NICE National Institute for Health and Care Excellence

Single Technology Appraisal

Atezolizumab with nab-paclitaxel for treating PD L1-positive, triple-negative, advanced breast cancer [ID1522]

Committee Papers

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

SINGLE TECHNOLOGY APPRAISAL

Atezolizumab with nab-paclitaxel for treating PD L1-positive, triple-negative, advanced breast cancer [ID1522]

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

Atezolizumab with nab-paclitaxel for treating PD L1-positive, triple-negative, advanced breast cancer

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	Breast Cancer Now	This promising treatment would represent a significant advance in care for certain patients with triple negative breast cancer, for which the main current treatment option is chemotherapy. We reiterate from our original patient submission that triple negative breast cancer is usually more aggressive and harder to treat than other types of breast cancer and often results in poorer outcomes. Being diagnosed with metastatic triple negative breast cancer is extremely difficult to come to terms with both for patients and their family and friends. Patients are desperate to find treatments that will halt progression and extend life for as long as possible but also ensure a good quality of life which enables them to spend quality time with their loved ones. In section 3.2 of the ACD, the committee also recognised that there is a very high unmet clinical need among people with metastatic triple negative breast cancer, and that the availability of a new immunotherapy is an important development in this condition. This cannot be underestimated. Evidence has shown that people having atezolizumab with nab-paclitaxel live longer before their condition gets worse, than people having placebo and nab-paclitaxel. Having a treatment option which improves progression-free survival is crucial. One patient told us the impact of having this treatment as an option: 'This doesn't just affect the patient. It gives hope to the whole family as its horrific watching someone slowly die before your eyes. I know my cancer is incurable however it could be much more manageable and give me a better quality of life.' Evidence also suggest that patients could live longer on average with this treatment option (section 3.8). Although there is no direct comparison with the treatments that are most commonly used on the NHS for this patient group (taxanes), the committee felt that it was reasonable to assume nab-	Thank you for your comments. Atezolizumab with nab-paclitaxel is recommended, within its marketing authorisation, for treating triple-negative, unresectable, locally advanced or metastatic breast cancer in adults whose tumours express PD L1 at a level of 1% or more and who have not had previous chemotherapy for metastatic disease (see FAD section 1.1 for more details).

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			paclitaxel has a similar efficacy to paclitaxel. Having access to a treatment which could offer substantial life-extension is crucial for this group of patients. It would enable them to have precious time to spend with their loved ones, doing the things that matter most to them, which is invaluable.	
2	Consultee	Breast Cancer Now	For a period of time this treatment option was available via an Early Access to Medicines Scheme. This was extremely welcomed as it enabled this promising new medicine to reach eligible patients faster. The hopes of this patient group will have now been raised. As this is a draft decision, we urge Roche, NICE and NHS England to work together to explore every possible solution, to ensure this treatment option can be recommended for use.	Thank you for your comments. Atezolizumab with nab-paclitaxel is recommended, within its marketing authorisation, for treating triple-negative, unresectable, locally advanced or metastatic breast cancer in adults whose tumours express PD L1 at a level of 1% or more and who have not had previous chemotherapy for metastatic disease (see FAD section 1.1 for more details).
3	Consultee	Breast Cancer Now	Section 3.15 – Whilst this section highlights that this treatment option cannot currently be considered for the Cancer Drugs Fund (CDF) as it does not have plausible potential for cost-effectiveness at the current price, it isn't clear if the CDF would be a potential option if the estimates regarding cost-effectiveness changed. This section highlights that whilst additional data may help to provide some information, it states that the main uncertainty could not be addressed by more data collection whilst on the CDF. Can this be clarified in further documentation?	Thank you for your comments. Atezolizumab with nab-paclitaxel is recommended, within its marketing authorisation, for treating triple-negative, unresectable, locally advanced or metastatic breast cancer in adults whose tumours express PD L1 at a level of 1% or more and who have not had previous chemotherapy for metastatic disease (see FAD section 1.1 for more details).
4	Consultee	Breast Cancer Now	This draft decision also demonstrates that there is still work to do to ensure the changes that were made to NICE appraisal processes in 2018 achieve what they set out to do and reach a positive decision more quickly. This example should now be considered as part of the ongoing NICE review of its methods and processes.	Thank you for your comment. Comment noted.
5	Consultee	UK Breast Cancer Group	The UKBCG considers this a very important advance in the worst prognosis sub-type of breast cancer. A new target for treating MBC reduces the number of patients with a very poor outlook. A median overall survival of 25.0 months in the PD-L1–positive subgroup with atezolizumab–nab-paclitaxel group which would be an important and clinically meaningful improvement. It compares favourably with 25.1 vs. 20.3 months improvement seen with the first phase III trial of trastuzumab with chemotherapy in metastatic breast cancer. We hope that NICE and Roche can come to an agreement on price so that this important advance in treatment will be available to our patients.	Thank you for your comments. Atezolizumab with nab-paclitaxel is recommended, within its marketing authorisation, for treating triple-negative, unresectable, locally advanced or metastatic breast cancer in adults whose tumours express PD L1 at a level of 1% or more and who have not had previous chemotherapy for metastatic disease (see FAD section 1.1 for more details).
6	Company	Roche	**1. Introduction** We have carefully reviewed the Committee's consideration of the	Thank you for your comments and the additional evidence submitted in response to ACD.

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			evidence for the single technology appraisal (STA) of atezolizumab with nab-paclitaxel for treating PD L1-positive, triple-negative, advanced breast cancer [ID1522]. We thank the National Institute for Health and Care Excellence (NICE) for the opportunity to comment on the Appraisal Consultation Document (ACD). We are disappointed by the conclusions reached by the Committee and the resulting preliminary guidance not to recommend atezolizumab with nab-paclitaxel. While we acknowledge that there is uncertainty in our NMA, there is also uncertainty with using the control arm from the IMpassion130 study. The weight of the clinical evidence available suggests that nab paclitaxel is similarly efficacious, if not slightly better than, weekly paclitaxel. Therefore, while there is uncertainty with either incremental cost-effectiveness ratio (ICER), the ICER derived from assuming equivalence of nab-paclitaxel clinical efficacy using data from IMpassion130, is at the highest end of the spectrum (overly conservative), and understates the potential value of atezolizumab to the National Health Service (NHS) and patients. We consider this to be particularly important given both the high burden of metastatic triple-negative breast cancer (mTNBC) for patients and their carer's, and the limited treatment options available, as was recognised by the Committee during their deliberations. We are committed to enabling access for patients to this therapy, and are working with NHS England (NHSE) on a commercial arrangement encompassing two ongoing NICE appraisals: triple negative breast cancer (TNBC [ID1522]) and small-cell lung cancer (SCLC [ID1504]). Details of the offer made to NHSE can be found in the accompanying Appendix A to this ACD response. We have also included updated cost-effectiveness results, for committee consideration. We note that all Committee preferred assumptions have been incorporated in this offer, despite our concerns surrounding the overly conservative assumptions, particularly around equivalent efficacy of nab-paclitaxel and paclitaxel. Roche have conceded on this as our preference is for baseline funding for TNBC patients. However, if this proposed offer is not accepted, we request to be considered for the Cancer Drugs Fund (CDF). The case for CDF has been outlined in the accompanying Appendix B. Atezolizumab plus nab-paclitaxel is an important innovation, and a major breakthrough in managing mTNBC. As stated by the Committee, it is the first treatment to substantially improve outcomes compared with chemotherapy in this population.	Atezolizumab with nab-paclitaxel is recommended, within its marketing authorisation, for treating triple-negative, unresectable, locally advanced or metastatic breast cancer in adults whose tumours express PD L1 at a level of 1% or more and who have not had previous chemotherapy for metastatic disease (see FAD section 1.1 for more details).

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			Below we outline our response to several points raised by the Committee within the ACD. We hope that this response, together with updated ICERs and the acknowledgment that atezolizumab plus nab-paclitaxel fulfils the end-of-life criteria, will allow the Committee to reach a final conclusion to recommend atezolizumab. [Appendix A & B were submitted as a part of additional evidence and are not reproduced here]	
7	Company	Roche	**2. Issues raised in the ACD** **2.1. Nab-paclitaxel has similar efficacy to weekly paclitaxel and docetaxel [paragraph 3.5]** We agree that the clinical experts consulted at the Appraisal Committee meeting consider that nab-paclitaxel provides similar or marginally better results compared with weekly paclitaxel. However, even a marginal difference in efficacy between nab-paclitaxel and paclitaxel has a large impact on the results of the cost effectiveness analysis of atezolizumab plus nab-paclitaxel. We consider that the marginal differences in effectiveness have been appropriately captured in the model via the network meta-analysis (NMA, Section 2.2) and consider the Committee decision to use nab-paclitaxel as a proxy for paclitaxel to be overly conservative (Section 2.3). At the Appraisal Committee meeting, one clinical expert explained that differences in survival at 12 months between paclitaxel and nab-paclitaxel would likely be small, at less than 5%. We note that, within the model submitted by Roche and using results from the NMA, overall survival (OS) at 12 months for patients receiving nab-paclitaxel is estimated to be 66.3% compared with 64.3% for paclitaxel. This is a 2% difference and therefore closely aligned with the views of the clinical experts consulted at the Appraisal Committee meeting. Further supporting this, as extensively detailed in Technical Engagement response, are data reported in the literature.(1-4) Most notably, the licensing studies for nab-paclitaxel compared with paclitaxel (Table 1).(1) While showing no statistically significant differences in PFS or OS, OS for nab-paclitaxel (Abraxane) was estimated to be 56.4 weeks compared with 46.7 weeks for paclitaxel: a nearly 10-week difference in average OS. This closely resembles the results of the NMA: no statistical difference in OS, but a mean 10.27 week life-year gain (LYG) estimated within the submitted economic analysis.	Thank you for your comments on section 3.5. The committee concluded in section 3.5: *"The committee concluded that nab-paclitaxel and weekly paclitaxel have broadly similar efficacy in advanced breast cancer."* No changes made.

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			Table 1 [not reproduced here] In addition to the literature provided as part of technical engagement, Roche would also like to highlight the CALGB 40502 study.(5) This study detected a similar trend in outcomes in an exploratory subset analysis of patients with Triple Negative disease: median PFS was found to be 6.4 months for paclitaxel and 7.4 months for nab-paclitaxel (HR, 0.79; 95% CI 0.55-1.12); and median OS reported as 15.3 months and 21.0 months, respectively (HR, 0.74; 95% CI 0.51-1.07), equating to a 24 week difference in average OS.(5) Given the views of the clinical experts and following review of the licencing studies and other identified literature for nab-paclitaxel, we would like to highlight that even a marginal difference in efficacy between nab-paclitaxel and paclitaxel has a large and important impact on results of the cost-effectiveness analysis. Therefore, by assuming equivalence of these therapies, the value of atezolizumab to the NHS is not being appropriately reflected. Instead, the analyses submitted by Roche are aligned with the literature and clinical expectations of difference between nab-paclitaxel and paclitaxel, and therefore reflect the true value of this treatment.	
8	Company	Roche	**2.2. Indirect comparison with taxanes [paragraph 3.9]** We are disappointed that the Committee has concluded that the network meta-analysis (NMA) is not reliable and lacks face validity. We hope that our response to this issue will provide the additional information that the Committee requires to have confidence in the results of the NMA. Each of the key issues outlined within paragraph 3.9 of the ACD are presented below with our response. 1. "It heard that the company adjusted for age, Eastern Cooperative Oncology Group (ECOG) status, previous taxane use, and the proportion of patients with liver metastases, visceral disease and bone metastases. The clinical experts confirmed that these are key characteristics that determine treatment response in this patient population. However, they also highlighted that time from previous treatment and proportion of de novo metastases are also an important determinant of response to further treatments and prognosis. Data on these characteristics were not included in the NMA." The matching variables used in the analysis for paclitaxel for both E2100 and MERIDIAN are presented in Table 4 to Table 7 in Appendix C below. As can be seen from these tables, time from initial diagnosis to metastatic disease was included within the matching for E2100 for both OS and PFS.	Thank you for your comments on section 3.9. 1. The text in 3.9 was updated to correct for the raised error describing the patient characteristics used in the NMA (see FAD section 3.9 for more details). 2. The section describes ERG opinions. No changes made 3. The committee concluded in 3.9: *"The committee appreciated that the company's NMA incorporated the very limited evidence available to estimate the relative effectiveness of the treatments. However, it thought that there was considerable heterogeneity among the trials which may not have been appropriately taken into account, given the limitations of the data. It also noted the poor face validity of the results. For these reasons, the committee concluded that*

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			We agree with the Committee that it is of critical importance to have the relevant data on patient characteristics in order for the match to be appropriate and the resulting "virtual study" to be unbiased. Nevertheless, all analyses are constrained by the evidence available, and, unfortunately, the proportion of de novo metastases was not readily available to incorporate. Given that one of the key baseline characteristics highlighted by the Committee as missing is, in fact, included in the analysis, and the results are reflective of the available literature, we are confident that the data in this response will go some way to ease the Committee concerns. 2. ERG concerns with the NMA including issues of unknown PD-L1 status and the lack of statistical significance Unknown PD-L1 status Except for IMpassion130, PD-L1 status was not collected in any of the trials included in the NMA. The comparator trials included in the NMA were completed prior to the ability to target PD-L1, and therefore expression was not routinely assessed. As PD-L1 was not a validated biomarker at the time of the studies, it is infeasible to collect evidence on PD-L1 expression from the trials included in the NMA. However, we consider that the PD-L1 status is unlikely to affect outcomes for patients receiving paclitaxel. This is because taxanes do not target the PD-L1 immune checkpoints, so there is no mechanistic rationale for PD-L1 status to be an effect modifier of chemotherapy. There is no evidence to suggest that the relative effects of nab-paclitaxel and paclitaxel are impacted by a selection of PD-L1-positive subpopulation. Moreover, the impact of no data within PD-L1+ specific subgroups may bias against atezolizumab plus nab-paclitaxel. Median OS and PFS for nab-paclitaxel is higher in the intent to treat (ITT) population of IMpassion130 (17.6 months, 5.5 months respectively) than the PD-L1 positive population (14.4 months, 3.9 months respectively). We could, from this, hypothesise that the prognosis of patients with PD-L1 expression not treated with an anti-PD-L1 agent is worse than that of the ITT. As the paclitaxel trials included in the NMA are expected to contain a mixture of PD-L1 positive and negative patients (i.e. the equivalent to the ITT in IMpassion130) it is plausible the NMA has, in fact, overestimated the OS and PFS absolute effects for paclitaxel. If the trials had been in PD-L1 positive populations only, one could anticipate a similar trend to poorer outcomes as witnessed in the nab-paclitaxel arm of the IMpassion130 trial. Lack of statistical significance	*there was great uncertainty in the NMA, and that the results were not robust and lacked face validity*." No changes made

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			The 95% credible intervals of hazard ratios and 5-year restricted mean survival times are accepted as wide. Indirect treatment comparisons are not powered to detect statistical significance; therefore, uncertainty is not uncommon. Given this, Roche believe this is an insufficient rationale for disregarding the results: • Appropriate use of statistical significances and p-values: Roche note that a statistically non-significant result does not prove the null hypothesis that there is no difference between groups or no effect of a treatment on some measured outcome. Indeed, this is supported by a recent comment piece, published in Nature by Amrehein and colleagues in 2019. The authors carried out an analysis of 791 articles across 5 journals and found that 51% of articles mistakenly assumed that non-significance of results means no effect, and the authors caution around this interpretation. Roche believe that a reliance on thresholds of statistical significance, as in this case, can be misleading. As detailed in Altman et al. 1995, "absence of evidence is not evidence of absence".(6) • Accounting for uncertainty in Bayesian indirect comparisons: Hazard ratios and 5-year restricted mean survival times point estimates are a representation of the likely result. However, the uncertainty surrounding point estimates (through the credible interval) is reflected in the probabilistic sensitivity analysis used within the cost-effectiveness analysis. This approach is supported by the NICE Decision Support Unit guidance: “simulation from a Bayesian posterior distribution supplies both statistical estimation and inference, and a platform for probabilistic decision making under uncertainty”. • That the treatment effect between nab-paclitaxel and paclitaxel is not statistically significant, is expected; indeed, this is supported by both clinical opinion and the results of the licencing studies and the wider literature for nab-paclitaxel as detailed in Section 2.1. 3. “The NMA predicted higher OS for docetaxel and paclitaxel compared with nab-paclitaxel in the first 5 months and then higher overall survival for nab-paclitaxel after 5 months. The clinical experts confirmed that paclitaxel and nab-paclitaxel are very similar therefore such differences were unlikely.” We acknowledge that the 5-month cut-off, which was driven by statistical fit, has produced non-statistically significant differences in effect direction which are not intuitive, and understand why these were queried by the Committee. However, we urge the Committee to consider the results of	

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			the NMA across the time horizon, rather than just the first 5 months, in order to assess the plausibility of results. For example, as detailed in Section 2.1, OS at 12 months for patients receiving nab-paclitaxel is estimated to be 66.3% compared with 64.3% for paclitaxel. This is a 2% difference between treatments and is therefore closely aligned with the views of the clinical experts consulted at the Appraisal Committee meeting. Moreover, the mean total difference in LYG between nab-paclitaxel and paclitaxel is estimated in the model to be around 10 weeks. This is closely aligned with the numerical difference estimated in the licencing trials for nab-paclitaxel and the wider literature versus paclitaxel and other taxanes, as described in Section 2.1 above, where results showed a nearly 10 week difference in OS for nab-paclitaxel versus paclitaxel (56.4 weeks versus 46.7 weeks).(1) We reiterate that, even though outcomes for nab-paclitaxel and paclitaxel are similar, the small expected differences have an large and important impact on the ICER and, we believe, should be accounted for when estimating the potential value of atezolizumab to the National Health Service (NHS) and patients with mTNBC. [Appendix C was submitted as a part of additional evidence and is not reproduced here]	
9	Company	Roche	**2.3. The Committee's preferred assumptions for modelling paclitaxel [paragraph 3.10]** "The Appraisal Committee did not consider that the 10.27 week life year gain predicted by the model was a trivial difference." We agree that a 10.27 week LYG is not trivial; however, it is consistent with the limited body of evidence which compares nab-paclitaxel with taxanes. This is detailed further in Section 2.1. The analyses submitted by Roche are aligned with the literature and clinical expectations of difference between nab-paclitaxel and paclitaxel, and therefore, we believe, reflect the true value of this treatment. "It accepted that using data from the placebo plus nab-paclitaxel arm of IMpassion130 as a proxy for the effectiveness of weekly paclitaxel was not a perfect approach. However, it considered a randomised, unbiased and contemporaneous comparison to be more reliable that the NMA" We are grateful for the acknowledgment that using nab-paclitaxel as a proxy for paclitaxel is not ideal. We understand the appeal of using nab-paclitaxel data as a proxy for paclitaxel given that head-to-head data is available in the relevant group of patients. However, we ask the	Thank you for your comments on section 3.10. Section 3.10 describes the committee's preference. No changes made

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			Committee to consider the uncertainty inherent with this assumption, and given the context of available clinical evidence and clinical opinion provided during the Committee meeting. While there is uncertainty with either ICER, the ICER derived from nab-paclitaxel clinical efficacy from IMpassion130 is at the highest end of the spectrum (overly conservative), thus understates the potential value of atezolizumab to the NHS and people with mTNBC.	
9	Company	Roche	**2.4. Treatment waning [paragraph 3.11]** We welcome the Committee conclusion that incorporating an arbitrary treatment waning effect for atezolizumab in this indication was not appropriate.	Thank you for your comment.
9	Company	Roche	**2.5. Treatment duration with paclitaxel [paragraph 3.12]** We are pleased that the Committee agreed that an 18-cycle treatment cap does not reflect clinical practice. We acknowledge the limitations of the original analysis, in which time to off-treatment (TTOT) for paclitaxel was set to PFS and highlight that this assumption was required due to a lack of data. While Roche believes assuming equivalence between nab-paclitaxel and paclitaxel is overly conservative, and understates the value of this medicine, to assist the Committee in their decision making, ICERs presented within Appendix A incorporate nab-paclitaxel data for PFS, OS and TTOT as a proxy for paclitaxel, alongside the removal of the paclitaxel limit on number of treatment cycles (Appendix A and B). [Appendix A & B were submitted as a part of additional evidence and are not reproduced here]	Thank you for your comments and the additional evidence submitted in response to ACD. Atezolizumab with nab-paclitaxel is recommended, within its marketing authorisation, for treating triple-negative, unresectable, locally advanced or metastatic breast cancer in adults whose tumours express PD L1 at a level of 1% or more and who have not had previous chemotherapy for metastatic disease (see FAD section 1.1 for more details).
9	Company	Roche	**2.6. End of life [paragraph 3.14]** Patients with mTNBC face a devastating diagnosis with limited treatment options, with outcomes such as OS falling considerably behind those of other breast cancer subtypes, with a median OS of less than 18 months for mTNBC compared with 4–5 years for HR+ and HER2+ subtypes.(7-9) We therefore welcome the Committee conclusion that atezolizumab plus nab-paclitaxel fulfils the end-of-life criteria, recognising that, in all scenario analyses presented, atezolizumab plus nab-paclitaxel offers more than 3 months' extension to life in a population that has a life expectancy of less than 24 months.	Thank you for your comments.
10	Clinical expert	Dr M B Mukesh	The NICE appraisal looked at the role of Nab-Paclitaxel and Atezolizumab in first line metastatic TNBC. As a clinician, it was disappointing that the drug combination has not been recommended based on the evidence	Thank you for your comments. Atezolizumab with nab-paclitaxel is recommended, within its marketing authorisation, for treating triple-

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			presented. Triple negative breast cancers (TNBC) are usually aggressive and the average life expectancy for metastatic TNBC with current treatments is around 18 months. No significant scientific breakthrough has been made in this disease for last 2 decades unlike ER positive and Her-2 positive breast cancers. This innovative drug combination is the first to have shown an improvement in patient's outcome with improvement in both Progression free survival and Median overall survival in TNBC. The drug combination was briefly available to suitable patients through the Early Access to Medicines Scheme (EAMS) and was well received by both patients and clinicians. The EAMS has now closed and suitable patients are unable to access this innovative drug combination. I would request both NICE and the Pharmaceutical company Roche to show flexibility and work together to make this drug available for patients.	negative, unresectable, locally advanced or metastatic breast cancer in adults whose tumours express PD L1 at a level of 1% or more and who have not had previous chemotherapy for metastatic disease (see FAD section 1.1 for more details).
11	Web comment	NHS	*Has all of the relevant evidence been taken into account?* As with all these treatments that are taken until progression and are additive to current treatment (even if it was only paclitaxel) they can NEVER be cost effective as additional treatment costs mean they will be more expensive than standard of care because they are more effective ie yet again living longer costs more and is penalised in NICE assessments. Other evidence needs to include ability to work, care for children and vunerable adults and more emphasis on being progression free. *Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence?* See above. *Are the recommendations sound and a suitable basis for guidance to the NHS?* This is are area on unmet need and immunotherapy with atezolizumab addresses many of the problems of rapidly advancing disease. Until you have seen the rapid response and improvement in quality of life these patients get with using immunotherapy then the current recommendations are not sound and suitable. Young women the triple negative disease , rapidly advancing who are caring for children and who through the use of these agent have a period of improved quality of life has to be accomadated in recommemndations. *Are there any aspects of the recommendations that need particular*	Thank you for your comments. Atezolizumab with nab-paclitaxel is recommended, within its marketing authorisation, for treating triple-negative, unresectable, locally advanced or metastatic breast cancer in adults whose tumours express PD L1 at a level of 1% or more and who have not had previous chemotherapy for metastatic disease (see FAD section 1.1 for more details).

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			consideration to ensure we avoid unlawful discrimination against any group of people on the grounds of race, gender, disability, religion or belief, sexual orientation, age, gender reassignment, pregnancy and maternity? No.	
12	Web comment	NHS	I am a clinical oncologist and lead for cancer research in Peninsula. This group of patients have a dismal outlook with no real improvement in their treatment options for years, except lots of not terribly effective chemotherapy regimes continuously until they die or give up! for the PDL-1 positive subgroup (40%) there is a clinically meaniful improvement in these patients outlooks with not much extra patient related toxicity. A few will get immunotherapy related toxicities, that can usually be dealt with by steroids/endocrine replacement. It would be a real shame if these patients missed out on this important research being implemented immediately in the UK. The eams offered some the opportunity, and there are a few trials open to a few. This will become the standard of care globally, so all ongoing studies will then include immunotherapy from now on as a standard of care. Therefore we in the UK need to keep up with the pace of change to be part of the commercial research in the world, with the huge benefit this brings to the Uk in terms of funding and patient benefit. I am sure some compromise, as usually can be made with NHS/pharma/ tax payers interests being mutually respected, so that patients can access this important new treatment option	Thank you for your comments. Atezolizumab with nab-paclitaxel is recommended, within its marketing authorisation, for treating triple-negative, unresectable, locally advanced or metastatic breast cancer in adults whose tumours express PD L1 at a level of 1% or more and who have not had previous chemotherapy for metastatic disease (see FAD section 1.1 for more details).
13	Web comment	NHS	*Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence?* No. Please see comments below. 1. The recommendations state that paclitaxel should remain the standard of care. This is seem very unreasonable in a population who will invariably have received this in the neoadjvuant/adjuvant setting and in many instances will have progressed on treatment. I would like to illustrate this by providing you with an example of a patient treated via the EAMS pathway from Kent. She was treated with neoadjuvant intent and her tumour grew through both antracycline but also the taxane/carboplatin elements of neoadjvant. Her disease remained operable and she underwent surgery then radiotherapy. Recognizing that neoadjuvant chemotherapy had been curtailed she elected to have adjuvant capecitibine. Sadly she relapsed within the liver only a few	Thank you for your comments. Atezolizumab with nab-paclitaxel is recommended, within its marketing authorisation, for treating triple-negative, unresectable, locally advanced or metastatic breast cancer in adults whose tumours express PD L1 at a level of 1% or more and who have not had previous chemotherapy for metastatic disease (see FAD section 1.1 for more details).

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
			months after completing this. This lady has already demonstrated resistance to paclitaxel so this would very definitely have been a futile choice for her. The short interval from completion of adjuvant capecitibine precluded her from participation in 1st line metastatic studies. Her relapse occurred just as the EAMS access opened and after testing was eligible for treatment. She is now close to 6 months into treatment with control demonstrated on imaging, resolution of liver related symptoms and excellent quality of life. I have no doubt that there is no other option from the currently available lines of chemotherapy that could have given her this time, indeed she has never been in the position until now of having a scan which shows response. 2. The nabpaclitaxel/atezolizumab target population are identified by the PD1 biomarker . This is a niche subpopulation of the already comparatively small TNBC (~35% of those tested within the EAMS pathway). NICE can therefore be reassured that a positive decision to fund these agents is not going to open the flood gates to large patient numbers. This is exemplified by the Kent experience. As a cancer center drawing from one of the largest catchment areas in the UK (ie whole of kent) we have identified only 7 patients tested through the EAMS pathway who would be eligible for treatment.	
14	Web comment	NHS	*Has all of the relevant evidence been taken into account?* Yes *Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence?* Yes *Are the recommendations sound and a suitable basis for guidance to the NHS?* Yes *Are there any aspects of the recommendations that need particular consideration to ensure we avoid unlawful discrimination against any group of people on the grounds of race, gender, disability, religion or belief, sexual orientation, age, gender reassignment, pregnancy and maternity?* No	Thank you for your comments. Atezolizumab with nab-paclitaxel is recommended, within its marketing authorisation, for treating triple-negative, unresectable, locally advanced or metastatic breast cancer in adults whose tumours express PD L1 at a level of 1% or more and who have not had previous chemotherapy for metastatic disease (see FAD section 1.1 for more details).

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
			Committee discussion section: IMpassion131 is looking at the use of weekly paclitaxel and will hopefully make this treatment more affordable. I feel that there is huge unmet need in treating metastatic TNBC. I work in south London with a large afrocarribean population who tend to present late with advanced disease and have a higher proportion of triple negative breast cancers. This would be a big step forward for these patients.	
15	Web comment	NHS	It is somewhat disappointing to see a negative opinion on nab-paclitaxel and atezolizumab in first line therapy for triple negative IC>1% breast cancer. This is a population of predominantly young women with very few treatment options. In addition the IMPASSION 131 study will undoubtedly report shortly examining the same question but with paclitaxel as the chemotherapy backbone. If the results of IMPASSION-131 are comparable then the extra cost of nab-paclitaxel will be relatively short-lived as paclitaxel would be substituted. If the result is negative this may call the use of atezolizumab into question altogether. There is a strong rationale, therefore, for accepting nab-paclitaxel atezolizumab with the condition that the approval is reviewed with IMPASSION-131 results in 2020.	Thank you for your comments. Atezolizumab with nab-paclitaxel is recommended, within its marketing authorisation, for treating triple-negative, unresectable, locally advanced or metastatic breast cancer in adults whose tumours express PD L1 at a level of 1% or more and who have not had previous chemotherapy for metastatic disease (see FAD section 1.1 for more details).

Document processed	Organisation name – Stakeholder or respondent	Disclosure on tobacco funding / links	Number of comments extracted	Comments
ID1522 ACD comments form Breast Cancer Now 22.10.19 [NoACIC].doc	Breast Cancer Now	None	4	
Other comments	Various	none	11	**Extracted manually**

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single Technology Appraisal (STA)

Atezolizumab with nab-paclitaxel for treating PD L1-positive, triple-negative, advanced breast cancer [ID1522]

Response to Appraisal Committee Document

Prepared by Roche

Date: February 2020

1. Introduction

We have carefully reviewed the Committee's consideration of the evidence for the single technology appraisal (STA) of atezolizumab with nab-paclitaxel for treating PD L1-positive, triple-negative, advanced breast cancer [ID1522]. We thank the National Institute for Health and Care Excellence (NICE) for the opportunity to comment on the Appraisal Consultation Document (ACD).

We are disappointed by the conclusions reached by the Committee and the resulting preliminary guidance not to recommend atezolizumab with nab-paclitaxel. While we acknowledge that there is uncertainty in our NMA, there is also uncertainty with using the control arm from the IMpassion130 study. The weight of the clinical evidence available suggests that nab paclitaxel is similarly efficacious, if not slightly better than, weekly paclitaxel. Therefore, while there is uncertainty with either incremental cost-effectiveness ratio (ICER), the ICER derived from assuming equivalence of nab-paclitaxel clinical efficacy using data from IMpassion130, is at the highest end of the spectrum (overly conservative), and understates the potential value of atezolizumab to the National Health Service (NHS) and patients. We consider this to be particularly important given both the high burden of metastatic triple-negative breast cancer (mTNBC) for patients and their carer's, and the limited treatment options available, as was recognised by the Committee during their deliberations.

We are committed to enabling access for patients to this therapy, and are working with NHS England (NHSE) on a commercial arrangement encompassing two ongoing NICE appraisals: triple negative breast cancer (TNBC [ID1522]) and small-cell lung cancer (SCLC [ID1504]).

Details of the offer made to NHSE can be found in the accompanying Appendix A to this ACD response. We have also included updated cost-effectiveness results, for committee consideration.

We note that all Committee preferred assumptions have been incorporated in this offer, despite our concerns surrounding the overly conservative assumptions, particularly around equivalent efficacy of nab-paclitaxel and paclitaxel. Roche have conceded on this as our preference is for baseline funding for TNBC patients. However, if this proposed offer is not accepted, we request to be considered for the Cancer Drugs Fund (CDF). The case for CDF has been outlined in the accompanying Appendix B.

Atezolizumab plus nab-paclitaxel is an important innovation, and a major breakthrough in managing mTNBC. As stated by the Committee, it is the first treatment to substantially improve outcomes compared with chemotherapy in this population.

Below we outline our response to several points raised by the Committee within the ACD. We hope that this response, together with updated ICERs and the acknowledgment that atezolizumab plus nab-paclitaxel fulfils the end-of-life criteria, will allow the Committee to reach a final conclusion to recommend atezolizumab.

2. Issues raised in the ACD

2.1. Nab-paclitaxel has similar efficacy to weekly paclitaxel and docetaxel [paragraph 3.5]

We agree that the clinical experts consulted at the Appraisal Committee meeting consider that nab-paclitaxel provides similar or marginally better results compared with weekly paclitaxel. However, even a marginal difference in efficacy between nab-paclitaxel and paclitaxel has a large impact on the results of the cost effectiveness analysis of atezolizumab plus nab-paclitaxel.

We consider that the marginal differences in effectiveness have been appropriately captured in the model via the network meta-analysis (NMA, Section 2.2) and consider the Committee decision to use nab-paclitaxel as a proxy for paclitaxel to be overly conservative (Section 2.3).

At the Appraisal Committee meeting, one clinical expert explained that differences in survival at 12 months between paclitaxel and nab-paclitaxel would likely be small, at less than 5%. We note that, within the model submitted by Roche and using results from the NMA, overall survival (OS) at 12 months for patients receiving nab-paclitaxel is estimated to be 66.3% compared with 64.3% for paclitaxel. This is a 2% difference and therefore closely aligned with the views of the clinical experts consulted at the Appraisal Committee meeting.

Further supporting this, as extensively detailed in Technical Engagement response, are data reported in the literature.(1-4) Most notably, the licensing studies for nab-paclitaxel compared with paclitaxel (Table 1).(1) While showing no statistically significant differences in PFS or OS, OS for nab-paclitaxel (Abraxane) was estimated to be 56.4 weeks compared with 46.7 weeks for paclitaxel: a nearly 10-week difference in average OS. This closely resembles the results of the NMA: no statistical difference in OS, but a mean 10.27 week life-year gain (LYG) estimated within the submitted economic analysis.

Table 1: Results for overall response rate, median time to disease progression, and progression-free survival as assessed by the investigator

Efficacy variable	Abraxane (260 mg/m^2)	Solvent-based paclitaxel (175 mg/m^2)	p-value
Response rate [95% CI] (%)			
> 1st-line therapy	26.5 [18.98, 34.05] (n = 132)	13.2 [7.54, 18.93] (n = 136)	0.006[a]
**Median time to disease progression [95% CI] (weeks)*			
> 1st-line therapy	20.9 [15.7, 25.9] (n = 131)	16.1 [15.0, 19.3] (n = 135)	0.011[b]
**Median progression free survival [95% CI] (weeks)*			
> 1st-line therapy	20.6 [15.6, 25.9] (n = 131)	16.1 [15.0, 18.3] (n = 135)	0.010[b]
**Survival [95% CI] (weeks)*			
> 1st-line therapy	56.4 [45.1, 76.9] (n = 131)	46.7 [39.0, 55.3] (n = 136)	0.020[b]

*This data is based on Clinical Study Report: CA012-0 Addendum dated Final (23 March-2005)
[a] Chi-squared test
[b] Log-rank test

In addition to the literature provided as part of technical engagement, Roche would also like to highlight the CALGB 40502 study.(5) This study detected a similar trend in outcomes in an exploratory subset analysis of patients with Triple Negative disease: median PFS was found to be 6.4 months for paclitaxel and 7.4 months for nab-paclitaxel (HR, 0.79; 95% CI 0.55-1.12); and median OS reported as 15.3 months and 21.0 months, respectively (HR, 0.74; 95% CI 0.51-1.07), equating to a 24 week difference in average OS.(5)

Given the views of the clinical experts and following review of the licencing studies and other identified literature for nab-paclitaxel, we would like to highlight that even a marginal difference in efficacy between nab-paclitaxel and paclitaxel has a large and important impact on results of the cost-effectiveness analysis. Therefore, by assuming equivalence of these therapies, the value of atezolizumab to the NHS is not being appropriately reflected. Instead, the analyses submitted by Roche are aligned with the literature and clinical expectations of difference between nab-paclitaxel and paclitaxel, and therefore reflect the true value of this treatment.

2.2. Indirect comparison with taxanes [paragraph 3.9]

We are disappointed that the Committee has concluded that the network meta-analysis (NMA) is not reliable and lacks face validity. We hope that our response to this issue will provide the additional information that the Committee requires to have confidence in the results of the NMA. Each of the key issues outlined within paragraph 3.9 of the ACD are presented below with our response.

1. *"It heard that the company adjusted for age, Eastern Cooperative Oncology Group (ECOG) status, previous taxane use, and the proportion of patients with liver metastases, visceral disease and bone metastases. The clinical experts confirmed that these are key characteristics that determine treatment response in this patient population. However, they also highlighted that time from previous treatment and proportion of de novo metastases are also an important determinant of response to further treatments and prognosis. Data on these characteristics were not included in the NMA."*

The matching variables used in the analysis for paclitaxel for both E2100 and MERIDIAN are presented in **Error! Reference source not found.** to **Error! Reference source not found.Error! Reference source not found.** in Appendix C below. As can be seen from these tables, time from initial diagnosis to metastatic disease was included within the matching for E2100 for both OS and PFS.

We agree with the Committee that it is of critical importance to have the relevant data on patient characteristics in order for the match to be appropriate and the resulting "virtual study" to be unbiased. Nevertheless, all analyses are constrained by the evidence available, and, unfortunately, the proportion of de novo metastases was not readily available to incorporate. Given that one of the key baseline characteristics highlighted by the Committee as missing is, in fact, included in the analysis, and the results are reflective of the available literature, we are confident that the data in this response will go some way to ease the Committee concerns.

2. *ERG concerns with the NMA including issues of unknown PD-L1 status and the lack of statistical significance*

Unknown PD-L1 status

Except for IMpassion130, PD-L1 status was not collected in any of the trials included in the NMA. The comparator trials included in the NMA were completed prior to the ability to target PD-L1, and therefore expression was not routinely assessed. As PD-L1 was not a validated biomarker at the time of the studies, it is infeasible to collect evidence on PD-L1 expression from the trials included in the NMA.

However, we consider that the PD-L1 status is unlikely to affect outcomes for patients receiving paclitaxel. This is because taxanes do not target the PD-L1 immune checkpoints, so there is no mechanistic rationale for PD-L1 status to be an effect modifier of chemotherapy. There is no evidence to suggest that the relative effects of nab-paclitaxel and paclitaxel are impacted by a selection of PD-L1-positive subpopulation.

Moreover, the impact of no data within PD-L1+ specific subgroups may bias against atezolizumab plus nab-paclitaxel. Median OS and PFS for nab-paclitaxel is higher in the intent to treat (ITT) population of IMpassion130 (17.6 months, 5.5 months respectively) than the PD-L1 positive population (14.4 months, 3.9 months respectively). We could, from this, hypothesise that the prognosis of patients with PD-L1 expression not treated with an anti-PD-L1 agent is worse than that of the ITT. As the paclitaxel trials included in the NMA are expected to contain a mixture of PD-L1 positive and negative patients (i.e. the equivalent to the ITT in IMpassion130) it is plausible the NMA has, in fact, overestimated the OS and PFS absolute effects for paclitaxel. If the trials had been in PD-L1 positive populations only, one could anticipate a similar trend to poorer outcomes as witnessed in the nab-paclitaxel arm of the IMpassion130 trial.

Lack of statistical significance

The 95% credible intervals of hazard ratios and 5-year restricted mean survival times are accepted as wide. Indirect treatment comparisons are not powered to detect statistical significance; therefore, uncertainty is not uncommon. Given this, Roche believe this is an insufficient rationale for disregarding the results:

- Appropriate use of statistical significances and p-values: Roche note that a statistically non-significant result does not prove the null hypothesis that there is no difference between groups or no effect of a treatment on some measured outcome. Indeed, this is supported by a recent comment piece, published in Nature by Amrehein and colleagues in 2019. The authors carried out an analysis of 791 articles across 5 journals and found that 51% of articles mistakenly assumed that non-significance of results means no effect, and the authors caution around this interpretation. Roche believe that a reliance on thresholds of statistical significance, as in this case, can be misleading. As detailed in Altman et al. 1995, "absence of evidence is not evidence of absence".(6)
- Accounting for uncertainty in Bayesian indirect comparisons: Hazard ratios and 5-year restricted mean survival times point estimates are a representation of the likely result. However, the uncertainty surrounding point estimates (through the credible interval) is reflected in the probabilistic sensitivity analysis used within the cost-effectiveness analysis. This approach is supported by the NICE Decision Support Unit guidance: “simulation from a Bayesian posterior distribution supplies both statistical estimation and inference, and a platform for probabilistic decision making under uncertainty”.
- That the treatment effect between nab-paclitaxel and paclitaxel is not statistically significant, is expected; indeed, this is supported by both clinical opinion and the results of the licencing studies and the wider literature for nab-paclitaxel as detailed in Section 2.1.

3. *“The NMA predicted higher OS for docetaxel and paclitaxel compared with nab-paclitaxel in the first 5 months and then higher overall survival for nab-paclitaxel after 5 months. The clinical experts confirmed that paclitaxel and nab-paclitaxel are very similar therefore such differences were unlikely.”*

We acknowledge that the 5-month cut-off, which was driven by statistical fit, has produced non-statistically significant differences in effect direction which are not intuitive, and

understand why these were queried by the Committee. However, we urge the Committee to consider the results of the NMA across the time horizon, rather than just the first 5 months, in order to assess the plausibility of results.

For example, as detailed in Section 2.1, OS at 12 months for patients receiving nab-paclitaxel is estimated to be 66.3% compared with 64.3% for paclitaxel. This is a 2% difference between treatments and is therefore closely aligned with the views of the clinical experts consulted at the Appraisal Committee meeting. Moreover, the mean total difference in LYG between nab-paclitaxel and paclitaxel is estimated in the model to be around 10 weeks. This is closely aligned with the numerical difference estimated in the licencing trials for nab-paclitaxel and the wider literature versus paclitaxel and other taxanes, as described in Section 2.1 above, where results showed a nearly 10 week difference in OS for nab-paclitaxel versus paclitaxel (56.4 weeks versus 46.7 weeks).(1)

We reiterate that, even though outcomes for nab-paclitaxel and paclitaxel are similar, the small expected differences have an large and important impact on the ICER and, we believe, should be accounted for when estimating the potential value of atezolizumab to the National Health Service (NHS) and patients with mTNBC.

2.3. The Committee's preferred assumptions for modelling paclitaxel [paragraph 3.10]

"The Appraisal Committee did not consider that the 10.27 week life year gain predicted by the model was a trivial difference."

We agree that a 10.27 week LYG is not trivial; however, it is consistent with the limited body of evidence which compares nab-paclitaxel with taxanes. This is detailed further in Section 2.1. The analyses submitted by Roche are aligned with the literature and clinical expectations of difference between nab-paclitaxel and paclitaxel, and therefore, we believe, reflect the true value of this treatment.

"It accepted that using data from the placebo plus nab-paclitaxel arm of IMpassion130 as a proxy for the effectiveness of weekly paclitaxel was not a perfect approach. However, it considered a randomised, unbiased and contemporaneous comparison to be more reliable that the NMA"

We are grateful for the acknowledgment that using nab-paclitaxel as a proxy for paclitaxel is not ideal. We understand the appeal of using nab-paclitaxel data as a proxy for paclitaxel given that head-to-head data is available in the relevant group of patients. However, we ask the Committee to consider the uncertainty inherent with this assumption, and given the context of available clinical evidence and clinical opinion provided during the Committee meeting. While there is uncertainty with either ICER, the ICER derived from nab-paclitaxel clinical efficacy from IMpassion130 is at the highest end of the spectrum (overly conservative), thus understates the potential value of atezolizumab to the NHS and people with mTNBC.

2.4. Treatment waning [paragraph 3.11]

We welcome the Committee conclusion that incorporating an arbitrary treatment waning effect for atezolizumab in this indication was not appropriate.

2.5. Treatment duration with paclitaxel [paragraph 3.12]

We are pleased that the Committee agreed that an 18-cycle treatment cap does not reflect clinical practice.

We acknowledge the limitations of the original analysis, in which time to off-treatment (TTOT) for paclitaxel was set to PFS and highlight that this assumption was required due to a lack of data.

While Roche believes assuming equivalence between nab-paclitaxel and paclitaxel is overly conservative, and understates the value of this medicine, to assist the Committee in their decision making, ICERs presented within Appendix A incorporate nab-paclitaxel data for PFS, OS and TTOT as a proxy for paclitaxel, alongside the removal of the paclitaxel limit on number of treatment cycles (Appendix A and B).

2.6. End of life [paragraph 3.14]

Patients with mTNBC face a devastating diagnosis with limited treatment options, with outcomes such as OS falling considerably behind those of other breast cancer subtypes, with a median OS of less than 18 months for mTNBC compared with 4–5 years for HR+ and HER2+ subtypes.(7-9)

We therefore welcome the Committee conclusion that atezolizumab plus nab-paclitaxel fulfils the end-of-life criteria, recognising that, in all scenario analyses presented, atezolizumab plus nab-paclitaxel offers more than 3 months' extension to life in a population that has a life expectancy of less than 24 months.

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1. Additional analysis

As detailed in the introduction, an offer for a commercial arrangement encompassing two ongoing NICE appraisals: Triple Negative Breast Cancer (TNBC [ID1522]) and Small-Cell Lung Cancer (SCLC [ID1504]) has been provided to NHSE.

All Committee preferred assumptions have been incorporated in to this offer, despite our concerns surrounding the overly conservative assumptions. Roche have conceded on this as our preference is for baseline funding for TNBC patients. However, if this proposed offer is not accepted, we would request to be considered for the Cancer Drugs Fund on the basis that there is plausible potential for the drug to satisfy the criteria for routine commissioning and additional data being collected which will inform areas of uncertainty.

To assist the Committee in their decision making, additional analyses and results have been provided for each of these scenarios in Appendix A (with TNBC and SCLC commercial arrangement) and B (Cancer Drug Fund).

The following assumptions are included across both scenarios to reflect committee preferred assumptions:

- The limit of 18-cycles for paclitaxel is removed, and patients receive paclitaxel until progression or discontinuation due to unacceptable toxicity (Section 3.12, page 14-15 of ACD)
- No treatment waning is implemented (Section 3.11, page 13 of ACD)
- Health state costs updated to reflect a monthly oncology visit (Section 3.0, page 4-5 of ACD)
- Weekly paclitaxel is agreed to be the most relevant comparator, and only weekly paclitaxel results are presented (Section 3.4, page 7 of ACD)

For the remaining assumptions implemented, please see the respective Appendices.

We look forward to hearing the Committee considerations on our response, which we hope will result in a positive final recommendation for atezolizumab in combination with nab-paclitaxel for PD-L1 positive, triple-negative breast cancer.

Appendix A – Offer to NHSE for Commercial Arrangement

We propose a [redacted] to the list price of atezolizumab, comprising [redacted]

This offer is on the basis [redacted]

Whilst we have not received formal sign off from NHSE on this offer, our understanding is that it is currently being considered through their approval and governance process.

The results below reflect the assumptions as outlined in Section 3 of our ACD response, in addition to the following:

- Nab-paclitaxel clinical data are presented as a proxy for paclitaxel, for OS, PFS and TTOT, instead of the NMA results (Section 3.10, page 12-13 of the ACD)
- An updated PAS for atezolizumab is included at [redacted]
- A range of values for a nab-paclitaxel discount are included given that the actual discount is unknown to Roche

We note that the ICERs presented below are conservative for a number of reasons: these estimates do not include consideration of the impact upon treatment with atezolizumab for carers, do not include dis-utilities associated with paclitaxel treatment and, most importantly, the ICERs for the equivalence scenario are likely to overstate the efficacy of paclitaxel by using nab-paclitaxel clinical data. Nab-paclitaxel is expected to be similar or marginally better than paclitaxel, and thus the relative benefit of atezolizumab is underestimated. We would like to reiterate the Committee's position that this assumption is "not a perfect approach", therefore the ICERs under this scenario can be considered the most conservative assessment.

As you will see from the results below, the [redacted] now means all scenarios are cost effective under the End of Life threshold, irrespective of the nab-paclitaxel discount level. Given this, with specific reference to the provisions of Section 3.5.42 (NICE "Guide to the processes of technology appraisal"), we would ask whether this could proceed without a second Committee meeting and the final appraisal document (FAD) be signed off by the Committee, electronically. We believe this would ensure patient access in a timely manner, while also conserving key NICE and Committee resources.

Nevertheless, if the Chair feels this is not appropriate, we request to be scheduled for the 24th March 2020 Committee meeting.

Table 1. Additional ICERs addressing the Committee preferred assumptions, with updated PAS

Nab-paclitaxel discount	ICER assuming paclitaxel and nab-paclitaxel equivalence
0%	£47,976
5%	£46,679
10%	£45,381
15%	£44,083
20%	£42,785
25%	£41,488
30%	£40,190
35%	£38,892
40%	£37,595
45%	£36,297
50%	£34,999
55%	£33,701
60%	£32,404
65%	£31,106
70%	£29,808
75%	£28,511
80%	£27,213
85%	£25,915
90%	£24,617
95%	£23,320
Key: ICER, incremental cost-effectiveness ratio; PAS, patient access scheme.	

Appendix B – Cancer Drugs Fund case

As the offer outlined in Appendix A has not received formal ratification from NHSE and, [redacted], Roche feel it pertinent to highlight our position for Cancer Drugs Fund (CDF), if the proposed offer is not accepted.

A CDF recommendation can be made when "*We consider that there is plausible potential for the drug to satisfy the criteria for routine commissioning, but there is significant remaining clinical uncertainty which needs more investigation, through data collection in the NHS or clinical studies."*(10) Based on these criteria, we believe that atezolizumab in combination with nab-paclitaxel is an eligible candidate for the CDF.

We consider that atezolizumab in combination with nab-paclitaxel can be considered plausibly cost-effective. However, as outlined in the ACD, there is one key clinical uncertainty remaining in this appraisal: can nab-paclitaxel be considered a proxy for paclitaxel in the assessment of efficacy? While there is uncertainty in the NMA developed for this appraisal, there is also uncertainty arising from the use of the control arm from IMpassion130. In fact, the weight of the clinical evidence available suggests that nab-paclitaxel is similarly efficacious, if not slightly better than weekly paclitaxel, and as such, the ICER derived from using nab-paclitaxel clinical efficacy from IMpassion130 as a proxy for paclitaxel, is at the highest end of the spectrum (overly conservative), thus understates the potential value of this medicine.

Table 2 highlights the uncertainty inherent for this decision problem by showing the range of ICERs atezolizumab plus nab-paclitaxel may be expected to achieve versus paclitaxel, based on different assumptions around the relative efficacy of paclitaxel versus nab-paclitaxel. These range from a 24-week LYG based on the CALGB 40502 study.(5); to zero LYG gain from the assumption of equivalence - with the NMA results incorporated within, at a 10-week LYG. The impact on the ICER is over £20,000 within this range.

This clinical uncertainty can be overcome through further data collection in clinical studies. Of note, the IMpassion131 trial, a Roche sponsored study of atezolizumab in combination with paclitaxel versus paclitaxel, due to read out with OS results [redacted], provides an opportunity to overcome this remaining clinical uncertainty. This study will contain mature, contemporaneous data for paclitaxel in a PD-L1 +ve population.

Based on this, if baseline funding is unavailable, we ask the committee to appraise us for inclusion in to the Cancer Drugs Fund. Atezolizumab plus nab-paclitaxel is an important innovation, and a major breakthrough in managing mTNBC. The unmet need in this population is evident from the uptake experienced in the EAMS and Free of Charge schemes ([redacted] patients, respectively). As stated by the Committee, it is the first treatment to substantially improve outcomes compared with chemotherapy in this population, who have been left behind in the wake of innovations and improvements in survival outcomes for patients with other types of breast cancer.

Table 2. Additional ICERs highlighting the impact of clinical uncertainty

Scenario >>	**Equivalence of paclitaxel and nab-paclitaxel**					**Company NMA**	
LYG, nab-paclitaxel versus paclitaxel >>	None	2 weeks	4 weeks	6 weeks	8 weeks	10 weeks	24 weeks
Supporting literature >>	None	Luhn et al.(3)	–	Liu et al.(2)	–	Gradishar et al.(1)	CALG.(5)
Atezolizumab PAS >>	[redacted]						
ICERs at varying nab-paclitaxel discounts:							
0%	**£72,401**	**£63,127**	**£60,109**	**£57,384**	**£54,910**	**£52,339**	**£41,128**
5%	£71,103	£61,902	£58,948	£56,280	£53,858	£51,341	£40,365
10%	£69,806	£60,678	£57,787	£55,176	£52,806	£50,343	£39,602
15%	£68,508	£59,454	£56,626	£54,072	£51,754	£49,345	£38,839
20%	£67,210	£58,230	£55,465	£52,968	£50,702	£48,346	£38,076
25%	£65,913	£57,005	£54,304	£51,865	£49,650	£47,348	£37,313
30%	£64,615	£55,781	£53,143	£50,761	£48,598	£46,350	£36,550
35%	£63,317	£54,557	£51,982	£49,657	£47,546	£45,352	£35,787
40%	£62,019	£53,333	£50,821	£48,553	£46,494	£44,354	£35,024
45%	£60,722	£52,108	£49,660	£47,449	£45,442	£43,356	£34,261
50%	£59,424	£50,884	£48,499	£46,345	£44,390	£42,358	£33,498
55%	£58,126	£49,660	£47,338	£45,241	£43,338	£41,360	£32,735
60%	£56,829	£48,436	£46,177	£44,137	£42,286	£40,362	£31,972
65%	£55,531	£47,211	£45,016	£43,034	£41,234	£39,364	£31,209
70%	£54,233	£45,987	£43,855	£41,930	£40,182	£38,365	£30,446
75%	£52,935	£44,763	£42,694	£40,826	£39,130	£37,367	£29,683
80%	£51,638	£43,538	£41,533	£39,722	£38,078	£36,369	£28,921
85%	£50,340	£42,314	£40,372	£38,618	£37,026	£35,371	£28,158
90%	£49,042	£41,090	£39,211	£37,514	£35,974	£34,373	£27,395
95%	£47,744	£39,866	£38,050	£36,410	£34,922	£33,375	£26,632
Key: ICER, incremental cost-effectiveness ratio; LYG, life years gained; NMA, network meta-analysis; OS, overall survival; PAS, patient access scheme. ICERs for alternative LYG estimated in a simple way by adjusting the relative effect of nab-paclitaxel to paclitaxel in the NMA piece for OS (5 months+)							

Appendix C

Table 3. Weighted summary statistics of matching variables for matching to the E2100 trial – OS

	E2100	Atezolizumab + nab-paclitaxel	p	SMD
n_{eff} (Effective sample size)	230.00	57.76		
age	54.69 (11.59)	54.65 (12.28)	0.984	0.003
Race: White	0.74 (0.44)	0.74 (0.44)	0.984	0.003
Race: Black	0.13 (0.34)	0.13 (0.34)	0.998	<0.001
Race: Asian	0.01 (0.09)	0.01 (0.10)	0.819	0.016
Time from init. to met. diagnosis	3.49 (3.74)	3.47 (4.28)	0.981	0.004
Metastatic disease	0.33 (0.93)	0.32 (0.28)	0.898	0.015
Number of disease sites	2.47 (1.17)	2.46 (1.08)	0.991	0.002
Bone metastases	0.37 (0.48)	0.36 (0.48)	0.984	0.003
Liver metastases	0.28 (0.45)	0.28 (0.45)	0.975	0.004
Lung metastases	0.53 (0.50)	0.53 (0.50)	0.992	0.001
Prior anthracycline therapy	0.57 (0.50)	0.57 (0.50)	0.982	0.003
Prior adjuvant taxane treatment	0.28 (0.45)	0.28 (0.45)	0.979	0.003

Key: sd: Standard deviation; p: P-value from a Chi-square test; SMD: Standardised mean difference defined as the difference in means divided by the pooled standard deviation.

Table 4. Weighted summary statistics of matching variables for matching to the E2100 trial – PFS

	E2100	Atezolizumab + nab-paclitaxel	p	SMD
n_{eff} (Effective sample size)	230.00	79.04		
age	54.69 (11.59)	54.69 (12.05)	1.000	<0.001
Race: White	0.74 (0.44)	0.74 (0.44)	0.999	<0.001
Race: Black	0.13 (0.34)	0.13 (0.34)	1.000	<0.001
Race: Asian	0.01 (0.09)	0.01 (0.09)	0.981	0.002
Time from init. to met. diagnosis	3.49 (3.74)	3.49 (4.40)	1.000	<0.001
Number of disease sites	2.47 (1.17)	2.47 (1.14)	1.000	<0.001
Bone metastases	0.37 (0.48)	0.37 (0.48)	0.999	<0.001
Liver metastases	0.28 (0.45)	0.28 (0.45)	1.000	<0.001
Lung metastases	0.53 (0.50)	0.53 (0.50)	1.000	<0.001
Prior anthracycline therapy	0.57 (0.50)	0.57 (0.50)	0.999	<0.001
Prior adjuvant taxane treatment	0.28 (0.45)	0.28 (0.45)	0.999	<0.001

Key: sd: Standard deviation; p: P-value from a Chi-square test; SMD: Standardised mean difference defined as the difference in means divided by the pooled standard deviation.

Table 5. Weighted summary statistics of matching variables for matching to the MERIDIAN trial – OS

	MERIDIAN	**A + nab-paclitaxel**	**P**	**SMD**
n_{eff}	78.00	95.08		
age	54.83 (11.41)	54.83 (13.50)	1.000	<0.001
height	160.88 (7.71)	160.88 (8.49)	1.000	<0.001
weight	72.99 (18.04)	72.99 (18.24)	1.000	<0.001
BMI	28.09 (6.11)	28.09 (6.22)	1.000	<0.001
regnaeu	0.42 (0.50)	0.42 (0.50)	1.000	<0.001
Region: Asia	0.24 (0.43)	0.24 (0.43)	1.000	<0.001
Race: White	0.56 (0.50)	0.56 (0.50)	1.000	<0.001
Race: Black	0.14 (0.35)	0.14 (0.35)	1.000	<0.001
Race: Asian	0.24 (0.43)	0.24 (0.43)	1.000	<0.001
ECOG status 0	0.64 (0.48)	0.64 (0.48)	1.000	<0.001
Number of disease sites	2.41 (1.13)	2.41 (1.09)	1.000	<0.001
Sum of longest diameters 18mm	72.19 (57.05)	72.19 (72.29)	1.000	<0.001
Bone metastases	0.26 (0.44)	0.26 (0.44)	1.000	<0.001
Liver metastases	0.26 (0.44)	0.26 (0.44)	1.000	<0.001
Lung metastases	0.47 (0.50)	0.47 (0.50)	1.000	<0.001
Prior anthracycline therapy	0.50 (0.50)	0.50 (0.50)	1.000	<0.001
Prior adjuvant taxane treatment	0.33 (0.47)	0.33 (0.47)	1.000	<0.001
Systolic blood pressure	124.85 (13.52)	124.85 (15.14)	1.000	<0.001
Body temperature	36.47 (0.40)	36.47 (0.43)	1.000	<0.001
Key: sd: Standard deviation; p: P-value from a Chi-square test; SMD: Standardised mean difference defined as the difference in means divided by the pooled standard deviation.				

Table 6. Weighted summary statistics of matching variables for matching to the MERIDIAN trial – PFS

	MERIDIAN	A +nab-paclitaxel	P	SMD
n_{eff} (Effective sample size)	78.00	87.10		
age	54.83 (11.41)	54.83 (13.49)	1.000	<0.001
height	160.88 (7.71)	160.88 (9.04)	1.000	<0.001
BMI	28.09 (6.11)	28.09 (6.17)	1.000	<0.001
regnaeu	0.42 (0.50)	0.42 (0.50)	1.000	<0.001
Region: Asia	0.24 (0.43)	0.24 (0.43)	1.000	<0.001

Race: White	0.56 (0.50)	0.56 (0.50)	1.000	<0.001
Race: Black	0.14 (0.35)	0.14 (0.35)	1.000	<0.001
Race: Asian	0.24 (0.43)	0.24 (0.43)	1.000	<0.001
ECOG status 0	0.64 (0.48)	0.64 (0.48)	1.000	<0.001
Number of disease sites	2.41 (1.13)	2.41 (1.06)	1.000	<0.001
Sum of longest diameters 18mm	72.51 (52.49)	72.51 (70.28)	1.000	<0.001
Time from met. diag. to rand.	0.27 (0.62)	0.27 (0.29)	1.000	<0.001
Bone metastases	0.26 (0.44)	0.26 (0.44)	1.000	<0.001
Liver metastases	0.26 (0.44)	0.26 (0.44)	1.000	<0.001
Lung metastases	0.47 (0.50)	0.47 (0.50)	1.000	<0.001
Prior anthracycline therapy	0.50 (0.50)	0.50 (0.50)	1.000	<0.001
Prior adjuvant taxane treatment	0.33 (0.47)	0.33 (0.47)	1.000	<0.001
Diastolic blood pressure	75.72 (10.51)	75.72 (9.58)	1.000	<0.001
Body temperature	36.46 (0.40)	36.46 (0.43)	1.000	<0.001
Key: sd: Standard deviation; p: P-value from a Chi-square test; SMD: Standardised mean difference defined as the difference in means divided by the pooled standard deviation.				

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NICE National Institute for Health and Care Excellence

Atezolizumab with nab-paclitaxel for treating PD L1-positive, triple-negative, advanced breast cancer

Consultation on the appraisal consultation document – deadline for comments 5pm on **Thursday 24 October 2019** **email:** 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):	Breast Cancer Now
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]

Comment number	**Comments**

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NICE National Institute for Health and Care Excellence

Atezolizumab with nab-paclitaxel for treating PD L1-positive, triple-negative, advanced breast cancer

Consultation on the appraisal consultation document – deadline for comments 5pm on **Thursday 24 October 2019** **email:** NICE DOCS

	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	It is extremely disappointing that NICE has provisionally been unable to recommend atezolizumab with nab-paclitaxel as a treatment option for women who have untreated locally advanced or metastatic triple negative breast cancer and whose tumours express PD-L1.
2	This promising treatment would represent a significant advance in care for certain patients with triple negative breast cancer, for which the main current treatment option is chemotherapy. We reiterate from our original patient submission that triple negative breast cancer is usually more aggressive and harder to treat than other types of breast cancer and often results in poorer outcomes. Being diagnosed with metastatic triple negative breast cancer is extremely difficult to come to terms with both for patients and their family and friends. Patients are desperate to find treatments that will halt progression and extend life for as long as possible but also ensure a good quality of life which enables them to spend quality time with their loved ones. In section 3.2 of the ACD, the committee also recognised that there is a very high unmet clinical need among people with metastatic triple negative breast cancer, and that the availability of a new immunotherapy is an important development in this condition. This cannot be underestimated. Evidence has shown that people having atezolizumab with nab-paclitaxel live longer before their condition gets worse, than people having placebo and nab-paclitaxel. Having a treatment option which improves progression-free survival is crucial. One patient told us the impact of having this treatment as an option: 'This doesn't just affect the patient. It gives hope to the whole family as its horrific watching someone slowly die before your eyes. I know my cancer is incurable however it could be much more manageable and give me a better quality of life.' Evidence also suggest that patients could live longer on average with this treatment option (section 3.8). Although there is no direct comparison with the treatments that are most commonly used on the NHS for this patient group (taxanes), the committee felt that it was reasonable to assume nab-paclitaxel has a similar efficacy to paclitaxel. Having access to a treatment which could offer substantial life-extension is crucial for this group of patients. It would enable them to have precious time to spend with their loved ones, doing the things that matter most to them, which is invaluable.
3	For a period of time this treatment option was available via an Early Access to Medicines Scheme. This was extremely welcomed as it enabled this promising new medicine to reach eligible patients faster. The hopes of this patient group will have now been raised. As this is a draft decision, we urge Roche, NICE and NHS England to work together to explore every possible solution, to ensure this treatment option can be recommended for use.
4	Section 3.15 – Whilst this section highlights that this treatment option cannot currently be considered for the Cancer Drugs Fund (CDF) as it does not have plausible potential for cost-effectiveness at the current price, it isn't clear if the CDF would be a potential option if the estimates regarding cost-effectiveness changed. This section highlights that whilst additional data may help to provide some information, it states that the main uncertainty could not be addressed by more data collection whilst on the CDF. Can this be clarified in further documentation?
5	This draft decision also demonstrates that there is still work to do to ensure the changes that were made to NICE appraisal processes in 2018 achieve what they set out to do and reach a positive decision more quickly. This example should now be considered as part of the ongoing NICE review of its methods and processes.

Insert extra rows as needed

Checklist for submitting comments

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NICE National Institute for Health and Care Excellence

Atezolizumab with nab-paclitaxel for treating PD L1-positive, triple-negative, advanced breast cancer

Consultation on the appraisal consultation document – deadline for comments 5pm on **Thursday 24 October 2019** **email:** NICE DOCS

- 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.

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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Atezolizumab with nab-paclitaxel for treating PD L1-positive, triple-negative, advanced breast cancer [ID1522]

Name	[redacted]
Role	[redacted]
Organisation	UK Breast Cancer Group
Location	Manchester
Comments on the ACD:	

The UKBCG considers this a very important advance in the worst prognosis sub-type of breast cancer. A new target for treating MBC reduces the number of patients with a very poor outlook. A median overall survival of 25.0 months in the PD-L1–positive subgroup with atezolizumab–nab-paclitaxel group which would be an important and clinically meaningful improvement. It compares favourably with 25.1 vs. 20.3 months improvement seen with the first phase III trial of trastuzumab with chemotherapy in metastatic breast cancer.
We hope that NICE and Roche can come to an agreement on price so that this important advance in treatment will be available to our patients.

Response to the Appraisal Consultation Document from clinical expert

The NICE appraisal looked at the role of Nab-Paclitaxel and Atezolizumab in first line metastatic TNBC. As a clinician, it was disappointing that the drug combination has not been recommended based on the evidence presented.

Triple negative breast cancers (TNBC) are usually aggressive and the average life expectancy for metastatic TNBC with current treatments is around 18 months. No significant scientific breakthrough has been made in this disease for last 2 decades unlike ER positive and Her-2 positive breast cancers. This innovative drug combination is the first to have shown an improvement in patient's outcome with improvement in both Progression free survival and Median overall survival in TNBC.

The drug combination was briefly available to suitable patients through the Early Access to Medicines Scheme (EAMS) and was well received by both patients and clinicians. The EAMS has now closed and suitable patients are unable to access this innovative drug combination. I would request both NICE and the Pharmaceutical company Roche to show flexibility and work together to make this drug available for patients.

Dr M B Mukesh

Atezolizumab with nab-paclitaxel for treating PD L1-positive, triple-negative, advanced breast cancer [ID1522]

Comments on the ACD received from the public through the NICE Website

Name	
Role	Public comment
Organisation	NHS
Location	
Conflict	
Notes	

Comments on the ACD:

Has all of the relevant evidence been taken into account?
As with all these treatments that are taken until progression and are additive to current treatment (even if it was only paclitaxel) they can NEVER be cost effective as additional treatment costs mean they will be more expensive than standard of care because they are more effective ie yet again living longer costs more and is penalised in NICE assessments. Other evidence needs to include ability to work, care for children and vunerable adults and more emphasis on being progression free.

Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence?
See above.

Are the recommendations sound and a suitable basis for guidance to the NHS?
This is are area on unmet need and immunotherapy with atezolizumab addresses many of the problems of rapidly advancing disease. Until you have seen the rapid response and improvement in quality of life these patients get with using immunotherapy then the current recommendations are not sound and suitable. Young women the triple negative disease , rapidly advancing who are caring for children and who through the use of these agent have a period of improved quality of life has to be accomadated in recommemndations.

Are there any aspects of the recommendations that need particular consideration to ensure we avoid unlawful discrimination against any group of people on the grounds of race, gender, disability, religion or belief, sexual orientation, age, gender reassignment, pregnancy and maternity?
No.

Name	
Role	Clinical oncologist
Organisation	
Location	
Conflict	
Notes	

Comments on the ACD:

I am a clinical oncologist and lead for cancer research in Peninsula. This group of patients have a dismal outlook with no real improvement in their treatment options for years, except lots of not terribly effective chemotherapy regimes continuously until they die or give up!

for the PDL-1 positive subgroup (40%) there is a clinically meaniful improvement in these patients outlooks with not much extra patient related toxicity. A few will get immunotherapy related toxicities, that can usually be dealt with by steroids/endocrine replacement. It would be a real shame if these patients missed out on this important research being implemented immediately in the UK. The eams offered some the opportunity, and there are a few trials open to a few. This will become the standard of care globally, so all ongoing studies will then include immunotherapy from now on as a standard of care. Therefore we in the UK need to keep up with the pace of change to be part of the commercial research in the world, with the huge benefit this brings to the Uk in terms of funding and patient benefit. I am sure some compromise, as usually can be made with NHS/pharma/ tax payers interests being mutually respected, so that patients can access this important new treatment option

Name	
Role	Public comment
Organisation	NHS
Location	
Conflict	
Notes	

Comments on the ACD:

Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence?
No. Please see comments below.

1. The recommendations state that paclitaxel should remain the standard of care. This is seem very unreasonable in a population who will invariably have received this in the neoadjvuant/adjuvant setting and in many instances will have progressed on treatment.

I would like to illustrate this by providing you with an example of a patient treated via the EAMS pathway from Kent. She was treated with neoadjuvant intent and her tumour grew through both antracycline but also the taxane/carboplatin elements of neoadjvant. Her disease remained operable and she underwent surgery then radiotherapy. Recognizing that neoadjuvant chemotherapy had been curtailed she elected to have adjuvant capecitibine. Sadly she relapsed within the liver only a few months after completing this. This lady has already demonstrated resistance to paclitaxel so this would very definitely have been a futile choice for her. The short interval from completion of adjuvant capecitibine precluded her from participation in 1st line metastatic studies. Her relapse occurred just as the EAMS access opened and after testing was eligible for treatment. She is now close to 6 months into treatment with control demonstrated on imaging, resolution of liver related symptoms and excellent quality of life. I have no doubt that there is no other option from the currently available lines of chemotherapy that could have given her this time, indeed she has never been in the position until now of having a scan which shows response.

2. The nabpaclitaxel/atezolizumab target population are identified by the PD1 biomarker . This is a niche subpopulation of the already comparatively small TNBC (~35% of those tested within the EAMS pathway). NICE can therefore be reassured that a positive decision to fund these agents is not going to open the flood gates to large patient numbers. This is exemplified by the Kent experience. As a cancer center drawing from one of the largest catchment areas in the UK (ie whole of kent) we have identified only 7 patients tested through the EAMS pathway who would be eligible for treatment.

Name	
Role	
Organisation	
Location	
Conflict	
Notes	

Comments on the ACD:

Has all of the relevant evidence been taken into account?
Yes

Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence?
Yes

Are the recommendations sound and a suitable basis for guidance to the NHS?
Yes

Are there any aspects of the recommendations that need particular consideration to ensure we avoid unlawful discrimination against any group of people on the grounds of race, gender, disability, religion or belief, sexual orientation, age, gender reassignment, pregnancy and maternity?
No

Committee discussion section:
IMpassion131 is looking at the use of weekly paclitaxel and will hopefully make this treatment more affordable.

I feel that there is huge unmet need in treating metastatic TNBC. I work in south London with a large afrocarribean population who tend to present late with advanced disease and have a higher proportion of triple negative breast cancers. This would be a big step forward for these patients.

Name	
Role	Public comment
Organisation	NHS
Location	
Conflict	
Notes	

Comments on the ACD:

It is somewhat disappointing to see a negative opinion on nab-paclitaxel and atezolizumab in first line therapy for triple negative IC>1% breast cancer. This is a population of predominantly young women with very few treatment options. In addition the IMPASSION 131 study will undoubtedly report shortly examining the same question but with paclitaxel as the chemotherapy backbone. If the results of IMPASSION-131 are comparable then the extra cost of nab-paclitaxel will be relatively short-lived as paclitaxel would be substituted. If the result is negative this may call the use of atezolizumab into question altogether. There is a strong rationale, therefore, for accepting nab-paclitaxel atezolizumab with the condition that the approval is reviewed with IMPASSION-131 results in 2020.