and NICE preferred base-case in the ACD, the relative effect from the ITT NMA is used to model long-term survival for subgroups, i.e. the PD-L1 low/negative and the EGFR/ALK positive population. Roche agrees with this approach, and this effectively represents an even more conservative way to model survival for EGFR/ALK positive patients, as the more modest relative treatment effect from the ITT population is used to inform long-term OS for this subgroup, instead of the more pronounced clinical benefit demonstrated specifically in EGFR/ALK positive patients. Moreover, the ACD does not make any reference to the 5-year OS estimates for the pemetrexed-based chemotherapy arm in the economic models (both from the company and the ERG). In the ERG base-case, which was used as the basis for the NICE-preferred analysis, the 5-year OS for EGFR/ALK positive patients in the pemetrexed-based chemotherapy arm is 16% (versus 26% for the atezolizumab combination). This is consistent with the committee discussions and clinical expert opinion in the meeting, as documented in the ACD (Section 3.16), that *"a difference of around 8% to 10% between the long-term overall survival estimates for people who had atezolizumab with bevacizumab, carboplatin and paclitaxel and people who had pemetrexed plus carboplatin or cisplatin and pemetrexed maintenance was plausible".* Therefore, we believe that the OS estimates for EGFR/ALK positive patients in the ERG base-case and in the NICE-preferred analysis are conservative, credible, in line with clinical expert estimates and appropriate to inform NICE's decision-making. More importantly however, as clearly outlined in comment number 1, we do not believe that the primary focus of the NICE committee should be the subgroup-specific analyses. Rather, the NICE committee should be focusing on the ITT-level comparison of Atezo+Bev+CP versus pemetrexed plus platinum plus pemetrexed maintenance. The ITT analysis demonstrates that the atezolizumab combination is a clinically- and cost-effective treatment option compared to pemetrexed-based chemotherapy. The subgroup-specific analyses and economic model results (for patients with low/negative PD-L1 expression and patients with EGFR/ALK+ NSCLC) should only be seen as complementary and supportive in nature, demonstrating that the ITT results are confirmed explicitly within these patient subgroups.	subgroup and were aware of the limitations of the data for this subgroup. The committee accepted that there are limitations and concluded that consideration of the ITT population is more appropriate for decision making (see section 3.16 of the FAD). In addition, the committee agreed that the company's revised analyses (using the hazard ratios from the ITT network meta-analysis excluding PARAMOUNT for each subgroup, as well as for the overall ITT population) were more appropriate than analyses using the hazard ratios from the network meta-analysis specific to the ITT population, PD-L1 less than 50% and EGFR- or ALK-positive NSCLC subgroups (see section 3.14 of the FAD).

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4	Consultee (company)	Roche Products Ltd	**Proportion treated with subsequent therapy** The ACD states in Section 3.20 *"The committee concluded that the assumption that 100% of people would have subsequent therapy did not reflect clinical practice and accepted that the appropriate proportion of people was much lower"* and in Section 3.25 *"The committee took into account its preferred assumptions that differed from the ERG's base case… assuming between 30% and 60% of people have subsequent therapy"* Whilst we agree that the assumption that 100% of people would have subsequent therapy does not reflect clinical practice, we want to highlight that the proportion of patients treated with subsequent therapy in the NICE-preferred base-case (between 30% and 60% of patients) is not consistent with the committee discussions in this appraisal (Section 3.20 of ACD), with estimates from other sources, as well as with recent precedent from the NICE Committee D decision for pembrolizumab with pemetrexed and platinum chemotherapy for untreated, metastatic, non-squamous NSCLC (TA557) (5). In particular, we believe that the lower end of the NICE-preferred range of patients being treated with subsequent therapy (30% of patients) is unreasonably low and not consistent with the committee discussions summarised in the ACD (Section 3.20), where for the standard-of-care arm: • *"The clinical experts explained that no more than 60% of people would be well enough to have subsequent therapy."* • *"The Cancer Drugs Fund clinical lead estimated this to be no more than 50%"* • *"The committee was aware that in previous technology appraisals for ALK-positive NSCLC, clinical experts estimated that 50% of people whose disease had progressed while taking alectinib would have subsequent therapy"* The only estimate within the ACD mentioning a lower proportion of patients receiving subsequent therapy, explicitly refers to patients after the atezolizumab combination: *"They estimated that 30% to 40% of people would have subsequent therapy after atezolizumab plus bevacizumab, carboplatin and paclitaxel in the larger centres but noted this estimate would be much lower in smaller centres."* Importantly, this proportion of 30% receiving subsequent therapy is also not consistent with the recent NICE Committee D decision for pembrolizumab with pemetrexed and platinum chemotherapy for untreated, metastatic, non-squamous NSCLC (TA557) (5) where 46.6% of patients in the standard-of-care arm were considered to receive subsequent therapy. We believe that this discrepancy seems unfair and unreasonable, and does not promote consistent decision-making in a highly competitive therapy area.	Thank you for your comment. During the appraisal, the committee considered the proportion of people receiving subsequent therapy (see section 3.19 of the FAD). The committee concluded that the company's revised analysis including 46.6% of people receiving subsequent therapy after treatment with atezolizuamb plus bevacizumab, carboplatin and paclitaxel and pemetrexed plus carboplatin or cisplatin with pemetrexed maintenance is appropriate for decision making.

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			In addition, the estimates from other sources on the proportion of NSCLC patients receiving subsequent therapy are much higher than 30%: • 55%: the estimate from NICE and NHS England during the budget impact discussions for this appraisal • 53%: estimate based on UK market research data (Kantar Health NSCLC tracker, Q4 2018 (6) Therefore, by taking into account the lower and higher end of these estimates above, we consider that the appropriate range of patients treated with subsequent therapy should be 46.6%-60% instead of 30%-60%. Clinical expert opinion in the ACD for the current appraisal (ID1210), as well as precedent from previous NICE appraisals (NICE TA557) (5), have confirmed that the proportion of patients treated with subsequent chemotherapy following first-line treatment with cancer immunotherapy should be assumed to be lower, compared to the proportion being treated in second-line following standard-of-care chemotherapy as a first-line option. However, for simplicity in the updated Roche base-case in our ACD response, we have assumed that the proportion being treated with subsequent therapy is the same regardless of first-line treatment. This should be viewed as a conservative assumption, as it assigns higher subsequent therapy costs to the atezolizumab combination arm; the impact on economic results however is anticipated to be limited.	
5	Consultee (company)	Roche Products Ltd	**Appropriate subsequent therapy options** The ACD states in Section 3.5 "The committee concluded that docetaxel would be offered as a subsequent therapy after atezolizumab plus bevacizumab, carboplatin and paclitaxel for people who are well enough to have further lines of therapy", in Section 3.6 "The committee concluded that the next line of treatment after pemetrexed plus carboplatin or cisplatin with or without pemetrexed maintenance is an immunotherapy monotherapy" and in Section 3.21 *"The committee heard that because nivolumab is recommended in the Cancer Drugs Fund and not routinely commissioned in the NHS in England, it should not be considered in decision making. The Cancer Drugs Fund clinical lead and the clinical experts explained that after treatment with pemetrexed plus carboplatin or cisplatin with or without pemetrexed maintenance people would have an immunotherapy (see section 3.6). Therefore, nivolumab and docetaxel were not considered to be appropriate subsequent therapies to be included in the analysis. The committee concluded that including nivolumab and docetaxel as options for subsequent therapy after treatment with pemetrexed plus carboplatin or cisplatin with or without pemetrexed maintenance was not appropriate for decision making."* We agree with the NICE-preferred assumptions in the ACD that the appropriate subsequent therapy:	Thank you for your comment. During the appraisal, the committee considered the subsequent therapy options after treatment with pemetrexed plus carboplatin or cisplatin with pemetrexed maintenance (see section 3.20 of the FAD). The committee concluded that the company's revised analyses submitted at consultation were more

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			• following the atezolizumab combination is docetaxel and • following pemetrexed plus carboplatin or cisplatin with or without pemetrexed maintenance is an immunotherapy monotherapy (either pembrolizumab or atezolizumab) Our updated base-case reflects the above assumptions. We used UK market research data (Kantar Health NSCLC tracker, Q4 2018 (6)) to inform the proportion of patients treated with an immunotherapy monotherapy (either pembrolizumab or atezolizumab) following pemetrexed-based chemotherapy: 69% would receive pembrolizumab and 39% atezolizumab as a subsequent therapy.	appropriate than analyses including treatment options that are not immunotherapies or not routinely commissioned in the NHS in England.
6	Consultee (company)	Roche Products Ltd	**ERG model inconsistency** We want draw the attention of the NICE technical team to an inconsistency we have identified in the ERG model. When applying the ERG changes to our company model (by changing the model switches in "Model Inputs" worksheet, cells J5 and L5), the price for pembrolizumab as a subsequent therapy is hard-coded (cell E47 of worksheet "Post disc. therapy cost"), therefore not being updated when changing the level of discount in the "Cost Inputs" worksheet. We have accounted for this error in the revised ERG economic model, based on which we have run our additional analyses. The revised ERG economic model is sent as a separate file alongside our ACD response.	Thank you for your comment. This inconsistency has been explored and was found to have no impact on the most plausible ICER.
7	Consultee (company)	Roche Products Ltd	**Continued treatment effect for pemetrexed maintenance** The ACD states in Section 3.20 *"A lifetime continued treatment effect for pemetrexed maintenance, even after treatment is stopped, is not supported by any evidence" and "The committee heard that including a lifetime continued effect of pemetrexed maintenance in the economic model was likely to overestimate the long-term survival gain for atezolizumab plus bevacizumab, carboplatin and paclitaxel and pemetrexed plus carboplatin or cisplatin and pemetrexed maintenance. The committee was aware that this led to the incremental cost-effectiveness ratio (ICER) for atezolizumab plus bevacizumab, carboplatin and paclitaxel compared with pemetrexed plus carboplatin or cisplatin without pemetrexed maintenance being underestimated."* We would like to highlight that the assumption on whether pemetrexed maintenance has a continued effect or not does not impact the ICER for the comparison of interest to decision-making in ID1210, i.e. Atezo+Bev+CP versus pemetrexed plus platinum plus pemetrexed maintenance. In the ERG base-case and in the NICE-preferred analysis, the network of studies excluding PARAMOUNT is included in the NMA; this is something that Roche finds reasonable and pragmatic. Using this network, only the comparison of Atezo+Bev+CP to pemetrexed plus platinum plus pemetrexed maintenance is feasible. For the comparison to the regimen without pemetrexed maintenance there is no connected network of studies; therefore, the assumption of whether pemetrexed maintenance has a continued effect is not relevant in the NICE-preferred analysis.	Thank you for your comment. Given that the company agreed at consultation that the PARAMOUNT trial should be excluded from the network meta-analysis (see section 3.12 of the FAD) and committee concluded that the relevant comparator for the appraisal is paclitaxel with pemetrexed plus carboplatin or cisplatin with pemetrexed maintenance (see section 3.2 of the FAD),

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			But even if all comparators were considered through an appropriate connected network, this assumption of continued treatment effect for pemetrexed maintenance would only impact the ICERs of Atezo+Bev+CP and pemetrexed plus platinum plus pemetrexed maintenance compared to the pemetrexed without pemetrexed maintenance regimen. This is consistent with what is stated in the ACD. However, the comparison of interest for this appraisal (Atezo+Bev+CP versus pemetrexed plus platinum plus pemetrexed maintenance) would not be affected, as the relative effect between these two comparators would still remain unchanged.	section 3.20 of the ACD has not been included in the FAD. A comparison of atezolizumab plus bevacizumab, carboplatin and paclitaxel with pemetrexed plus carboplatin or cisplatin without pemetrexed maintenance is not possible when PARAMOUNT is removed from the network.
8	Consultee (company)	Roche Products Ltd	**The atezolizumab combination would only be considered as a treatment option for people who are well enough** The ACD states in Section 3.4 *"The Cancer Drugs Fund clinical lead confirmed that only people with an Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1 would have atezolizumab plus bevacizumab, carboplatin and paclitaxel. This is because atezolizumab and bevacizumab are being added to chemotherapy and the dose of carboplatin would be higher (area under the curve [AUC] 6) than usually used in clinical practice."* This is in line with the IMPower 150 study population and our anticipated marketing authorisation. Only people with an ECOG performance status of 0 or 1 were recruited in IMpower 150 and this is expected to be reflected in the anticipated marketing authorisation for the atezolizumab combination.	Thank you for your comment. During the appraisal, the committee considered the ECOG performance status of people who could receive atezolizumab plus bevacizumab, carboplatin and paclitaxel in clinical practice (see section 3.4 of the FAD). The committee concluded that atezolizumab plus bevacizumab, carboplatin and paclitaxel would only be considered as a treatment option for people who are well enough.
9	Consultee (company)	Roche Products Ltd	**Atezolizumab combination as a treatment option for people with brain metastases.** The ACD states in Section 3.4 *"The clinical experts noted that atezolizumab plus bevacizumab,*	Thank you for your comment. During the

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			carboplatin and paclitaxel would not be a treatment option for people with brain metastases." We would like to highlight that this statement is neither consistent with results from IMpower 150, nor with published literature. The IMpower150 protocol allowed the inclusion of patients with a history of treated asymptomatic central nervous system (CNS) metastases, provided they meet specific criteria (7). A limited number of these patients were however included in IMpower150 and therefore a subgroup analysis of efficacy results for patients with CNS metastases is not available. In addition, several recent studies have shown no additional safety issues for NSCLC patients with asymptomatic brain metastases, including no increase in bleeding events (8-10). An evidence-based review has demonstrated that there is no significantly increased risk of CNS haemorrhage in patients with NSCLC receiving anti-VEGF therapy (11). Several studies have also shown similar efficacy between NSCLC patients with or without brain metastases, when treated with chemotherapy in combination with bevacizumab, including the prospective BRAIN study (12-14). Importantly, all three UK-practicing clinical experts we consulted with confirmed that they believe patients with asymptomatic CNS metastases should be eligible for treatment with the atezolizumab combination. Despite the lack of direct data for this group of patients, clinical experts agreed that the principal of treating this group of patients as per the IMpower 150 protocol is appropriate, based on the historical benefit / risk profile for these patients. The three experts consulted were happy for their names to be provided in this response; Dr Sanjay Popat, Dr Tom Newsom-Davies, Dr Riyaz Shah.	appraisal the committee considered the population who could receive atezolizumab plus bevacizumab, carboplatin and paclitaxel in clinical practice (see section 3.4 of the FAD). Reference to atezolizumab plus bevacizumab, carboplatin and paclitaxel as a treatment option for people with brain metastases has been not been included in the FAD. The committee concluded that atezolizumab plus bevacizumab, carboplatin and paclitaxel would only be considered as a treatment option for people who are well enough.
10	Consultee (company)	Roche Products Ltd	**Updated PAS for bevacizumab** An updated PAS for bevacizumab has been submitted and is considered within our ACD response. The level of discount for bevacizumab in the updated PAS is a [redacted] discount from list price.	Thank you for your comment. During the appraisal, the committee considered the results that included the updated PAS for bevacizumab (see section 3.22 of the FAD).
11	Consultee (company)	Roche Products Ltd	**Updated Roche base case** The assumptions used in the updated Roche base-case are outlined below:	Thank you for your comments. The

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All changes included in the ERG preferred base-case are incorporated
The inconsistency identified in the ERG model is accounted for (see comment 6)
The NICE-preferred assumption that only immunotherapies are subsequent therapies after treatment with pemetrexed plus carboplatin or cisplatin and pemetrexed maintenance is included. The proportion of patients receiving each therapy is informed by UK market share data (6) (pembrolizumab 69%, atezolizumab 31%).
The updated Roche base-case uses a range of 46.6%-60% of patients receiving subsequent therapy

Roche do not agree with the NICE-preferred assumption that between 30% and 60% of people have subsequent therapy
Our estimates for the proportion of patients receiving subsequent therapy are based on committee discussions in the ACD for this appraisal, the recent precedent from the NICE Committee D decision for pembrolizumab with pemetrexed and platinum chemotherapy for untreated, metastatic, non-squamous NSCLC (TA557) as well as other relevant estimates (see comment 4 for more details)

The ICERs from the updated Roche base-case are presented in Table 1 - Table 2. The upper and lower end of the range of the proportion of patients receiving subsequent therapy is used (46.6% and 60%), to demonstrate the range of resulting ICERs from the economic model.

Table 1: Updated base-case results: Atezo+Bev+CP vs. pemetrexed plus platinum plus pemetrexed maintenance – list price
<table>
<tr><th></th><th>ICER</th><th>Rationale</th></tr>
<tr><td colspan="3">46.6% of patients treated with subsequent therapy</td></tr>
<tr><td>ITT</td><td>[redacted]</td><td rowspan="3">Recent precedent from NICE NICE TA557</td></tr>
<tr><td>PD-L1 low/negative</td><td>[redacted]</td></tr>
<tr><td>EGFR/ALK positive</td><td>[redacted]</td></tr>
<tr><td colspan="3">60% of patients treated with subsequent therapy</td></tr>
<tr><td>ITT</td><td>[redacted]</td><td rowspan="3">Higher end of estimates mentioned during NICE committee meeting for ID1210</td></tr>
<tr><td>PD-L1 low/negative</td><td>[redacted]</td></tr>
<tr><td>EGFR/ALK positive</td><td>[redacted]</td></tr>
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ICER, incremental cost-effectiveness ratio; ITT, intention to treat
</td><td>company’s revised cost-effectiveness analysis was considered by the committee during the appraisal. The committee considered the ICERs from the company’s revised base case for the ITT population including 46.6% of people receiving subsequent therapy, recalculated by the ERG to include the commercial arrangements for atezolizumab, bevacizumab, pemetrexed maintenance and pembrolizumab (which are confidential so the ICERs cannot be reported here). The company’s base-case ICER comparing atezolizumab plus bevacizumab, carboplatin and paclitaxel with pemetrexed plus carboplatin or cisplatin with pemetrexed maintenance was within £50,000 per quality-adjusted life year (QALY) gained for the ITT population. The</td></tr>
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<tr><td></td><td></td><td></td><td>
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ICER, incremental cost-effectiveness ratio; ITT, intention to treat

At list price for all comparators and therapies included in the treatment pathway, [redacted]. At PAS price for atezolizumab and bevacizumab and list price for all comparators (and therapies in the treatment pathway) Atezo+Bev+CP either dominates pemetrexed plus platinum plus pemetrexed maintenance or has an ICER of £1,282 - £16,389, well below the cost-effectiveness threshold for end-of-life therapies. Therefore, at PAS price, Atezo+Bev+CP demonstrates a clinically- and cost-effective treatment option for the NHS.

The same conclusion can be drawn when we apply our assumptions for the confidential discount of pemetrexed maintenance and pembrolizumab as a subsequent therapy. Atezo+Bev+CP remains a clinically- and cost-effective treatment option compared to pemetrexed-based chemotherapy for patients with untreated metastatic non-squamous NSCLC. ICERs are below the cost-effectiveness threshold for end-of-life therapies in both in the ITT population as well as in relevant subgroups of interest (i.e. patients with low/negative PD-L1 expression and patients with EGFR/ALK+ NSCLC).

Therefore, Atezo+Bev+CP represents good value for money to the NHS and should be recommended as an additional treatment option for untreated metastatic non-squamous NSCLC patients who do not have routine access to a cancer immunotherapy (i.e. patients who are not eligible for treatment with pembrolizumab monotherapy), including EGFR/ALK positive patients who
</td><td>committee concluded that the company's base case was appropriate for decision making (see section 3.22 of the FAD).</td></tr>
</table>

Comment number	Type of stakeholder	Organisation name	Stakeholder comment Please insert each new comment in a new row	NICE Response Please respond to each comment
			have progressed on appropriate TKI therapies.	

Document processed	Organisation name – Stakeholder or respondent	Disclosure on tobacco funding / links	Number of comments extracted	Comments

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NICE National Institute for Health and Care Excellence

Atezolizumab in combination for treating advanced non-squamous non-small-cell lung cancer [ID1210]

Consultation on the appraisal consultation document – deadline for comments 5pm on Monday 4 March 2019 **email:** TACommD@nice.org.uk/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**
Disclosure Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	**N/A**
Name of commentator person completing form:	**Eleftherios Sideris**

Atezolizumab in combination for treating advanced non-squamous non-small-cell lung cancer [ID1210]

Consultation on the appraisal consultation document – deadline for comments 5pm on Monday 4 March 2019 **email:** TACommD@nice.org.uk/NICE DOCS

Comment number	Comments
	Roche are disappointed with the negative preliminary NICE recommendation for appraisal [ID1210]. Our response to the negative ACD is provided in this document, and addresses: • factual inaccuracies and clarifications in the ACD document • more importantly, key concerns regarding: i. the relevance of the ITT analysis versus subgroup-specific analyses ii. statements and conclusions in the ACD for the ERFG/ALK positive data from our clinical study and the long-term OS estimates from the economic model for this population iii. the NICE-preferred assumptions for the proportion of patients receiving subsequent therapies.
1	**Relevance of ITT analysis versus subgroup-specific analyses** Before providing our responses to the statements and conclusions in the ACD for the EGFR- or ALK-positive subgroup, we want to highlight that we believe the primary focus of the NICE committee should not be on the subgroup-specific analyses. Rather, the NICE committee should be focusing on the ITT-level comparison of Atezo+Bev+CP versus pemetrexed plus platinum plus pemetrexed maintenance. The ITT comparison is a much more robust and appropriate analysis to inform NICE's decision-making, based on the fact that the ITT population: (i) provides larger patient numbers and greater statistical power in study IMPower 150, (ii) provides a more robust NMA to derive relative effect estimates versus pemetrexed-based chemotherapy, without relying on subgroup-specific assumptions and (iii) reflects the marketing authorisation for the atezolizumab combination in this indication. The ITT analysis demonstrates that the atezolizumab combination is a clinically- and cost-effective treatment option compared to pemetrexed-based chemotherapy for patients with untreated metastatic non-squamous NSCLC. Atezo+Bev+CP should therefore be recommended as an additional treatment option for untreated metastatic non-squamous NSCLC patients who do not have routine access to a cancer immunotherapy (i.e. patients with low/negative PD-L1 expression and patients with EGFR/ALK+ NSCLC). The subgroup-specific analyses and economic model results should be seen as complementary and supportive in nature; they provide additional evidence to explicitly demonstrate the clinical- and cost-effectiveness of Atezo+Bev+CP in these subgroups.

Atezolizumab in combination for treating advanced non-squamous non-small-cell lung cancer [ID1210]

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2	**EGFR- or ALK-positive metastatic non-squamous NSCLC population** **<u>Size of population and grouping of EGFR- and ALK-positive patients</u>** The ACD states in Section 3.9 *"The committee concluded that the EGFR- or ALK-positive NSCLC subgroup in IMpower150 was small, there was no biological reason for combining the groups and the survival data were immature. These factors substantially add to the uncertainty about survival."* Whilst we acknowledge that the EGFR- or ALK-positive NSCLC subgroup in IMpower150 is small, the numbers in the study (~8% EGFR-positive and ~3% ALK-positive) are aligned with mutation rates seen in UK clinical practice (1). We also consider that it is realistic for these patients to be combined, as both are NSCLC adenocarcinomas with driver mutations, and these patients have similar clinical characteristics such as younger age and being predominantly non-smokers (2). Importantly, combining these two subgroups provides additional statistical power, reduces uncertainty and therefore is a more robust basis for decision-making, compared to assessing EGFR- and ALK-positive patients separately. In addition, the grouped EGFR/ALK positive patient population represents patients with an unmet need for a CIT option following targeted therapies. Therefore, grouping these patients is reasonable, appropriate and very relevant from a reimbursement perspective as well. More importantly however, we do not believe that the primary focus of the NICE committee should be the subgroup-specific analyses. Rather, the NICE committee should be focusing on the ITT-level comparison of Atezo+Bev+CP versus pemetrexed plus platinum plus pemetrexed maintenance. The ITT comparison is a much more robust and appropriate analysis to inform NICE's decision-making (see comment 1 for more details). This is also consistent with previous NICE appraisals of atezolizumab and pembrolizumab in previously treated NSCLC (3) (4), where despite the fact that EGFR/ALK positive patients were included in the ITT study population and in the NICE recommendation, no economic analyses specific to the EGFR/ALK positive subgroup were used or requested to inform decision-making. In terms of efficacy in patients with EGFR/ALK positive non-squamous NSCLC, study IMpower 150 demonstrated that the Atezo+Bev+CP combination showed a clinically and statistically significant reduction in death of 46% for these patients (HR=0.54, CI: 0.29,1.03). This is clinically important as the only remaining option for these patients after targeted therapies is chemotherapy alone, which yields sub-standard results. Importantly, study IMpower 150 also showed that the atezolizumab combination demonstrates a clinical benefit in the EGFR- and ALK- positive patient populations independently, with the point estimates for the OS HR being [redacted] (see

Figure **1** below). The forest plot in

Figure **1** also demonstrates that the uncertainty in the estimates increases when smaller subgroups of patients are being assessed, therefore justifying the approach of combining EGFR and ALK positive patients to reduce uncertainty in the efficacy estimates.

Figure 1: [redacted]

Notably, the clinical significance of the efficacy results, as well as the unmet need in the EGFR/ALK positive population were recognised by the MHRA which awarded an EAMS for the atezolizumab combination in this population in December 2018, and also by the EMA which has included the EGFR/ALK positive population in their positive CHMP opinion for the Atezo+Bev+CP combination.

Survival data for EGFR- and ALK-positive patients

In Section 3.9 the ACD also states that survival data are immature for the EGFR/ALK positive population. Whilst we acknowledge that this is true, we would like to point out that the ACD does not recognise or mention the fact that we have used the most conservative approach when extrapolating these data, and model long-term OS in our evidence submission for this subgroup. This conservative approach aimed to ensure that the long-term OS estimates for EGFR/ALK positive patients are as credible, relevant and appropriate as possible for NICE's decision-making. Please see more details on our approach to the long-term survival estimates for the EGFR- and ALK-positive subgroup in comment 3.

	It should also be noted that the median follow-up in the EGFR/ALK positive subgroup is similar to the ITT population of the study; 18.6 months for the EGFR/ALK positive patients and 19.7 months for the ITT population.
3	**Extrapolating overall survival data in EGFR- or ALK-positive population** The ACD states in Section 3.16 *"The committee agreed that the long-term overall survival estimates from the company's model were too high and not credible. But, a difference of around 8% to 10% between the long-term overall survival estimates for people who had atezolizumab with bevacizumab, carboplatin and paclitaxel and people who had pemetrexed plus carboplatin or cisplatin and pemetrexed maintenance was plausible. The committee concluded that the company's estimates of long-term overall survival for people with EGFR- or ALK-positive NSCLC were too high and not credible. It accepted that atezolizumab plus bevacizumab, carboplatin and paclitaxel increased overall survival but by how much was uncertain."* We would like to note that the ACD does not acknowledge the fact that in the company model, when extrapolating the OS data for the EGFR/ALK positive population, we have used one of the most conservative parametric models, in order to provide long-term OS estimates in our evidence submission for this subgroup that are as credible as possible. Other parametric extrapolations (Log-logistic, General Gamma) provide a much higher 5-year OS for Atezo+Bev+CP, ranging from 35%-42%. It should therefore be acknowledged that we made every possible effort to use the most conservative OS extrapolation for this subgroup, and produce long-term OS estimates that are relevant and appropriate as a basis for decision-making. In addition, in the ERG approach and NICE preferred base-case in the ACD, the relative effect from the ITT NMA is used to model long-term survival for subgroups, i.e. the PD-L1 low/negative and the EGFR/ALK positive population. Roche agrees with this approach, and this effectively represents an even more conservative way to model survival for EGFR/ALK positive patients, as the more modest relative treatment effect from the ITT population is used to inform long-term OS for this subgroup, instead of the more pronounced clinical benefit demonstrated specifically in EGFR/ALK positive patients. Moreover, the ACD does not make any reference to the 5-year OS estimates for the pemetrexed-based chemotherapy arm in the economic models (both from the company and the ERG). In the ERG base-case, which was used as the basis for the NICE-preferred analysis, the 5-year OS for EGFR/ALK positive patients in the pemetrexed-based chemotherapy arm is 16% (versus 26% for the atezolizumab combination). This is consistent with the committee discussions and clinical expert opinion in the meeting, as documented in the ACD (Section 3.16), that *"a difference of around 8% to 10% between the long-term overall survival estimates for people who had*

	atezolizumab with bevacizumab, carboplatin and paclitaxel and people who had pemetrexed plus carboplatin or cisplatin and pemetrexed maintenance was plausible". Therefore, we believe that the OS estimates for EGFR/ALK positive patients in the ERG base-case and in the NICE-preferred analysis are conservative, credible, in line with clinical expert estimates and appropriate to inform NICE's decision-making. More importantly however, as clearly outlined in comment number 1, we do not believe that the primary focus of the NICE committee should be the subgroup-specific analyses. Rather, the NICE committee should be focusing on the ITT-level comparison of Atezo+Bev+CP versus pemetrexed plus platinum plus pemetrexed maintenance. The ITT analysis demonstrates that the atezolizumab combination is a clinically- and cost-effective treatment option compared to pemetrexed-based chemotherapy. The subgroup-specific analyses and economic model results (for patients with low/negative PD-L1 expression and patients with EGFR/ALK+ NSCLC) should only be seen as complementary and supportive in nature, demonstrating that the ITT results are confirmed explicitly within these patient subgroups.
4	**Proportion treated with subsequent therapy** The ACD states in Section 3.20 *"The committee concluded that the assumption that 100% of people would have subsequent therapy did not reflect clinical practice and accepted that the appropriate proportion of people was much lower"* and in Section 3.25 *"The committee took into account its preferred assumptions that differed from the ERG's base case… assuming between 30% and 60% of people have subsequent therapy"* Whilst we agree that the assumption that 100% of people would have subsequent therapy does not reflect clinical practice, we want to highlight that the proportion of patients treated with subsequent therapy in the NICE-preferred base-case (between 30% and 60% of patients) is not consistent with the committee discussions in this appraisal (Section 3.20 of ACD), with estimates from other sources, as well as with recent precedent from the NICE Committee D decision for pembrolizumab with pemetrexed and platinum chemotherapy for untreated, metastatic, non-squamous NSCLC (TA557) (5). In particular, we believe that the lower end of the NICE-preferred range of patients being treated with subsequent therapy (30% of patients) is unreasonably low and not consistent with the committee discussions summarised in the ACD (Section 3.20), where for the standard-of-care arm: • *"The clinical experts explained that no more than 60% of people would be well enough to have subsequent therapy."*

- *"The Cancer Drugs Fund clinical lead estimated this to be no more than 50%"*
- *"The committee was aware that in previous technology appraisals for ALK-positive NSCLC, clinical experts estimated that 50% of people whose disease had progressed while taking alectinib would have subsequent therapy"*

The only estimate within the ACD mentioning a lower proportion of patients receiving subsequent therapy, explicitly refers to patients after the atezolizumab combination: *"They estimated that 30% to 40% of people would have subsequent therapy after atezolizumab plus bevacizumab, carboplatin and paclitaxel in the larger centres but noted this estimate would be much lower in smaller centres."*

Importantly, this proportion of 30% receiving subsequent therapy is also not consistent with the recent NICE Committee D decision for pembrolizumab with pemetrexed and platinum chemotherapy for untreated, metastatic, non-squamous NSCLC (TA557) (5) where 46.6% of patients in the standard-of-care arm were considered to receive subsequent therapy. We believe that this discrepancy seems unfair and unreasonable, and does not promote consistent decision-making in a highly competitive therapy area.

In addition, the estimates from other sources on the proportion of NSCLC patients receiving subsequent therapy are much higher than 30%:

- 55%: the estimate from NICE and NHS England during the budget impact discussions for this appraisal
- 53%: estimate based on UK market research data (Kantar Health NSCLC tracker, Q4 2018 (6)

Therefore, by taking into account the lower and higher end of these estimates above, we consider that the appropriate range of patients treated with subsequent therapy should be 46.6%-60% instead of 30%-60%.

Clinical expert opinion in the ACD for the current appraisal (ID1210), as well as precedent from previous NICE appraisals (NICE TA557) (5), have confirmed that the proportion of patients treated with subsequent chemotherapy following first-line treatment with cancer immunotherapy should be assumed to be lower, compared to the proportion being treated in second-line following standard-of-care chemotherapy as a first-line option. However, for simplicity in the updated Roche base-case in our ACD response, we have assumed that the proportion being treated with subsequent therapy is the same regardless of first-line treatment. This should be viewed as a conservative assumption, as it assigns higher subsequent therapy costs to the atezolizumab combination arm; the impact on economic results however is anticipated to be limited.

Atezolizumab in combination for treating advanced non-squamous non-small-cell lung cancer [ID1210]

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5	**Appropriate subsequent therapy options** The ACD states in Section 3.5 "The committee concluded that docetaxel would be offered as a subsequent therapy after atezolizumab plus bevacizumab, carboplatin and paclitaxel for people who are well enough to have further lines of therapy", in Section 3.6 "The committee concluded that the next line of treatment after pemetrexed plus carboplatin or cisplatin with or without pemetrexed maintenance is an immunotherapy monotherapy" and in Section 3.21 *"The committee heard that because nivolumab is recommended in the Cancer Drugs Fund and not routinely commissioned in the NHS in England, it should not be considered in decision making. The Cancer Drugs Fund clinical lead and the clinical experts explained that after treatment with pemetrexed plus carboplatin or cisplatin with or without pemetrexed maintenance people would have an immunotherapy (see section 3.6). Therefore, nivolumab and docetaxel were not considered to be appropriate subsequent therapies to be included in the analysis. The committee concluded that including nivolumab and docetaxel as options for subsequent therapy after treatment with pemetrexed plus carboplatin or cisplatin with or without pemetrexed maintenance was not appropriate for decision making."* We agree with the NICE-preferred assumptions in the ACD that the appropriate subsequent therapy: • following the atezolizumab combination is docetaxel and • following pemetrexed plus carboplatin or cisplatin with or without pemetrexed maintenance is an immunotherapy monotherapy (either pembrolizumab or atezolizumab) Our updated base-case reflects the above assumptions. We used UK market research data (Kantar Health NSCLC tracker, Q4 2018 (6)) to inform the proportion of patients treated with an immunotherapy monotherapy (either pembrolizumab or atezolizumab) following pemetrexed-based chemotherapy: 69% would receive pembrolizumab and 39% atezolizumab as a subsequent therapy.
6	**ERG model inconsistency** We want draw the attention of the NICE technical team to an inconsistency we have identified in the ERG model. When applying the ERG changes to our company model (by changing the model switches in "Model Inputs" worksheet, cells J5 and L5), the price for pembrolizumab as a subsequent therapy is hard-coded (cell E47 of worksheet "Post disc. therapy cost"), therefore not being updated when changing the level of discount in the "Cost Inputs" worksheet. We have accounted for this error in the revised ERG economic model, based on which we have run our additional analyses. The revised ERG economic model is sent as a separate file alongside our

	ACD response.
7	**Continued treatment effect for pemetrexed maintenance** The ACD states in Section 3.20 *"A lifetime continued treatment effect for pemetrexed maintenance, even after treatment is stopped, is not supported by any evidence" and "The committee heard that including a lifetime continued effect of pemetrexed maintenance in the economic model was likely to overestimate the long-term survival gain for atezolizumab plus bevacizumab, carboplatin and paclitaxel and pemetrexed plus carboplatin or cisplatin and pemetrexed maintenance. The committee was aware that this led to the incremental cost-effectiveness ratio (ICER) for atezolizumab plus bevacizumab, carboplatin and paclitaxel compared with pemetrexed plus carboplatin or cisplatin without pemetrexed maintenance being underestimated."* We would like to highlight that the assumption on whether pemetrexed maintenance has a continued effect or not does not impact the ICER for the comparison of interest to decision-making in ID1210, i.e. Atezo+Bev+CP versus pemetrexed plus platinum plus pemetrexed maintenance. In the ERG base-case and in the NICE-preferred analysis, the network of studies excluding PARAMOUNT is included in the NMA; this is something that Roche finds reasonable and pragmatic. Using this network, only the comparison of Atezo+Bev+CP to pemetrexed plus platinum plus pemetrexed maintenance is feasible. For the comparison to the regimen without pemetrexed maintenance there is no connected network of studies; therefore, the assumption of whether pemetrexed maintenance has a continued effect is not relevant in the NICE-preferred analysis. But even if all comparators were considered through an appropriate connected network, this assumption of continued treatment effect for pemetrexed maintenance would only impact the ICERs of Atezo+Bev+CP and pemetrexed plus platinum plus pemetrexed maintenance compared to the pemetrexed without pemetrexed maintenance regimen. This is consistent with what is stated in the ACD. However, the comparison of interest for this appraisal (Atezo+Bev+CP versus pemetrexed plus platinum plus pemetrexed maintenance) would not be affected, as the relative effect between these two comparators would still remain unchanged.
8	**The atezolizumab combination would only be considered as a treatment option for people who are well enough** The ACD states in Section 3.4 *"The Cancer Drugs Fund clinical lead confirmed that only people with an Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1 would have atezolizumab plus bevacizumab, carboplatin and paclitaxel. This is because atezolizumab and bevacizumab are being added to chemotherapy and the dose of carboplatin would be higher (area*

	under the curve [AUC] 6) than usually used in clinical practice." This is in line with the IMPower 150 study population and our anticipated marketing authorisation. Only people with an ECOG performance status of 0 or 1 were recruited in IMpower 150 and this is expected to be reflected in the anticipated marketing authorisation for the atezolizumab combination.
9	**Atezolizumab combination as a treatment option for people with brain metastases.** The ACD states in Section 3.4 *"The clinical experts noted that atezolizumab plus bevacizumab, carboplatin and paclitaxel would not be a treatment option for people with brain metastases."* We would like to highlight that this statement is neither consistent with results from IMpower 150, nor with published literature. The IMpower150 protocol allowed the inclusion of patients with a history of treated asymptomatic central nervous system (CNS) metastases, provided they meet specific criteria (7). A limited number of these patients were however included in IMpower150 and therefore a subgroup analysis of efficacy results for patients with CNS metastases is not available. In addition, several recent studies have shown no additional safety issues for NSCLC patients with asymptomatic brain metastases, including no increase in bleeding events (8-10). An evidence-based review has demonstrated that there is no significantly increased risk of CNS haemorrhage in patients with NSCLC receiving anti-VEGF therapy (11). Several studies have also shown similar efficacy between NSCLC patients with or without brain metastases, when treated with chemotherapy in combination with bevacizumab, including the prospective BRAIN study (12-14). Importantly, all three UK-practicing clinical experts we consulted with confirmed that they believe patients with asymptomatic CNS metastases should be eligible for treatment with the atezolizumab combination. Despite the lack of direct data for this group of patients, clinical experts agreed that the principal of treating this group of patients as per the IMpower 150 protocol is appropriate, based on the historical benefit / risk profile for these patients. The three experts consulted were happy for their names to be provided in this response; Dr Sanjay Popat, Dr Tom Newsom-Davies, Dr Riyaz Shah.
10	**Updated PAS for bevacizumab** An updated PAS for bevacizumab has been submitted and is considered within our ACD response. The level of discount for bevacizumab in the updated PAS is a [redacted] discount from list price.
11	**Updated Roche base case** The assumptions used in the updated Roche base-case are outlined below: • All changes included in the ERG preferred base-case are incorporated

- The inconsistency identified in the ERG model is accounted for (see comment 6)
- The NICE-preferred assumption that only immunotherapies are subsequent therapies after treatment with pemetrexed plus carboplatin or cisplatin and pemetrexed maintenance is included. The proportion of patients receiving each therapy is informed by UK market share data (6) (pembrolizumab 69%, atezolizumab 31%).
- The updated Roche base-case uses a range of 46.6%-60% of patients receiving subsequent therapy
    - Roche do not agree with the NICE-preferred assumption that between 30% and 60% of people have subsequent therapy
    - Our estimates for the proportion of patients receiving subsequent therapy are based on committee discussions in the ACD for this appraisal, the recent precedent from the NICE Committee D decision for pembrolizumab with pemetrexed and platinum chemotherapy for untreated, metastatic, non-squamous NSCLC (TA557) as well as other relevant estimates (see comment 4 for more details)

The ICERs from the updated Roche base-case are presented in Table 1 - Table 2. The upper and lower end of the range of the proportion of patients receiving subsequent therapy is used (46.6% and 60%), to demonstrate the range of resulting ICERs from the economic model.

Table 1: Updated base-case results: Atezo+Bev+CP vs. pemetrexed plus platinum plus pemetrexed maintenance – list price

	ICER	Rationale
46.6% of patients treated with subsequent therapy		
ITT	[redacted]	Recent precedent from NICE NICE TA557
PD-L1 low/negative	[redacted]	
EGFR/ALK positive	[redacted]	
60% of patients treated with subsequent therapy		
ITT	[redacted]	Higher end of estimates mentioned during NICE committee meeting for ID1210
PD-L1 low/negative	[redacted]	
EGFR/ALK positive	[redacted]	

ICER, incremental cost-effectiveness ratio; ITT, intention to treat

Table 2: Updated base-case results: Atezo+Bev+CP vs. pemetrexed plus platinum plus pemetrexed maintenance – with PAS for atezolizumab and bevacizumab and list price for relevant comparators

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PD-L1 low/negative	Dominant	
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ICER, incremental cost-effectiveness ratio; ITT, intention to treat

At list price for all comparators and therapies included in the treatment pathway, [redacted]. At PAS price for atezolizumab and bevacizumab and list price for all comparators (and therapies in the treatment pathway) Atezo+Bev+CP either dominates pemetrexed plus platinum plus pemetrexed maintenance or has an ICER of £1,282 - £16,389, well below the cost-effectiveness threshold for end-of-life therapies. Therefore, at PAS price, Atezo+Bev+CP demonstrates a clinically- and cost-effective treatment option for the NHS.

The same conclusion can be drawn when we apply our assumptions for the confidential discount of pemetrexed maintenance and pembrolizumab as a subsequent therapy. Atezo+Bev+CP remains a clinically- and cost-effective treatment option compared to pemetrexed-based chemotherapy for patients with untreated metastatic non-squamous NSCLC. ICERs are below the cost-effectiveness threshold for end-of-life therapies in both in the ITT population as well as in relevant subgroups of interest (i.e. patients with low/negative PD-L1 expression and patients with EGFR/ALK+ NSCLC).

Therefore, Atezo+Bev+CP represents good value for money to the NHS and should be recommended as an additional treatment option for untreated metastatic non-squamous NSCLC patients who do not have routine access to a cancer immunotherapy (i.e. patients who are not eligible for treatment with pembrolizumab monotherapy), including EGFR/ALK positive patients who have progressed on appropriate TKI therapies.

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.

Note: We reserve the right to summarise and edit comments received during consultations, or not to publish them at all, if we consider the comments are too long, or publication would be unlawful or otherwise inappropriate.

Comments received during our consultations are published in the interests of openness and transparency, and to promote understanding of how recommendations are developed. The comments are published as a record of the comments we received, and are not endorsed by NICE, its officers or advisory committees.

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Evidence Review Group Report commissioned by the NIHR HTA Programme on behalf of NICE

Atezolizumab in combination for treating advanced non-squamous non-small-cell lung cancer

ERG response to Roche's comments on the ACD

Contains Patient Access Scheme discount prices for atezolizumab and bevacizumab only

Produced by Southampton Health Technology Assessments Centre (SHTAC)

Correspondence to Dr Jonathan Shepherd
Southampton Health Technology Assessments Centre (SHTAC)
Wessex Institute
Alpha House
Enterprise Road, University of Southampton Science Park
Southampton SO16 7NS
www.southampton.ac.uk/shtac

Date completed **13th March 2019**

This document is a response by the ERG to some of the comments made by the company, Roche, on the Appraisal Consultation Document (ACD) issued by NICE in February 2019 for the appraisal of Atezolizumab in combination for treating advanced non-squamous non-small-cell lung cancer [ID1210].

Proportion of patients treated with subsequent therapy

In their response to the ACD the company argue that, instead of the appraisal committee's estimate of 30%-60% of patients receiving subsequent treatment, the range should be between 46.6% and 60%.

The company states that the ACD refers to estimates between 50-60% of patients receiving subsequent treatment from clinical experts and the Cancer Drugs Fund clinical lead. Further, the clinical experts estimated that 30-40% of patients would have subsequent therapy after atezolizumab plus bevacizumab, carboplatin and paclitaxel in larger treatment centres but noted this estimate would be much lower in smaller centres.

The company argues that this lower estimate for subsequent treatment is not consistent with the most recent appraisal of pembrolizumab with pemetrexed and platinum chemotherapy for untreated, metastatic, non-squamous non-small-cell lung cancer (TA557), where 46.6% of patients in the standard-of-care arm of the KEYNOTE-189 trial received any subsequent treatment. From that appraisal 55% of patients were assumed to receive subsequent treatment by NICE in the budget impact discussion. Further, the estimate of subsequent treatment based on UK market research data was 53%. On this basis the company suggest that the proportion of patients receiving subsequent treatment is between 46.6% and 60%.

The ERG suggests there is much uncertainty in the estimate of the proportion of patients receiving subsequent therapy. It is unclear how representative the IMPower150 and the KEYNOTE-189 trials are of UK clinical practice. We therefore prefer the NICE committee's range of 30-60% and have used this range in our analysis of the company's updated model.

Updated Roche base case

The company updated their base case analyses by:

- accepting all changes included in the ERG preferred base-case,
- including NICE's preferred assumption that only immunotherapies are subsequent therapies after treatment with pemetrexed plus carboplatin or cisplatin and

pemetrexed maintenance (The proportion of patients receiving each therapy is informed by UK market share data: pembrolizumab 69%, atezolizumab 31%).

- Using a range of 46.6% - 60% of patients receiving subsequent therapy,
- Including an updated PAS discount for bevacizumab of [redacted].

The ERG has checked and verified the company's updated base case. The results of the company's updated base case is shown in Table 1 below. For completeness, the ERG has also included the NICE-preferred lower range of 30% subsequent treatment uptake and the uptake in the IMPower150 trial of [redacted]. The results are shown with the PAS price for atezolizumab and bevacizumab only. We have prepared a separate addendum that includes PAS prices for pemetrexed and pembrolizumab. The ICER for the company's updated base case ranges from £1,282 - £13,410 per QALY gained.

Table 1 Reduced uptake of subsequent therapy: ERG base case ITT population (PAS for atezolizumab and bevacizumab only)

Proportion of patients with subsequent therapy	Atezo+Bev+CP		Pem+platinum+Pem maintenance		ICER (£ per QALY)
	Total QALYs	Total costs	Total QALYs	Total costs	
Base case 100%	[redacted]	[redacted]	[redacted]	[redacted]	Dominant
60%	[redacted]	[redacted]	[redacted]	[redacted]	£1,282
46.6%	[redacted]	[redacted]	[redacted]	[redacted]	£13,410
[redacted]%	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
30%	[redacted]	[redacted]	[redacted]	[redacted]	£28,434

In Table 2 below, we test the assumption that for the pemetrexed arm, the proportion of patients on subsequent treatment receiving pembrolizumab and atezolizumab is 50% each, rather than 69% and 31% respectively.

Table 2 ERG scenario analysis – 50% pembrolizumab, 50% atezolizumab

Proportion of patients with subsequent therapy	Atezo+Bev+CP		Pem+platinum+Pem maintenance		ICER (£ per QALY)
	Total QALYs	Total costs	Total QALYs	Total costs	
Base case 100%	[redacted]	[redacted]	[redacted]	[redacted]	Dominant
60%	[redacted]	[redacted]	[redacted]	[redacted]	£6,976
46.6%	[redacted]	[redacted]	[redacted]	[redacted]	£17,833
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
30%	[redacted]	[redacted]	[redacted]	[redacted]	£31,282

For this scenario, the ICERs range from £6,976 to £31,282 per QALY gained for 30% to 60% subsequent treatment uptake.

It should be acknowledged that the above scenarios only adjust the costs, but not the effects on OS, of adjusting the proportion of patients on subsequent treatments. It is not possible to adjust for second-line treatment effects in the company's model. However, for illustrative purposes we conduct an ERG scenario below with costs based on available evidence on subsequent second line treatments used in the Atezo+Bev+CP arm of the IMPower150 trial, and in the pemetrexed+platinum+pemetrexed maintenance arm of the KEYNOTE-189 trial.

Trial based scenario analysis

In this scenario, we apply trial arm-specific proportions for subsequent treatment uptake and include the actual subsequent treatments included in the trial arms. The rationale for doing this scenario was to include consistent assumptions about the costs and survival effects of subsequent treatments. However, it should be acknowledged that this does not entirely reflect actual NHS practice in England as some of the subsequent treatments are not used in practice in these patients.

Our assumptions are as follows:
Atezo+Bev+CP arm [redacted] subsequent treatment uptake with treatments as in CS Table 37:

- pemetrexed plus platinum 63%,
- docetaxel 17%,
- nivolumab 11%,
- bevacizumab 9%

Pemetrexed+platinum+pemetrexed maintenance arm 46.6% subsequent treatment uptake, with values from KEYNOTE-189 trial:

- pemetrexed plus platinum 2.4%,
- single chemotherapy (docetaxel) 2.4%,
- immunotherapy 41.8%
    - atezolizumab 1.5%,
    - nivolumab 6.8%,
    - pembrolizumab 33.5%

The results are shown in Table 3 and show an ICER of [redacted] per QALY.

Table 3 Trial based analysis

Proportion of patients with subsequent therapy	Atezo+Bev+CP		Pem+platinum+Pem maintenance		ICER
	Total QALYs	Total costs	Total QALYs	Total costs	(£ per QALY)
Atezo+Bev+CP: [redacted]% Pemetrexed arm: 46.6%	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

ERG model inconsistency

The company highlights an inconsistency in the way that the price for pembrolizumab is included in the ERG model (comment number 6 (page 8) of the company's response to the ACD). We do not agree with the company's view that this is an inconsistency. The only difference between the ERG and company formulas is 'Cost Inputs'!K31 (ERG model) and 'Cost Inputs'!K18 (new company model). However, since cell K31 is set equal to cell K18, the outputs of these two formulas/models will not differ.

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Evidence Review Group Report commissioned by the NIHR HTA Programme on behalf of NICE

Atezolizumab in combination for treating advanced non-squamous non-small-cell lung cancer

ERG exploratory analysis on OS extrapolations for EGFR/ALK subgroup

Contains Patient Access Scheme discount prices for atezolizumab and bevacizumab only

Produced by Southampton Health Technology Assessments Centre (SHTAC)

Correspondence to Dr Jonathan Shepherd
Southampton Health Technology Assessments Centre (SHTAC)
Wessex Institute
Alpha House
Enterprise Road, University of Southampton Science Park
Southampton SO16 7NS
www.southampton.ac.uk/shtac

Date completed **18th March 2019**

ACD conclusions on survival with EGFR- or ALK-positive NSCLC

The Appraisal Consultation Document (ACD) for the NICE appraisal of atezolizumab in combination with bevacizumab for metastatic non-squamous non-small-cell lung cancer was published in February 2019. The committee concluded that people with EGFR- or ALK-positive disease would benefit from having more treatment options after targeted therapy, but that survival data are limited for this subgroup. The IMpower150 trial only included 41 EGFR- or ALK-positive people randomised to the atezolizumab plus bevacizumab, carboplatin and paclitaxel combination, and only 13 deaths occurred in this group over the median follow up of 18 months (January 2018 data cut).

The committee's preferred functions for extrapolating overall survival, exponential or Weibull, yielded very similar estimates for the EGFR/ALK subgroup: 27% or 26%, respectively, of people surviving to 5 years if treated with the atezolizumab combination compared with 18% (both functions) if treated a conventional pemetrexed combination. However, based on expert opinion, the committee concluded that these estimates were too high, and that more plausible estimates were in the range of 5% to 10% 5-year survival with the pemetrexed combination, and an additional 8% to 10% with the atezolizumab combination (ACD 3.16).

Company response to the ACD

In response, the company makes several points:

- The exponential and Weibull functions for modelling survival in the EGFR/ALK subgroup are both more conservative than the alternative parametric functions tested in the model (log-normal, log-logistic, generalised gamma and Gompertz).
- The committee concluded that the relative effects of treatment in the subgroups should be modelled using the ITT NMA (excluding PARAMOUNT). This yields more conservative results than subgroup-specific NMA results: 5-year EGFR/ALK survival with pemetrexed-based treatment of 16%.
- Thus, the ERG's base case for the EGFR/ALK subgroup - Weibull function for survival with the atezolizumab combination (26% alive at 5 years) and ITT NMA excluding PARAMOUNT to model survival with the pemetrexed combination (16% alive at 5 years) – is consistent with the committee's estimate of a difference of around 8% to 10% in long-term survival.
- The company also argues that the primary focus for the committee should be the ITT-level comparison, rather than the subgroup-specific analyses. They state that the ITT comparison is more robust and note that economic analyses for EGFR/ALK

positive patients were not used to inform decision making in the NICE appraisals of atezolizumab and pembrolizumab in previously treated NSCLC (TA520 and TA531).

ERG view on survival extrapolations for the EGFR/ALK positive subgroup

The ERG broadly agrees with these points. The Weibull and exponential overall survival curves are very similar and more conservative than other fitted distributions in the EGFR/ALK positive subgroup. And the difference between 5-year estimates in our base case model (Weibull function with ITT NMA excluding PARAMOUNT) is around 10% (26% - 16%), which is consistent with one end of the committee's estimated range. However, the estimated survival rate with conventional pemetrexed-based treatment does substantially exceed the expected range of 5% to 10%. The fitted survival curves for the EGFR/ ALK subgroup therefore lack face validity. This is not surprising as the sample of people with EGFR- or ALK-positive disease in the IMpower150 atezolizumab plus bevacizumab study group is very small, with few observed events (ACD 3.9).

Nevertheless, we acknowledge that the committee has expressed a view that the EGFR- or ALK-positive subgroup is distinct, has a need for alternative treatment options, and that it is 'biologically plausible' that the atezolizumab combination would give particular benefits in this group (ACD 3.16). We therefore present a simple sensitivity analysis, adjusting overall survival for atezolizumab combination treatment to illustrate the impact on the ICER.

Illustrative ERG sensitivity analysis for EGFR/ALK survival

We use a simple manual calibration approach: applying an exponential function for overall survival in the atezolizumab arm of the model and varying the assumed hazard rate to obtain projected estimates of survival in the expected range. The exponential function fitted to the IMpower150 EGFR/ALK subgroup data has a hazard of 0.022. With hazards of 0.036 and 0.028, 5-year survival estimates with the pemetrexed combination are approximately 5% and 10%, respectively.

Other committee preferred assumptions are applied, including use of the ITT NMA excluding PARAMOUNT and persistence of relative treatment effects for atezolizumab versus pemetrexed combinations for 5 years (3 years beyond the maximum treatment duration of 2 years) (ACD 3.25).

Survival estimates based on this illustrative sensitivity analysis are shown in Table 1 below, alongside estimates with the committee-preferred exponential and Weibull functions for the ITT population, and PD-L1 low or negative and EGFR/ALK positive subgroups. We also show graphs of selected survival projections for the ITT population (Figure 1, Figure 2 and Figure 5) and the EGFR/ALK positive subgroup (Figure 3, Figure 4 and Figure 6).

Table 1 Five-year survival estimates from company model (post ACD version)

OS distribution	Atezolizumab combination [1]	Pemetrexed combination [2]	Gain in 5-year survival
ITT population			
Exponential	13.1%	6.1%	7.1%
Weibull	9.6%	3.9%	5.7%
PD-L1 less than 50% subgroup			
Exponential	11.8%	5.2%	6.5%
Weibull	7.1%	2.6%	4.6%
EGFR- or ALK- positive subgroup			
Exponential	27.1%	16.5%	10.6%
Weibull	26.4%	15.9%	10.5%
Scenario: hazard 0.028 [3]	18.7%	9.9%	8.8%
Scenario: hazard 0.036 [3]	11.6%	5.1%	6.5%

1 OS distribution for atezo + bev + CP estimated by parametric survival function fitted to patient data in IMpower150 trial.

2 OS distribution for pem + CP with pem maintenance estimated by applying hazard ratio relative to atezo + bev + CP from NMA (fixed effects, ITT excluding PARAMOUNT study)

3 ERG illustrative scenarios with OS distribution for pemetrexed combination estimated to approximate the Committee's plausible assumptions about 5-year survival with pemetrexed combination treatment (5-10%).

Cost-effectiveness results associated with the survival scenarios for the EGFR/ALK positive subgroup are shown in Table 2 below. These estimates are based on the revised version of the company's model submitted with their response to the ACD, which incorporates the committee's preferred assumptions (ACD 3.25).

We adapted this model to enable our illustrative scenario analysis for overall survival, and to include other company base case assumptions for the EGFR/ALK subgroup:

- fully parametric log-normal distribution for progression-free survival (PFS) (CS B.3.3.3 page 112);
- fully parametric exponential distribution for time to treatment discontinuation (TTD) of atezolizumab and bevacizumab (CS B.3.3.4 page 114).

We note that the company have not changed the PFS and TTD distributions for the EGFR/ALK positive subgroup in the results reported in their ACD response (Tables 1 and 2):

instead they use the same distributions as for the ITT analysis (KM + exponential tail for TTD, and KM + log-logistic tail for PFS). This explains why our reported ICERs for the EGFR/ALK subgroup are higher than those reported in the company's ACD response. We also stratify results for a range of assumptions about the proportion of patients who have subsequent therapy, applying the same proportion to both treatment arms, and assuming use of docetaxel only after the atezolizumab combination, and 69% pembrolizumab and 31% atezolizumab after pemetrexed combination treatment. Results in Table 2 include the revised PAS discount for bevacizumab ([redacted]) as well as the PAS discount for atezolizumab ([redacted]), but no discount for pemetrexed or pembrolizumab. Results including all PAS discounts are shown in a separate ERG addendum.

Table 2 Cost-effectiveness: EGFR/ALK (PAS for atezolizumab & bevacizumab only)

	Atezolizumab combination		**Pemetrexed combination**		**ICER** (£ per QALY gained)
	Costs	QALYs	Costs	QALYs	
Proportion of patients receiving subsequent treatment: **20%**					
Exponential	[redacted]	[redacted]	[redacted]	[redacted]	36,569
Weibull	[redacted]	[redacted]	[redacted]	[redacted]	36,963
Scenario: hazard 0.028	[redacted]	[redacted]	[redacted]	[redacted]	40,386
Scenario: hazard 0.036	[redacted]	[redacted]	[redacted]	[redacted]	46,180
Proportion of patients receiving subsequent treatment: **30%**					
Exponential	[redacted]	[redacted]	[redacted]	[redacted]	30,314
Weibull	[redacted]	[redacted]	[redacted]	[redacted]	30,617
Scenario: hazard 0.028	[redacted]	[redacted]	[redacted]	[redacted]	33,270
Scenario: hazard 0.036	[redacted]	[redacted]	[redacted]	[redacted]	37,788
Proportion of patients receiving subsequent treatment: [redacted]					
Exponential	[redacted]	[redacted]	[redacted]	[redacted]	24,685
Weibull	[redacted]	[redacted]	[redacted]	[redacted]	24,905
Scenario: hazard 0.028	[redacted]	[redacted]	[redacted]	[redacted]	26,866
Scenario: hazard 0.036	[redacted]	[redacted]	[redacted]	[redacted]	30,234
Proportion of patients receiving subsequent treatment: **46.6%**					
Exponential	[redacted]	[redacted]	[redacted]	[redacted]	19,931
Weibull	[redacted]	[redacted]	[redacted]	[redacted]	20,082
Scenario: hazard 0.028	[redacted]	[redacted]	[redacted]	[redacted]	21,458
Scenario: hazard 0.036	[redacted]	[redacted]	[redacted]	[redacted]	23,856
Proportion of patients receiving subsequent treatment: **60%**					
Exponential	[redacted]	[redacted]	[redacted]	[redacted]	11,549
Weibull	[redacted]	[redacted]	[redacted]	[redacted]	11,578
Scenario: hazard 0.028	[redacted]	[redacted]	[redacted]	[redacted]	11,922
Scenario: hazard 0.036	[redacted]	[redacted]	[redacted]	[redacted]	12,610

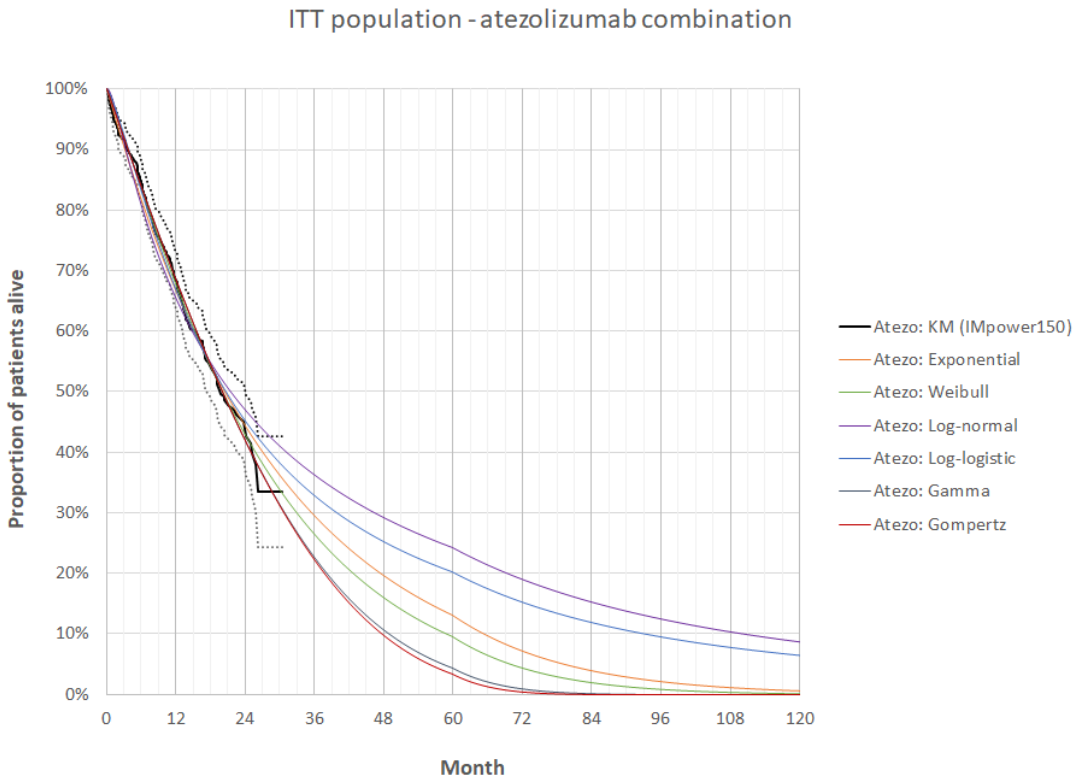

Figure 1 Overall survival for ITT population with atezolizumab combination

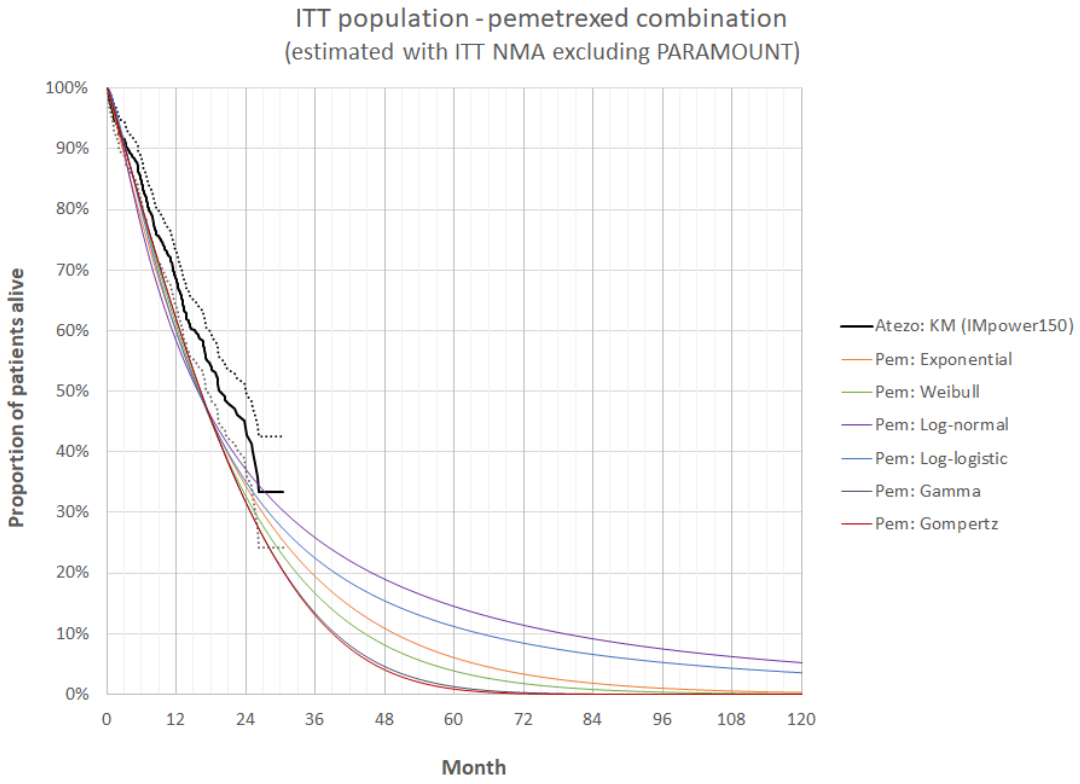

Figure 2 Overall survival for ITT population with pemetrexed combination

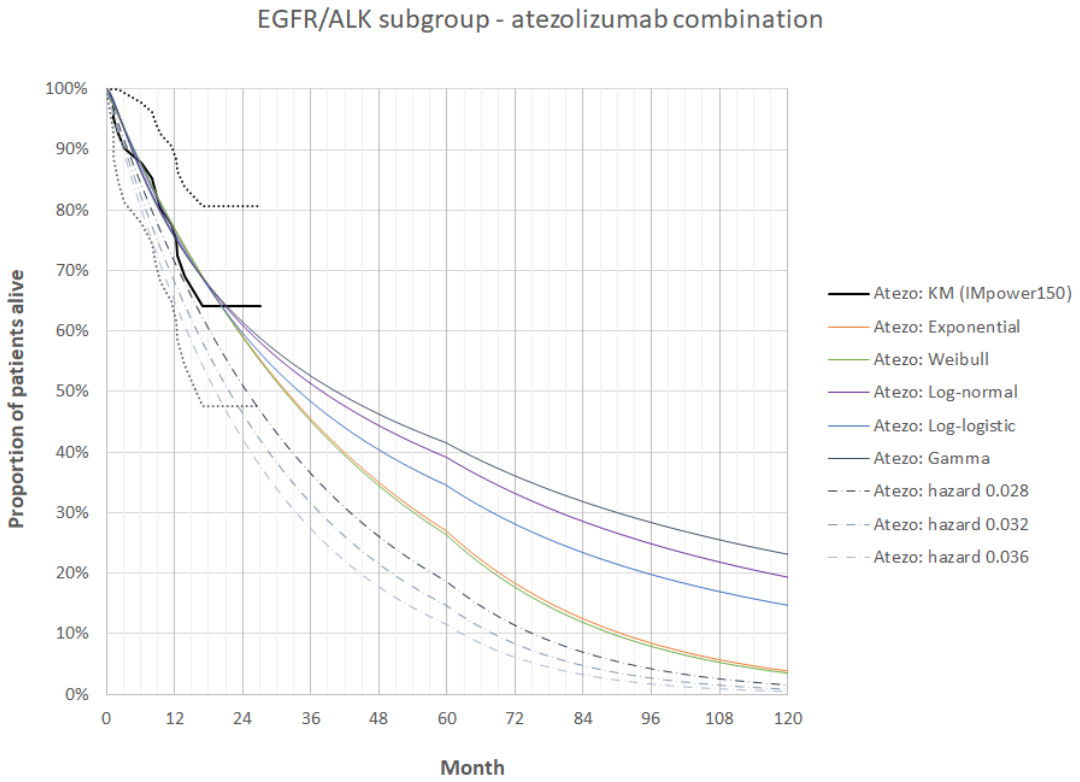

Figure 3 Overall survival for EGFR/ALK subgroup with atezolizumab combination

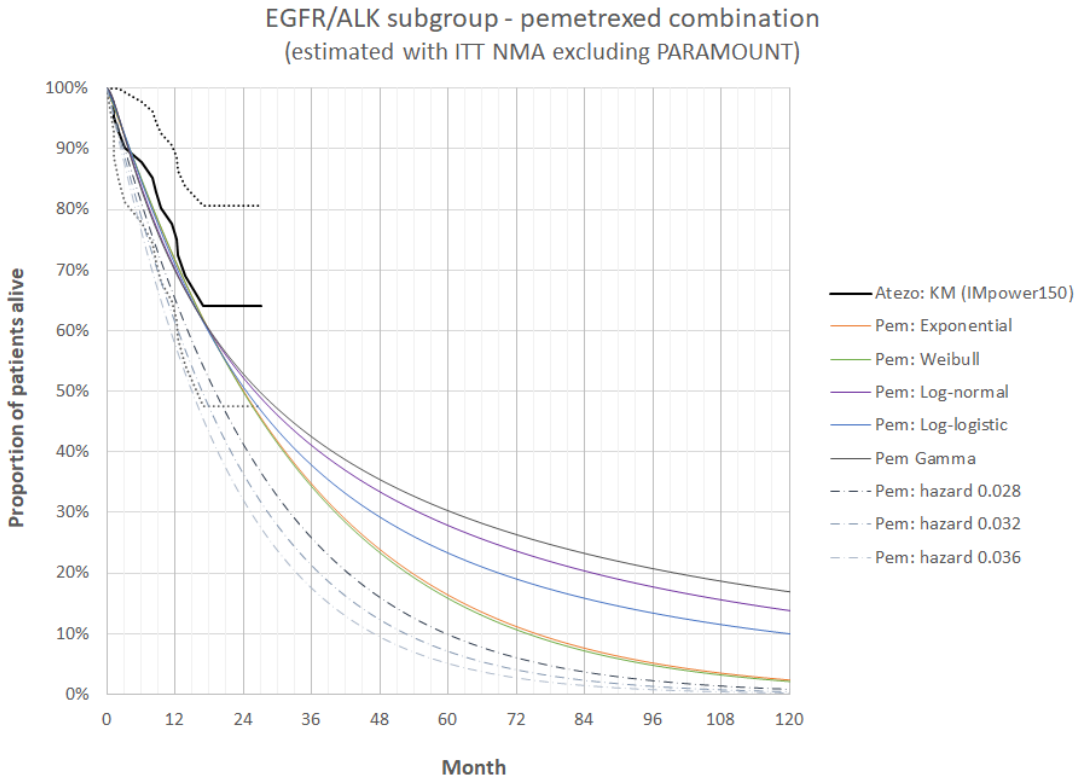

Figure 4 Overall survival for EGFR/ALK subgroup with pemetrexed combination

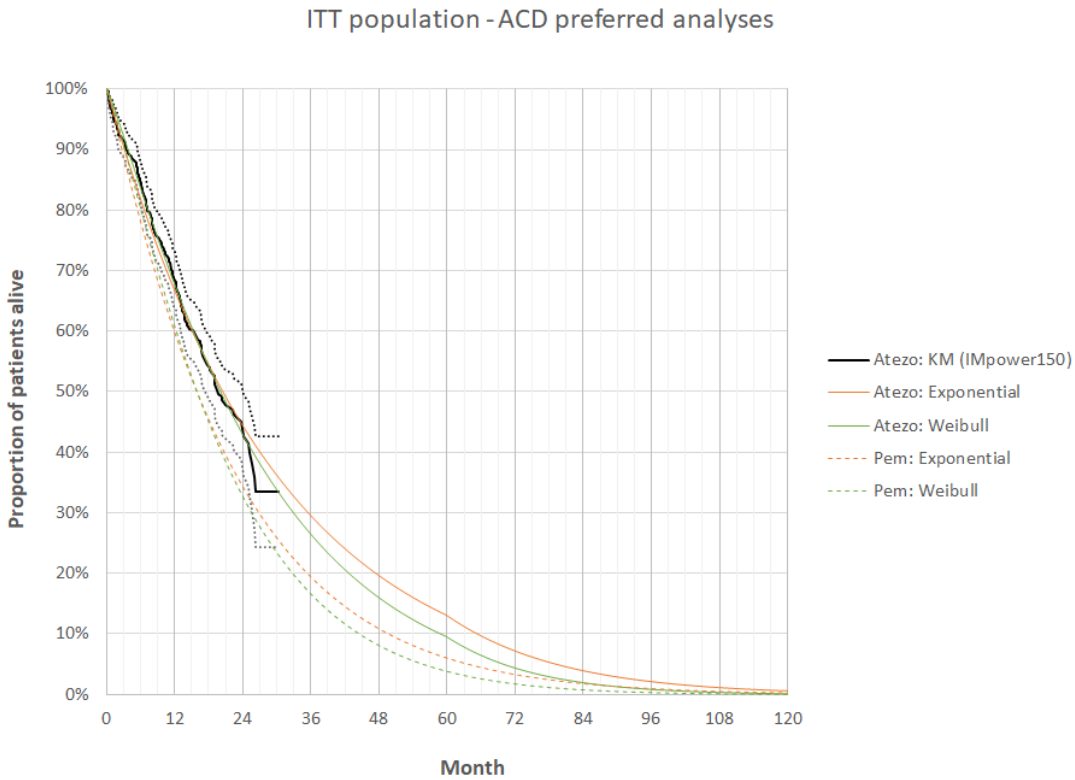

Figure 5 Overall survival for ITT population with preferred assumptions

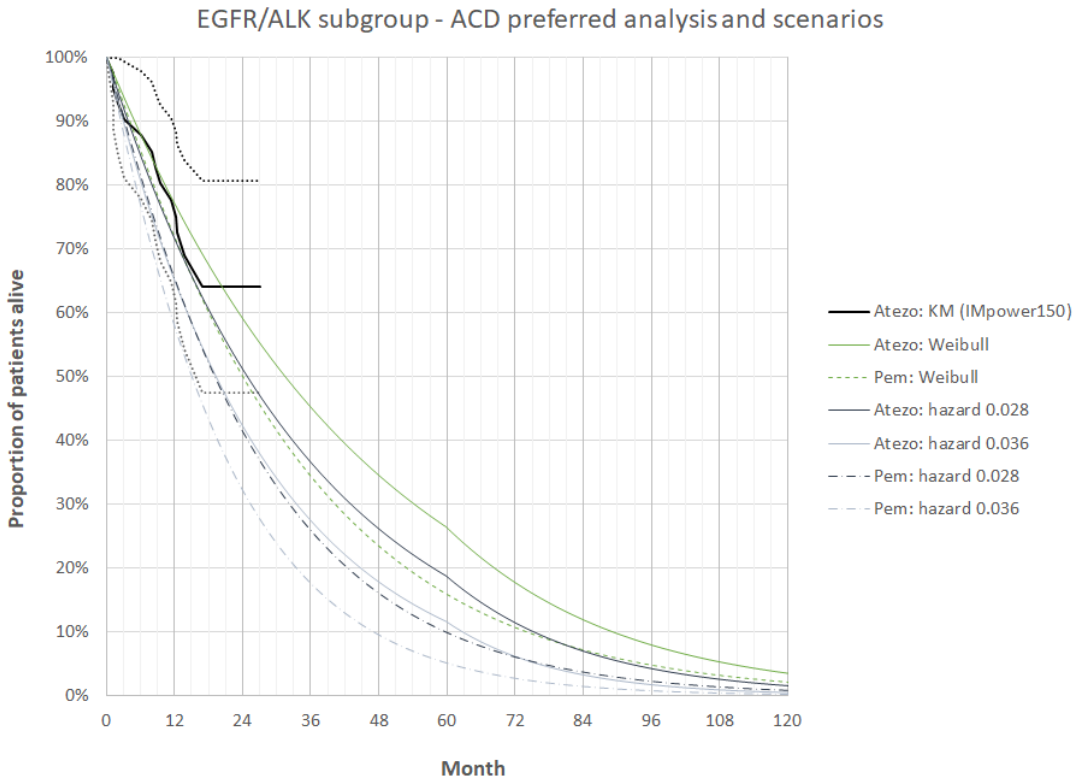

Figure 6 Overall survival for EGFR/ALK subgroup with preferred assumptions and ERG illustrative scenario analysis