NICE National Institute for Health and Care Excellence

Single Technology Appraisal

Pembrolizumab plus chemotherapy for untreated, triple-negative, locally recurrent unresectable or metastatic breast cancer [ID1546]

Committee Papers

NICE National Institute for Health and Care Excellence

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

SINGLE TECHNOLOGY APPRAISAL

Pembrolizumab plus chemotherapy for untreated, triple-negative, locally recurrent unresectable or metastatic breast cancer [ID1546]

Contents:

The following documents are made available to consultees and commentators:

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

Appraisal title

Single Technology Appraisal

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

Type of stakeholder:

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

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

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

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

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

Comment number	Type of stakeholder	Organisation name	Stakeholder comment Please insert each new comment in a new row	NICE Response Please respond to each comment
1	Company (consultee)	MSD	Choice of relevant comparator for this technology appraisal (§ 3.3 of ACD). We welcome the Committee's conclusion that high unmet medical need remains for untreated, locally recurrent unresectable metastatic breast cancer TNBC and especially for people who cannot have atezolizumab in combination with nab-paclitaxel. Within the ACD it is stated that the Committee concluded that the relevant comparators for this appraisal should be paclitaxel, docetaxel and atezolizumab + nab-paclitaxel. MSD understands that conclusion was reached on the basis of post-hoc clinical trial data from Rugo et al 2020 [3] which demonstrated a limited overlap between the IMpassion-130 and KEYNOTE-355 study populations (36% based on the Rugo et al 2020 publication). Considering the updated positioning for pembrolizumab + taxanes for the distinct subgroup of people who cannot have atezolizumab combination (whose tumour is PD-L1 <1% with SP-142 but PD-L1 +ve CPS ≥10 by Dako 22C3 Assay), MSD considers that atezolizumab + nab-paclitaxel is no longer a relevant comparator for this STA. We therefore focus our response specifically to the relevance of paclitaxel and docetaxel comparators for the purpose of the HTA and quantify the impact of the cost effectiveness comparisons for each of these. Weekly paclitaxel was chosen as the preferred regimen over Q3W in KEYNOTE-355 as the former is better tolerated and superior in efficacy [4]. In 2020 TA639 the Committee concluded that paclitaxel was the most relevant chemotherapy comparator at that time. However, during ID1546, based on clinical opinion and due to capacity issues faced by the NHS during COVID, docetaxel utilisation was noted to have increased, followed by some limited use of nab-paclitaxel. These agents (docetaxel and nab-paclitaxel) can be administered Q3W compared with paclitaxel (QW). It was also noted that docetaxel utilisation was likely to remain in NHS chemotherapy units post-COVID-19 due to its capacity benefit. The clinical expert noted that docetaxel would not be used if a patient had had it before in the curative setting, but a proportion of patients would access it as a treatment option (Page 7 of the ACD).	Comment noted. At its second meeting, the committee considered the most appropriate comparators. The committee concluded a blended comparator was not appropriate and that the relevant comparators were paclitaxel and docetaxel (Final Appraisal Determination sections 3.3 and 3.4)

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			At the time of submitting this appraisal to NICE (November 2020), the primary chemotherapy comparator and this is also reflected in KEYNOTE-355. Even with the capacity benefits described above, clinical experts have stated docetaxel would not be the chemotherapy of choice due to the lower tolerability profile. COVID interim guidelines for the delivery of systemic anticancer treatments (NG161) provide NHS Trusts the option of using nab-paclitaxel for mTNBC instead of paclitaxel which is better tolerated and therefore reduces the toxicities and potential for admission [5]. This can be procured at a commercial in confidence discount by the NHS. Since docetaxel is used primarily in earlier disease stages and in fit patients, experts commented that it is very likely paclitaxel (or nab-paclitaxel which can be accessed as a result of COVD interim guidelines) would be used instead due to their superior safety profiles. Patients with de-novo metastatic disease, who therefore have not received treatment in the early setting, may receive docetaxel if the clinician feels it is appropriate. After consulting with clinicians during the ACD response period, MSD understands the use of docetaxel in TNBC patients varies by hospital and some centres do not use it at all for mTNBC (Table 1). This feedback is consistent with our original positioning of docetaxel as a secondary chemotherapy comparator. Assuming that docetaxel is the most relevant comparator for has a detrimental impact on the cost-effectiveness which is part due to the lower acquisition and administration costs versus paclitaxel. MSD is concerned with the likely inconsistencies arising in future HTA evaluations by a precedent being set up, whereby alternative secondary comparators which is not extensively used in the NHS (as is the case for docetaxel based on clinical expert opinion) could be used to estimate the C/E of a technology against in future appraisals. Considering the above, MSD considers pembrolizumab is disadvantaged by being assessed versus docetaxel when the Committee previously concluded that paclitaxel was the most relevant comparator for TA639. Due to the lack of docetaxel data from the literature or the trial, a simplifying assumption was made that the efficacy of all taxanes is equivalent and can be proxied using the taxane comparator arm data from KEYNOTE-355. This assumption may bias against pembrolizumab + taxanes since the safety profile for docetaxel is informed by data from paclitaxel or nab-paclitaxel. It is accepted that these agents are better tolerated compared with docetaxel, which may lead to some element of under-estimation in the cost of managing adverse events (AEs). Due to its safety profile, docetaxel is used to treat earlier stages of disease, with the exception of the de novo metastatic patients mentioned above. In KEYNOTE-355 within	

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			the CPS ≥ 10 score subgroup the percentage of de-novo metastatic patients was 31.6%. Based on the clinical expert opinion gathered by MSD and to address the Committee's concerns around the impact of docetaxel use in the C/E estimates, we present a 70:30 paclitaxel to docetaxel ratio. This assumes that 30% of the patients presenting with advanced/metastatic disease have not been previously treated at an earlier setting with docetaxel and therefore the first chemotherapy option could be that of docetaxel. This scenario is exploratory in nature but supported by the clinical expert input sought during the consultation period (Table 1). These analyses adjust the drug regimen comparator and drug administration costs of the model accordingly (all other cost and effect inputs remain unchanged; Table 2 presents detailed calculations). These analyses may reflect closer the true ICER for this intervention by accounting for some docetaxel. This increases the ICER to £37,137 per QALY (vs £34,887 with 100% paclitaxel use) However, it is important to note that the impact on the C/E is lower versus when 100% docetaxel is used as a comparator. Table 3 presents the C/E results assuming a mix of paclitaxel 70% and 30% docetaxel. The ICERs remain below £50,000 QALY across a number of alternative scenarios. Finally, since pembrolizumab can be used in combination with nab-paclitaxel which is a branded medicine, the 70:30 chemotherapy mix (paclitaxel/nab-paclitaxel 70%: docetaxel 30%) ICERs should be interpreted as a pessimistic and upper C/E estimate for this technology. 3. Rugo HS, Loi S, Adams S, Schmid P, Schneeweiss A, Barrios CH, et al. PD-L1 Immunohistochemistry Assay Comparison in Atezolizumab plus nab-Paclitaxel-Treated Advanced Triple-Negative Breast Cancer. J Natl Cancer Inst. 2021. 4. Seidman AD, Berry D, Cirrincione C, Harris L, Muss H, Marcom PK, et al. Randomized phase III trial of weekly compared with every-3-weeks paclitaxel for metastatic breast cancer, with trastuzumab for all HER-2 overexpressors and random assignment to trastuzumab or not in HER-2 nonoverexpressors: final results of Cancer and Leukemia Group B protocol 9840. J Clin Oncol. 2008;26(10):1642-9. 5. NICE. NHS England interim treatment options during the COVID-19 pandemic 2022 [Available from: https://www.nice.org.uk/guidance/ng161/resources.	
2	Company (consultee)	MSD	Uncertainty in the long term benefit of pembrolizumab + taxanes (§ 3.5 of ACD). MSD understands that the question around the uncertainty of long-term benefit for pembrolizumab + taxanes is raised with regards to long term survivorship trajectory beyond the KEYNOTE-355 trial follow up. We would like to take the opportunity to correct a typographical error in our part which is	Comment noted. At its second meeting, the committee considered the long-term benefit of pembrolizumab. It concluded pembrolizumab is more effective than paclitaxel or nab-paclitaxel (see Final Appraisal

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			contained within the technical engagement response (page 4). Nonetheless, the arguments around the long term benefit of the intervention remain valid considering the substantial follow up which is observed alongside a very aggressive cancer such as mTNBC. We would like to clarify that the median follow up of KEYNOTE-355 as the median OS time ([redacted] for Pembrolizumab + taxanes vs taxanes alone). The values above refer to the CPS ≥ 10 population all chemotherapy patients and is "actual =follow-up duration" which is defined from randomization until earliest of the date of death or the database cutoff date if the subject is still alive. We offer the corrected values specifically to the CPS ≥ 10 taxane subgroup below. The final analysis (FA) in KEYNOTE-355 which took place on the 15th of June 2021, the follow up CPS≥10 taxane subgroup was [redacted] months for pembrolizumab + taxanes and taxanes alone respectively (see Table 7). The median theoretical follow up of the study with regards to the PD-L1 CPS ≥ 10 taxane subgroup at the final analysis was reported elsewhere exceeds 4 months (Table 8). This uses a definition from randomization to database-cut off date regardless of survival status with maximum follow up is approximately [redacted]. Throughout the follow up period we see a clear and sustained separation of the OS Kaplan-Meier (KM) curves throughout the follow up period (although we acknowledge some censoring in the tail of the KM curves). This is reflected in the favorable and statistically significant OS HR (0.54, 95% CI: 0.36, 0.82). Considering the aggressiveness of mTNBC, the follow up of KEYNOTE-355 is very robust and indicative of a long term benefit for these patients. Further, the OS of KEYNOTE-355 CPS≥10 population has been formally tested for and has met statistical significance. The magnitude of OS benefit is consistent for the pembrolizumab + taxanes versus taxanes alone in this population. MSD sought clinical expert opinion to inform the submission development process. Clinical experts noted that the aggressiveness of metastatic TNBC means that most patients would not survive beyond the first 3 years given the aggressiveness of mTNBC. This has been observed across a number of RWE publications 14, 40, 43]. The small percentage of long survivors (those beyond 3 years) with current chemotherapy would be expected to have a lower risk of death of a result of mTNBC (but an increased risk of death due to all-cause mortality as the cohort ages over time). Clinical studies clearly demonstrate the short life expectancy of mTNBC patients this since only a very small percentage survive beyond 2 years ([redacted] from KEYNOTE-355 PD-L1 CPS ≥ 10 taxane subgroup (34% across all PD-L1 CPS ≥ 10 or 36.65% of IMpassion 130 IC 1% population) [6].	Determination section 3.6)

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			Based on their prior experience with IOs in solid tumors, clinical experts noted that a stabilisation and subsequent plateau in would OS be expected to be observed from around year 3 onwards. This is due to the unique mode of action of IO therapies such as pembrolizumab which is widely recognised to contribute towards an immunotherapeutic effect. This has been observed across a number of metastatic trials and tumors (including Non-Small Cell Lung Cancer, Melanoma and Head & Neck), whereby a percentage of patients achieves long term survival due to the unique mode of action of IO agents [7-9]. Since pembrolizumab + taxanes is associated with significant OS benefit, a higher percentage of patients would be expected to be long-term survivors. Within the current model [redacted] patients alive at year 3 for pembrolizumab + taxanes versus [redacted] in the taxane arm (observed survivorship from KEYNOTE-355). Survival estimates for the current standard of care chemotherapies at year 3 extracted from the literature range between 6.7% (TA639 estimate for nab-paclitaxel) to 22.6% (Battisti et al 2018 DFI > 12months). Clinical experts advised MSD that Battisti et al 2018 with some long term adjustments at year 5 and year 10 survivorship is a good proxy of long term OS survival with current chemotherapies. For taxanes, estimates obtained were; [redacted] at year 5 and [redacted] at year 10 which are in line with the RWE sources included in the submission. Specific to metastatic TNBC and considering the unique mode of action of IO therapies, clinical experts suggested a [redacted] survival at year 5 and a [redacted] of long term survivors at 10 year when patients were treated with pembrolizumab + taxanes [10]. The survival analyses and parametric curve selection for OS used in the base-case followed the NICE TSD DSU 14 to identify the most appropriate parametric models for OS extrapolations. In brief, the process included visual inspections, the assessment of goodness of fit statistics (AIC/BIC), clinical plausibility and validity of long term projections of long term survival projections. MSD has previously raised concerns on the ERG's preference to model the long term OS for pembrolizumab + taxanes using the exponential curve due to its overly simplistic in nature due its reliance in constant hazards which may not adequately capture the long term survivors with IO agents. We have explored the impact of alternative long term OS projections and in the C/E. Keeping all of the other company base-case assumptions unchanged; the ICER using exponential to model pembrolizumab + taxanes OS increases to £49,426/QALY. Figure 2 below shows the impact of the exponential curve versus the company's preferred log-	

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			normal distribution in terms of long term predications. Overall, using the exponential function~ [redacted] of patients are expected to be alive at year 10 for pembrolizumab +taxanes versus [redacted] in taxane arm. Considering that Battisti et al reports a 10 year survival of 3.49%, the exponential distribution is highly conservative with regards to the cost-effectiveness itself when used in isolation to model pembrolizumab + taxanes alone. Alternative scenarios with more optimistic estimates of survival are presented below based on the current clinical data from KEYNOTE-355 and their impact on the C/E estimates. MSD's current base-case using log-normal to model OS results in an ICER of £34,887/QALY and a 10 year survival of [redacted] (2nd best curve based on AIC/BIC, visual inspection, and clinical opinion and assessment versus RWE). Using a log-logistic distribution to model P+T OS (3rd best based on AIC/BIC, visual inspection and clinical opinion and assessment versus RWE) results in an ICER of £34,597/QALY and [redacted] survivorship at year 10. Using Generalised Gamma (worst ranked model based on AIC/BIC but only 5.73 points difference vs exponential which is preferred by the ERG) results in an ICER of £41,558/QALY and [redacted] survivorship at year [redacted] Figure 3 below includes all OS curves discussed above (exponential, log-normal, log-logistic, gen-gamma). Table 3 presents the impact on the C/E results using alternative OS extrapolations. The ICERs remain below £50,000 QALY, even when a chemotherapy mix (paclitaxel 70% : docetaxel to 30%) is assumed alongside alternative plausible extrapolations with or without treatment waning. The conservatism of using exponential to model for pembrolizumab + taxanes, is even more apparent when compared with long term survivorship estimates by Deluche et al 2020. Clinical experts noted that this source contained overly optimistic long term OS projections with SoC chemotherapies; 10 year survivorship at 6.65% (Figure 4 and Table 10), which could only probably be explained if clinical trial participants were included in this retrospective study. Nonetheless, using the exponential to model the long term OS for pembrolizumab + taxanes results in a 10 year OS which is [redacted] and less than the [redacted] that could be long term survivors based on expert opinion and prior experience with IO agents. MSD urges the NICE AC to consider the C/E analyses results using the exponential survival model as high conservative for the purposes of decision making. 6. Schmid P, Adams S, Rugo HS, Schneeweiss A, Barrios CH, Iwata H, et al. IMpassion130: updated overall survival (OS) from a global, randomized, double-blind, placebo-controlled, Phase III study of atezolizumab (atezo) + nab- paclitaxel (nP) in	

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			previously untreated locally advanced or metastatic triple-negative breast cancer. Journal of Clinical Oncology. 2019;37(15_suppl):1003-. 7. Garon EB, Hellmann MD, Rizvi NA, Carcereny E, Leighl NB, Ahn MJ, et al. Five-Year Overall Survival for Patients With Advanced NonSmall-Cell Lung Cancer Treated With Pembrolizumab: Results From the Phase I KEYNOTE-001 Study. J Clin Oncol. 2019;37(28):2518-27. 8. Robert C, Ribas A, Wolchok JD, Hodi FS, Hamid O, Kefford R, et al. Anti-programmed-death-receptor-1 treatment with pembrolizumab in ipilimumab-refractory advanced melanoma: a randomised dose-comparison cohort of a phase 1 trial. Lancet. 2014;384(9948):1109-17. 9. Schadendorf D, Hodi FS, Robert C, Weber JS, Margolin K, Hamid O, et al. Pooled Analysis of Long-Term Survival Data From Phase II and Phase III Trials of Ipilimumab in Unresectable or Metastatic Melanoma. J Clin Oncol. 2015;33(17):1889-94. 10. NICE. TA639: Atezolizumab with nab-paclitaxel for untreated PD-L1-positive, locally advanced or metastatic, triple-negative breast cancer Technology appraisal guidance [TA639]. 2020.	
3	Company (consultee)	MSD	Uncertainty in the indirect treatment comparison results between pembrolizumab + taxanes versus atezolizumab + nab-paclitaxel. Considering the updated positioning for pembrolizumab + taxanes proposed for the distinct subgroup of people who cannot have atezolizumab combination (whose tumour is PD-L1 <1% with SP-142 but PD-L1 +ve CPS ≥10 by Dako 22C3 Assay), atezolizumab + nab-paclitaxel is no longer a relevant comparator for this STA. However, we would like to take the opportunity to comment on the uncertainties associated with the indirect treatment comparison. MSD raised at multiple occasions during the HTA process some key differences between the two studies informing the ITC (including trial recruitment criteria, PFS assessment), trial populations (baseline characteristics and differences in PD-L1 ascertainment) and the limited data reported concerning the subgroup of interest for this indication (CPS score ≥ 10). We did this proactively because we wanted to be transparent on the challenges that could be encountered later on during decision making. Considering these limitations, we positioned atezolizumab +nab-paclitaxel as a secondary alternative IO comparator since we understand that these two agents are not directly interchangeable for patients which are diagnosed with mTNBC. This is due to the limited overall overlap between study populations which is estimated to be ~36% based on a single post-hoc analysis from Impassion-130 by Rugo et al 2020.	Comment noted. At its second committee meeting, the committee concluded atezolizumab was no longer a relevant comparator and that the indirect treatment comparison was no longer needed for decision making (see Final Appraisal Determination section 3.7).

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			Nonetheless, the analyses were conducted by following the NICE DSU methodology and the updated NMA presented, were based upon the final database lock from KEYNOTE-355 leveraging the statistically significant OS results. The updated NMA results remain consistent with the earlier NMA results presented in the main submission (with the IA2 OS) and continue [redacted] pembrolizumab + taxanes versus Atezo + nab-paclitaxel for OS and PFS across the selected base-case and sensitivity analyses conducted. In brief, the selected base-case NMA results for OS HR = [redacted] and for the base case PFS by Investigator HR = 0[redacted] We were unable to provide the updated NMA results using Random Effects, but we do agree with the conclusions reached that RE analysis would not likely influence the point estimates of the results provided. Whilst we understand that the ITC results are no longer relevant for decision making purposes given the new positioning proposed for this technology, we would like to take the opportunity and thank both the Appraisal Committee and the ERG for their time critiquing this element of the submission.	
4	Company (consultee)	MSD	Choice of parametric extrapolation curves used to model pembrolizumab + taxanes (§ 3.9 of ACD). Within the ACD it is noted that; “The ERG agreed with the company’s choice of log-logistic extrapolation for paclitaxel but preferred an exponential model for pembrolizumab combination. It explained that the goodness of fit statistics between the exponential and log-normal models both corresponded with the observed data. However, it noted that the log-normal distribution showed a turning point within the first year whereas the smoothed hazard plot of the observed data did not show a turning point in the underlying hazard. The exponential distribution did not have a turning point.” MSD has already cautioned against over-interpreting smooth hazard plots in isolation when it comes to parametric model selection. We have discussed extensively in Comment 2 above why we disagree with the choice to model OS using an exponential distribution. We consider it overly simplistic to assume a constant hazard for an IO agent given the prior experience in treating solid tumors with IO therapies. It also results in overly pessimistic OS predictions over time based upon clinical opinion and based on long-term validity of OS projections versus RWE data. We would like to opportunity to position the exponential curve as highly conservative and as potentially biasing the C/E results against pembrolizumab + taxanes. This is especially the case when the ERG has accepted that the taxane chemotherapy arm which uses a log-logistic and assumes a decreasing hazard of death over time, has indeed been appropriately modelled. The conservatism of exponential distribution to model the OS for Pembrolizumab + taxanes is even more apparent when treatment waning is applied, which	Comment noted. At its second committee meeting, the committee discussed the choice of extrapolation curve for pembrolizumab. It concluded the exponential distribution for extrapolating overall survival better fitted the smoothed hazard plot (see Final Appraisal Determination section 3.9).

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			improves the ICER (due to the lower level of model adjustments introduced in the model). This is counterintuitive to how treatment waning normally work and adds further evidence to the conservatism of the exponential function used in the base-case. Regarding the lack of turning point to the hazard of OS for pembrolizumab + taxanes, this could be due to the method used to generate the "smoothed" hazard plots, or due to the sample size which is not big enough to show it. Goodness-of-fit should not be measured by the hazard plots but instead be evaluated versus the survival curves – this is according to NICE DSU guidelines (NICE DSU 14) and with clinical plausibility in mind regarding the validity of long-term projections [11]. Based on experience with IOs in other solid tumors, we expect the OS stabilisation and subsequent plateau to become more apparent as the data mature further. This is due to the unique mode of action of IO therapies such as pembrolizumab which is widely recognised to contribute towards an immunotherapeutic effect that has been observed across a number of tumours (including NSCLS, Melanoma and Head & Neck), whereby a percentage of patients achieves long term survival due to the unique mode of action of IO agents [7-9]. This immunotherapeutic effect cannot be captured using simple constant hazards assumptions for OS extrapolations. An example of modelled long term outcomes using the exponential function is presented below in Figure 1 depicts a 10 year survivorship with an IO agent siting well below the real world chemotherapy projections presented. This means that the Committee should consider the C/E results using an exponential function as highly conservative in nature. Other more plausible parametric survival options and their impact on the C/E have been described in comment 2 above and C/E results are presented in Table 5 below. These are appropriate to inform the Committee's decision for mTNBC patients whose tumour is PD-L1 <1% with SP-142 but PD-L1 +ve CPS ≥10 score by Dako 22C3 Assay. 11. Latimer N. NICE DSU TECHNICAL SUPPORT DOCUMENT 14: SURVIVAL ANALYSIS FOR ECONOMIC EVALUATIONS ALONGSIDE CLINICAL TRIALS - EXTRAPOLATION WITH PATIENT-LEVEL DATA. 2013.	
5	Company (consultee)	MSD	Assumptions on time to treatment discontinuation (TTD) for atezolizumab + nab-paclitaxel (§ 3.10 of ACD). Considering the updated positioning for pembrolizumab + taxanes proposed for the distinct subgroup of people who cannot have atezolizumab combination (whose tumour is	Comment noted. At its second committee meeting, the committee concluded atezolizumab was no longer a relevant comparator and that the

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			PD-L1 <1% with SP-142 but PD-L1 +ve CPS ≥10 by Dako 22C3 Assay), atezolizumab + nab-paclitaxel is no longer a relevant comparator for this STA. However, we would like to take the opportunity to comment on the most robust way used to inform assumptions around atezolizumab + nab-paclitaxel TTD. MSD considers the ERG's preferred assumptions around TTD modelling for atezolizumab + nab-paclitaxel, is very likely introducing bias against pembrolizumab + taxanes in the associated analyses. Evidence of this can be sourced from the TTD for atezolizumab + nab-paclitaxel reported in the TA639 Company submission documents (Table 48 for atezolizumab and Table 49 for nab-paclitaxel and company Technical Engagement Response for more information). Within each submission the company estimates a % of patients continuing treatment with atezolizumab between 9.0%-11.0% at year 2 dropping to 2.8%-4.6% at year 3. For nab-paclitaxel this was 2.8%-6.5% at year 2 dropping to 0.3%-3.0% at year 3. Our updated base-case assumption for TTD (equal to TTD from pembrolizumab + taxanes) results in 10.2% at year 2 and 4.3% at year 3. This demonstrates that assuming TTD being equal to that of pembrolizumab + taxanes is more robust to inform these comparisons (although we acknowledge that TTD data may not be directly transferable between studies. In contrast, the ERG's approach would result towards a lower TTD for atezolizumab + nab-paclitaxel. This demonstrates that assuming TTD being equal to that of pembrolizumab + taxanes is more robust to inform these comparisons (although we acknowledge that TTD data may not be directly fully transferable between studies). We would like to re-iterate that KEYNOTE-355 including a stopping rule (pembrolizumab + taxanes) for pembrolizumab but this is not the case for IMpassion-130. Therefore, assumptions which result in lower TTD (as the one employed by the ERG) are methodologically inconsistent. Whilst we understand that this issue is no longer relevant for decision making purposes given the new positioning proposed for this technology, we wanted to leverage this opportunity to briefly re-iterate the methodological inconsistencies, and to take the opportunity thank both the Appraisal Committee and the ERG for their time critiquing this element of the submission.	TTD for atezolizumab was no longer needed for decision making (see Final Appraisal Determination section 3.7).
6	Company (consultee)	MSD	Duration of treatment effect benefit over time for pembrolizumab + taxanes (§ 3.11 of ACD). MSD retains its position that the clinical data from KEYNOTE-355 does not show any	Comment noted. At its second meeting, the committee concluded the duration of benefit for pembrolizumab combination

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			evidence of treatment effect waning for pembrolizumab + taxanes during the follow up period which is approximately [redacted] in the taxane arm. Whilst KEYNOTE-355 included a maximum treatment with pembrolizumab for 35 cycles (or ~ 2 years; taxane treatment can be continued beyond this point), the unique mode of action of pembrolizumab means that patients continue to experience benefit beyond pembrolizumab cessation as demonstrated by the updated clinical data from KEYNOTE-355. Continued treatment benefit has also consistently been observed across a number of tumours whereby a small subset of patients experiences long term survival benefit. Due to lack of relevant clinical data to data from KEYNOTE-355 which can be used to inform robust modelling around this assumption, we do not agree with the application of treatment waning into the base-case assumptions. We caution against over-interpreting these results and the impact of waning for decision making given the level of conservatism that is associated with methods used to model treatment waning. Despite our concerns around the modelling of treatment waning, we have explored its impact in scenario analysis within the original submission using two alternative options for the modelling of treatment waning (described below). Option one which assumes an abrupt treatment effect stop at a specific time point (implies a HR = 1 for OS from that time point onwards which is not clinically plausible; similar to the preferences of Committee C). In this submission the ERG preferred a maximum treatment benefit of 5 years. This implies that the treatment benefit is only maintained for 3 years after pembrolizumab cessation and diminishes instantaneously thereafter which should be considered as a highly conservative for the purposes of decision making. An alternative pragmatic methodology of gradual treatment waning has also been explored. This was based upon a SEER dataset analysis. This applies a constant hazard rate after 4 years across both treatment arms which results in a gradual treatment waning adjustments being made from that timepoint onwards. In contrast to the methodology preferred by the ERG which functions by setting the OS hazard rate of pembrolizumab + taxanes equal to the OS hazard rate of the taxanes arm after year 5 (clinically implausible), the treatment waning analyses using SEER are more pragmatic and reflective of the real word setting since it applies a gradual treatment benefit decrease over time. Given this evidence we ask that the AC consider the 5Y treatment waning ICERs generated as highly conservative in nature for decision making. It further demonstrates the conservatism of the ERG's preferred choice of OS extrapolations using the exponential curve since treatment waning in fact improves the cost-effectiveness when applied.	should include an assumption that the treatment effect wanes after stopping treatment (see Final Appraisal Determination section 3.10).

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			Table 5 presents different waning scenarios discussed above and their associated impact on the ICER. All of these scenarios (including the ERG's preferred assumptions, and a mix chemotherapy comparator result in ICERs of less than £50,000 per QALY gained. MSD believes that the additional analyses presented mitigate against any further concerns around the C/E of this technology.	
7	Company (consultee)	MSD	Application of end-of-life criteria within this submission focusing on evidence for short life expectancy criterion for taxanes, comparisons of life expectancy versus TA639 and validity of modeled life years (§ 3.14 of ACD). The Guide to the methods of technology appraisal 2013 by NICE discussed in section 6.2.10 specifies: "In the case of a 'life-extending treatment at the end of life', the Appraisal Committee will satisfy itself that all of the following criteria have been met:[12] • the treatment is indicated for patients with a short life expectancy, normally less than 24 months and • there is sufficient evidence to indicate that the treatment has the prospect of offering an extension to life, normally of a mean value of at least an additional 3 months, compared with current NHS treatment. Below we summarise the end-of-life relevant data and we discuss these versus TA639. We also provide evidence from the literature which support the short-life-expectancy criterion taking into account the updated positioning proposed for this technology. Within the ACD document particular focus is given as to whether the short life expectancy criterion is fulfilled for patients treated with taxanes. MSD considers that end of life criteria and in particular, short life expectancy (normally less than 24 months), are met for this appraisal for the distinct subgroup whose tumour is PD-L1 <1% with SP-142 IC but PD-L1 +ve CPS ≥10 by Dako 22C3 Assay. To ensure a compelling case for End of Life has been put forward for consideration we explored the median, mean and 2-year survivorship across this submission and from TA639. Assessment of life years (LYs) and median survival reported from TA339 demonstrates a high level of consistency in modelled short-term predictions in. In TA639, trial design and population differences alongside alternative assumptions employed around the choice of parametric functions in the taxane OS extrapolation, all impact to a degree the mean taxane LYs reported within that submission. However, the minor differences in mean modelled LYs reported within TA639 versus this submission do not preclude the relevance of end-of-life criteria for taxane treated patients in this submission since patients treated with taxanes also have a short survival (as we	Comment noted. At its second meeting, the committee discussed the end of life criteria. It concluded that end of life criteria was met for pembrolizumab (Final Appraisal Determination section 3.14)

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

demonstrate below). Understanding these inherent differences is fundamental to enable a robust decision whilst avoiding any equity issues in the final recommendation, in particular for a subgroup of patients which is currently underserved with access only to standard chemotherapies.

Short life expectancy:
TNBC is known to be an aggressive cancer that disproportionately impacts younger women (mean age of diagnosis 53.0 years) and black women are nearly three times more likely to be diagnosed with the subtype than white women [2, 13].

MSD is aware that the application of end-of-life criteria is discussed by Appraisal Committees with regards to median and mean survival estimates in context to the disease severity and the current treatment options available within the NHS.

For the updated positioning and population now under consideration for this submission (tumour is PD-L1 <1% with SP-142 but PD-L1 positive CPS ≥10 by Dako 22C3 Assay) the only treatment option currently available is chemotherapy. The table below offers a top line summary of trial-reported outcomes where available (median survival and 2 year survival) with standard chemotherapies. It also reports the mean life years across mTNBC TA639 and ID1546. However, as noted above, some factors (trial design, populations and assumptions on extrapolations) can impact upon the mean LY estimates generated from health economic modelling (more information in Table 5 below). It is currently estimated approximately 17% of patients with metastatic TNBC would have a tumour that would be IC <1% (SP142 assay; ineligible for atezolizumab + nab-paclitaxel) but be CPS ≥10 (22C3 Dako Assay). These patients could therefore benefit from pembrolizumab + taxanes and could be disadvantaged if the current technology was not assessed with end-of-life criteria in consideration.

The estimates presented below (also Table 5) clearly demonstrate that the short life expectancy criterion (normally less than 24 months) is met for patients who are currently treated with taxanes (such as those whose tumour is PD-L1 <1% with SP-142 IC but PD-L1 +ve CPS ≥10 by Dako 22C3 Assay).

Study		Mean (months)	Median (months)	% alive at 24 months
KEYNOTE-355 Taxanes	Observed	NA	[redacted]	[redacted]
	Modelled	[redacted]	[redacted]	[redacted]
IMpassion130 nab-paclitaxel	Observed	N/A	17.9±	36.65%≠
	Modelled	1.6 LYs or 19.2	13.8 to 14.3	Paclitaxel[1]: 21% to

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		months updated to 1.797 LYs or 21.5 months[3≠]	updated to 18.6 - 21.6 by ERG[3]	22.7% Docetaxel[2:] 26% to 26.8%

Notes: extracted from TA639 Committee Documents: [1]; Table 40 CS, [2]; Table 41 CS, [3]; Table 33 ERG (we assume LY estimates are undiscounted). ± Medians extracted from latest IM-130 publication by Emens et al 2020 [14]; PD-L1 +ve, ≠ 2Y OS extracted from earlier IMpassion-130 publication by Schmid et al 2019 [6]; PD-L1 +ve.

We have also responded to the Committee's queries around the validity of the modelled LYs in this submission versus the estimates reported in TA639, although as noted above, we recognise that the extent to which we can make robust comparisons across HTAs is hindered by a number of reasons.

End-of-Life assessment discussion within TA639:
The following information was extracted from TA639 (Page 17 of 114 of ID1522 ERG report (sections 1.7 and 1.8).

"A technology meets NICE End of Life criteria if (i) life expectancy with standard of care treatments for the target population is under 24 months and (ii) the increase in life expectancy with the technology being appraised is at least 3 months. The estimates generated by the company model are that median life expectancy is 13.8 months for patients treated with paclitaxel and 14.3 months for patients treated with docetaxel. Results from the company model also show that, compared to treatment with paclitaxel and docetaxel, treatment with A+nabPx offers a median extension to life of 12.6 months and 11.6 months respectively.

After applying the ERG amendment of using data from the P+nabPx arm of the IMpassion130 trial to model OS for patients treated with paclitaxel and docetaxel, results showed that treatment with paclitaxel or docetaxel offered a median life expectancy of 18.6 months and a mean life expectancy of 21.6 months."

Based on the above information, both the ERG and the NICE AC were satisfied at the time that mTNBC patients treated with standard chemotherapy (paclitaxel or docetaxel) experienced a short life expectancy of less than 2 years.

Comparison of median, mean and 2 year survivorship with the current submission (taxanes from KN-355):

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			As further evidence towards the short life expectancy criterion being met for this indication for the patients treated currently with taxanes, we have extracted the taxane chemotherapy OS mean, median and the 2 year survivorship from the current economic model (Table 4). The taxane arm modelled median ranges from [redacted] months (log-logistic OS company preferred base-case which is also preferred by the ERG) to [redacted] (using the exponential function). These estimates are very close to the observed OS median ([redacted]) from KEYNOTE-355. The mean undiscounted life-months from the deterministic analysis range from [redacted] months (with alternative OS extrapolation using exponential) to [redacted] months (log-logistic OS for extrapolation of taxanes which is preferred by company and ERG for the base-case). This demonstrates that the subtle differences in mean survival are primarily driven by the choice of parametric extrapolations which is based upon the clinical data itself which warrant the log-logistic as most suitable for OS extrapolation in the taxane arm of KEYNOTE-355. The fact that mean survival exceeds slightly 24 months should not lead to the conclusion that the short life criterion is not met for this indication. Based on the median, 50% of patients survive on average less than [redacted] and therefore "the normal expected survival" is less than 24 months. Further evidence to this is the 2 year survivorship from parametric models ranges from [redacted] (log-logistic OS company preferred base-case which is also preferred by the ERG) to [redacted] (with alternative OS extrapolation using exponential). These estimates are very close to the observed 2 year OS estimate from KEYNOTE-355 which is [redacted] The median survival estimates for the taxanes arm within this submission can be considered broadly aligned with those reported in TA639 (range between 13.8 and 18.6 for paclitaxel after the ERG updates). Any minor differences can be attributed to alternative assumptions arising from the data itself and long term survival extrapolations. Subsequent final OS analysis results have been reported from IMpassion-130 (median OS estimate for placebo + nab-paclitaxel: 17.9 months)[14]. The 2-year survivorship modelled in TA639, the Impassion-130 (median OS estimate for placebo + nab-paclitaxel: 17.9 months) and 3 year OS at 22 months) [14]. The 2-year survivorship estimates modelled in TA639 ranged from 21% to 22.7% for paclitaxel (CS Table 40) or from 26% to 26.8% for docetaxel (CS Table 41), whereas the observed placebo + nab-paclitaxel OS estimate in the primary analysis was 36.65% (CS: Table 40). These estimates are not dissimilar to the 2 year survivorship estimates with taxanes generated from the current economic model (see Table 5).	

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			Table 33 of the ERG report from TA639 includes the life year estimates for paclitaxel (1.6 LYs [or 19.2 months] using the Company's preferred assumptions, subsequently updated to 1.797 LYs [or 21.5 months] by the ERG). The above predictions are consistent with the lower estimate of mean life months alive from this submission using alternative and worse fitting parametric distributions to the taxane arm (see Table 5; range of life months; [redacted] to 27.09). The current model also diverges from TA639 in the sense that it employs a longer time horizon which may potentially skew the mean life expectancy further. Using a 15 year time horizon results in a mean life expectancy for taxanes of [redacted] months. MSD has followed a rigorous process with regards to OS parametric survival curve selection and is confident with the robustness of its modeling. Whilst the log-logistic curve leads to an upper estimate of 27.07 mean life months of survivorship in this patient population, the selection of this parametric model is justified by the data from KEYNOTE-355. Although we understand the limitations associated with small sample sizes when looking at specific subgroups, it is also worth noting that differences in performance between nab-paclitaxel and paclitaxel in KEYNOTE-355 (see Table 5) were observed. When paclitaxel is selected as a comparator (+log-logistic distribution and rationale as per current base-case) and mean life years are outputted, the mean life months of expected survival is [redacted] the economic model contains the option to run C/E with paclitaxel only). Given these considerations, the mean survivorship of 27.07 months should therefore be considered as an upper estimate of mean survival for this very aggressive type of cancer for patients treated with chemotherapy. The comparison between mean life years, medians and 2 year survivorship estimates demonstrates that the model produces robust estimates of life expectancy for taxane treated patients. Scientific literature support: Within our submission we have included an extensive list of Real World Evidence (RWE) publications that consistently demonstrate the short life expectancy criterion associated with chemotherapies for patients with mTNBC. A number of sources were available at the time of developing the original submission and were used for validation of the chemotherapy modelled OS [6, 13, 15-18]. Clinical experts were consulted to identify those that were more generalizable and could be used to validate the SoC chemotherapy arm model projections. Based on the advice received, the SoC OS chemotherapy arm was primarily validated using Battisti et al 2018 study, which was a UK audit publication reporting OS outcomes	

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			for advanced TNBC by Disease Free Interval (DFI) status (DFI ≤ 12 months or DFI > 12months) over an 11 year period [16]. The Aly et al 2018 publication for patients receiving 1 line of therapy for advanced disease was also used to validate short to medium term model projections for the OS of SoC chemotherapies (US SEER database analysis) as this source fits the line of therapy for this indication [15]. Deluche et al 2020 which offers 10 year follow up was not used for validation since clinical experts noted that it predicted an OS plateau of ~6.65% at year 10 which was not deemed as reflective of UK survival estimates (considered too optimistic and experts noted that most patients would be dead at year 10 if treated with standard chemotherapies) [13]. Exploration of RWE sources demonstrates that median OS ranged from 14.3 months (Battisti DFI within 12 months) to 21.3 months (Battisti DFI after 12 months) and the 2 year % survivorship ranged from 12.1% (Battisti DFI within 12 months) to 36.58% (Battisti DFI after 12 months) [16]. Deluche et al 2020 and all other RWE median and 2 year estimates fell within the range noted above. Figure 4 present these RWE versus long term taxane OS validations. Clinicians note that the survival profile for patients treated with chemotherapies has not changed (i.e. survival remains very limited). Figure 2 and Table 9 present the modelled SoC chemotherapy OS versus OS estimates reported in various RWE sources including Battisti 2018, Aly et al 2019 and Deluche et al 2020 [13, 15, 16]. It is clear that the model predicts accurately the short to medium term taxane OS projections as well as the longer term OS estimates for up to 12 years for which RWE is available. This adds more supportive evidence and clearly demonstrates the poor survival profile associated with mTNBC patients treated with taxanes. This is indicative of the short life expectancy criterion being met especially for the 17% of patients with mTNBC with a tumour that is IC <1% (SP142 assay) but CPS ≥10 (22C3 Dako Assay) which are still treated with taxanes. We understand that there was extensive discussion of the end-of-life criteria in the recent ID3735 for Avelumab in Metastatic Urothelial Carcer. The contextualization, interpretation, and application of the end-of-life criteria was recently discussed very extensively during ID3735 [19]. A few key discussion points are presented from that document in context to the current HTA: • Point 87: It would be “unreasonable to state that life-expectancy was not “normally less than 24 months”, even if the mean life expectancy was greater than 24 months, …if the significant majority, in the modelled cohort had died prior to 24 months”. This is the case in the current submission. • Point 89: “The panel understood the concern about using means in one context and medians in another, but the end of life criteria are a stand-alone test that have to be	

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			considered on their own terms." • Point 90: The need for flexibility "The panel also agreed that "normally" allowed a committee a discretion to apply end of life criteria even if it felt on some measures of life expectancy might be somewhat over 24 months. Even if it had been correct to use the mean as the main driver of a decision in this case, given that the median and clinical expert opinion was all significantly below 24 months, and the mean was not substantially above 24 months, this was a case where that discretion would have needed to have been discussed." This is the case in the current submission. Considering the above points, the Appeal Panel concluded that in the context of the ID3735 end of life criteria appear to have been met and therefore would be relevant for consideration by the Committee. For patients whose tumor expresses IC <1% using the SP142 assay but CPS ≥10 by 22C3 Dako Assay, the only treatment option is currently taxane chemotherapy. It is estimated that ~17% of patients with mTNBC do not currently have access to IO therapies and could benefit from approving this indication for use in the NHS. MSD strongly believes that the end-of-life criteria, and in particular the short life expectancy for patients treated with taxane chemotherapies, are met for this appraisal. We have demonstrated this by showing consistency between the clinical data and model projections presented across submissions (mean, median and 2 year survival) and our understanding of the end-of-life criteria discussion to date from ID3735. We therefore urge the Committee to apply these fully when making a final recommendation in this subgroup of patients to ensure that these patients with a significant unmet need are not disadvantaged from gaining access to an effective treatment option. 2. McCarthy AM, Friebel-Klingner T, Ehsan S, He W, Welch M, Chen J, et al. Relationship of established risk factors with breast cancer subtypes. Cancer Med. 2021;10(18):6456-67. 6. Schmid P, Adams S, Rugo HS, Schneeweiss A, Barrios CH, Iwata H, et al. IMpassion130: updated overall survival (OS) from a global, randomized, double-blind, placebo-controlled, Phase III study of atezolizumab (atezo) + nab- paclitaxel (nP) in previously untreated locally advanced or metastatic triple-negative breast cancer. Journal of Clinical Oncology. 2019;37(15_suppl):1003-. 12. NICE. Guide to the methods of technology appraisal 2013 2013 [Available from: https://www.nice.org.uk/process/pmg9/chapter/Foreword. 13. Deluche E, Antoine A, Bachelot T, Lardy-Cleaud A, Dieras V, Brain E, et al. Contemporary outcomes of metastatic breast cancer among 22,000 women from the multicentre ESME cohort 2008-2016. European Journal of Cancer. 2020;129:60-70.	

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			14. Emens L, Adams S, Barrios C, Dieras V, Iwata H, Loi S, et al., editors. LBA16 - IMpassion130: Final OS analysis from the pivotal phase III study of atezolizumab + nab-paclitaxel vs placebo + nab-paclitaxel in previously untreated locally advanced or metastatic triple-negative breast cancer. ESMO Virtual Congress 2020; 2020; Virtual. 15. Aly A, Shah R, Hill K, Botteman MF. Overall survival, costs and healthcare resource use by number of regimens received in elderly patients with newly diagnosed metastatic triple-negative breast cancer. Future Oncol. 2019;15(9):1007-20. 16. Battisti NML, Okonji D, Manickavasagar T, Mohammed K, Allen M, Ring A. Outcomes of systemic therapy for advanced triple-negative breast cancer: A single centre experience. Breast. 2018;40:60-6. 17. Luhn P, Chui SY, Hsieh AF, Yi J, Mecke A, Bajaj PS, et al. Comparative effectiveness of first-line nab-paclitaxel versus paclitaxel monotherapy in triple-negative breast cancer. J Comp Eff Res. 2019;8(14):1173-85. 18. Skinner KE, Haiderali A, Huang M, Schwartzberg LS. Real-world effectiveness outcomes in patients diagnosed with metastatic triple-negative breast cancer. Future Oncol. 2020. 19. NICE. Avelumab for maintenance treatment of locally advanced or metastatic urothelial cancer after platinum-based chemotherapy [ID3735] 2022 [Available from: https://www.nice.org.uk/guidance/indevelopment/gid-ta10624/documents.	
8	Company (consultee)	MSD	Size of PD-L1 +ve CPS ≥10 score population versus PD-L1 +ve IC 1% population Within the ACD in page 6, it is stated that “The clinical expert and Cancer Drugs Fund clinical lead agreed that there is an overlap between the 2 measurements. However, they explained that the population with a CPS of 10 or more would be larger than the population with an IC of 1% or more.” MSD would like to take the opportunity to offer some additional clarifications around this statement as we do not consider to be fully reflective the prevalence of this biomarker. In KEYNOTE-355 38.1% of patients had tumours that expressed CPS≥10 and for IMpassion130 40.9% had IC≥1% [20, 21]. Rugo et al (2020) reports a post-hoc analysis of a sub population within IMpassion130 (68% of the ITT population). The percentage identified as CPS≥10 with 22C3, 52.9%, are a sub-group of a sub-population. This is inferior to prospective PD-L1 testing in registrational studies and we do not agree with using Rugo (2020) to conclude the population with a CPS≥10 would be larger than the population with IC≥ 1%. The paper was presented as evidence for the suboptimal overall percentage agreement	Comment noted. The incorrect text was removed from the ACD.

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			between the two assays of 22C3 and SP142. Also, to demonstrate a proportion of patients would be IC<1% but CPS≥10 and therefore able to benefit from pembrolizumab. The updated positioning proposed for pembrolizumab + taxanes would mean that 17% of the mTNBC cohort would belikely eligible for treatment under this indication. 20. Cortes J, Cescon DW, Rugo HS, Nowecki Z, Im SA, Yusof MM, et al. Pembrolizumab plus chemotherapy versus placebo plus chemotherapy for previously untreated locally recurrent inoperable or metastatic triple-negative breast cancer (KEYNOTE-355): a randomised, placebo-controlled, double-blind, phase 3 clinical trial. Lancet. 2020;396(10265):1817-28. 21. Schmid P, Rugo HS, Adams S, Schneeweiss A, Barrios CH, Iwata H, et al. Atezolizumab plus nab-paclitaxel as first-line treatment for unresectable, locally advanced or metastatic triple-negative breast cancer (IMpassion130): updated efficacy results from a randomised, double-blind, placebo-controlled, phase 3 trial. Lancet Oncol. 2020;21(1):44-59.	
9	Consultee	[Breast Cancer Now]	It is disappointing that NICE has provisionally been unable to recommend this pembrolizumab combination as it would have improved the options available for this group of patients. There is currently a group of patients who may be ineligible for the atezolizumab combination that is available on the NHS but could be eligible for pembrolizumab as a result of the different tools used to measure PD-L1 expression. We are pleased that the committee has recognised the unmet need for this group of patients. We urge the company, MSD and NICE to work together during this consultation period to consider every possible solution, with a focus on the end of life criteria, so that the drug can be recommended for routine use on the NHS.	Comment noted. The committee considered the additional evidence provided by the company. It concluded that pembrolizumab combination is within what NICE considers a cost-effective use of NHS resources (Final Appraisal Determination section 3.15).
10	Consultee	[Breast Cancer Now]	The poor life expectancy of this group of patients and the urgent need for new effective treatments is well documented and we reiterate the unmet need as per our initial patient organisation submission and comments made during the appraisal meeting. The mean versus median approach regarding the end of life criteria was raised by the clinical expert in the committee meeting and whilst we appreciate that the committee did not want to discuss this further as they are well aware of the issues, we do want to raise the fact that we can't be left in a situation where dependent on how the criteria is applied in this situation that a group of patients are potentially disadvantaged. We hope that flexibility and discretion will be used in this situation as it has been for other appraisals regarding the end of life criteria.	Comment noted. The committee considered the additional end of life evidence provided by the company. It concluded that pembrolizumab combination meets the end of life criteria (Final Appraisal Determination section 3.14).

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11	Consultee	[Breast Cancer Now]	To highlight the unmet need we have an example from a patient with secondary triple negative breast cancer. It is unclear why the patient may have been tested with a non-Roche PDL1 assay initially when currently only the atezolizumab combination is available, however, it illustrates that different tests can provide different results opening up the doors to important treatment options. *A patient told us "I received atezolizumab with nab-paclitaxel which was effective for me for around 8-9 months. When I was originally tested to see if I was PDL1 positive at the hospital, the test showed up negative. My clinician then said Roche had a specific test for atezolizumab and that I should be re-tested. This showed that I was PDL1 positive and I then started on atezolizumab. This shows different tests can pick up PDL1 differently which is why it's important that pembrolizumab and the test associated with it are made available alongside atezolizumab to ensure no patients are missed and that everyone has the chance to benefit from an effective immunotherapy"*	Comment noted, the committee acknowledged the unmet need for patients with secondary triple negative breast cancer (Final Appraisal Determination section 3.2).

Summary of comments received from members of the public

Theme	Response
Do not agree with the ACD decision to not recommend tucatinib combination	Comment noted.
Disease impact	
There is a crucial unmet need for patients with triple negative breast cancer, particularly for those ineligible for atezolizumab combination	Comment noted, the committee acknowledged the unmet need for patients with secondary triple negative breast cancer (Final Appraisal Determination section 3.2).
Comparators	
Atezolizumab evidence has not been considered	Comment noted. The company restricted the population eligible for pembrolizumab combination and atezolizumab is no longer considered a comparator (Final Appraisal Determination section 3.14).
End of life criteria	
Disappointed that the committee did not think pembrolizumab combination met the end of life criteria	Comment noted. The committee considered the additional end of life evidence provided by the company. It concluded that pembrolizumab combination meets the end of life criteria (Final Appraisal Determination section 3.3).

Theme	Response
Equality	
Triple negative breast cancer disproportionately affects younger people and people of colour.	Comment noted. The committee considered the equality issues at its second committee meeting but concluded there are no implications for this guidance.

Document processed	Organisation name – Stakeholder or respondent	Disclosure on tobacco funding / links	Number of comments extracted	Comments
ID1546 MSD UK ACD response_v0.1_29_03_2022_[ACIC]	Merck Sharp & Dohme (UK) Limited	N/A	8	
ID1546 Breast Cancer Now_ACD stakeholder comments v0.1 290322 NoACIC	Breast Cancer Now	N/A	3	

29th March 2022

Merck Sharp & Dohme (UK) Limited
Registered in England No. 233687
Registered Office: 120 Moorgate,
London, United Kingdom EC2M 6UR
T: [redacted]
E: [redacted]

To: [redacted] – Committee A, Centre for Health Technology Evaluation

RE: ID1546: Pembrolizumab plus chemotherapy for untreated, triple-negative, locally recurrent unresectable or metastatic breast cancer (KEYNOTE-355) ACD – MSD Response

Dear [redacted],

Thank you for the opportunity to comment on the Appraisal Consultation Document (ACD) for ID1546 for pembrolizumab + chemotherapy for untreated locally recurrent, unresectable or metastatic triple negative breast cancer (TNBC).

MSD is disappointed with the draft decision not to recommend pembrolizumab in this indication. Metastatic TNBC is a very aggressive form of cancer which affects younger patients and black women, when compared with white women, are nearly three times more likely to be diagnosed with the subtype [1, 2].

We are particularly concerned that the current draft decision would leave TNBC patients whose tumour PD-L1 expression by SP142 IC is <1% and are PD-L1 positive CPS ≥10 by Dako 22C3 without access to innovative treatment (which are currently treated with taxanes). We agree the Committee's view that a high unmet medical need remains for these patients. Approximately 17% of patients could benefit from pembrolizumab + taxanes if approved for use within the NHS in this specific group of patients [3].

In response to the ACD, MSD is now seeking access for pembrolizumab combination only in patients whose tumours express IC <1% and CPS ≥10. We discuss in our response areas of disagreement that relate to both the ITT and the IC <1% and CPS ≥10 sub-group. Nevertheless, MSD considers there to be enormous value for pembrolizumab in combination in the 17% of patients which are IC <1% and CPS ≥10 subgroups.

The decision not to recommend the above technology within its marketing authorisation was largely based upon the following areas of uncertainty in the Committee's view:

- Uncertainty in the relevant taxane chemotherapy comparators
- Uncertainty in the long-term benefit of pembrolizumab + taxanes

- Uncertainty as to whether the end-of-life criteria are met, particularly for those TNBC patients treated with taxanes and whether mean survival is normally less than 24 months.

In our appraisal consultation response, we consider each of the above points. We present evidence from clinical experts around the use of taxane chemotherapies in the NHS, explore the impact of alternative utilization on the ICER. We demonstrate the conservatism in the ERG's preferred overall survival modelling assumptions. Finally, we present strong evidence to support the application of end-of-life criteria including an assessment of median, mean and 2-year survivorship estimates from the latest mTNBC clinical trials to demonstrate the very poor prognosis for patients treated with taxanes.

MSD is confident that the latest information presented in this ACD response should satisfy the Committee's concerns around the cost-effectiveness of this indication. Even under the most conservative assumptions the ICERs remain below the £50,000 per QALY (MSD base case: £34,887, ERG range from: £44,930 [Exploratory analysis 7 with waning] to £49,426 [exploratory analysis 1 ERG no waning]) which is considered a cost-effective use of NHS resources under end-of-life (refer to Table 3).

We strongly urge the Committee to consider this indication for patients IC <1% and CPS ≥10 in the context of end-of-life criteria for its final recommendation. A positive recommendation will enable access to a new and innovative treatment option for nearly 1 in 5 mTNBC patients, leading to a positive impact for them, their families, the NHS and the society overall.

Kind regards

[redacted]

[redacted], MSD

NICE National Institute for Health and Care Excellence

Pembrolizumab plus chemotherapy for untreated, triple-negative, locally recurrent unresectable or metastatic breast cancer [ID1546]

Consultation on the appraisal consultation document – deadline for comments **5pm on Tuesday 29 March 2022. Please submit via NICE Docs.**

	Please read the checklist for submitting comments at the end of this form. We cannot accept forms that are not filled in correctly. The Appraisal Committee is interested in receiving comments on the following: • has all of the relevant evidence been taken into account? • are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence? • are the provisional recommendations sound and a suitable basis for guidance to the NHS? NICE is committed to promoting equality of opportunity, eliminating unlawful discrimination and fostering good relations between people with particular protected characteristics and others. Please let us know if you think that the preliminary recommendations may need changing in order to meet these aims. In particular, please tell us if the preliminary recommendations: • could have a different impact on people protected by the equality legislation than on the wider population, for example by making it more difficult in practice for a specific group to access the technology; • could have any adverse impact on people with a particular disability or disabilities. Please provide any relevant information or data you have regarding such impacts and how they could be avoided or reduced**.**
Organisation name – Stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder please leave blank):	**Merck Sharp & Dohme (UK) Limited**
Disclosure Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	N/A
Name of commentator person completing form:	[redacted]

MSD's response to key issues pertaining to the cost-effectiveness in response to the draft negative decision issued by NICE for ID-1546 is included below.	
Comment number	**Comments**
1	**Choice of relevant comparator for this technology appraisal (§ 3.3 of ACD).** We welcome the Committee's conclusion that high unmet medical need remains for untreated, locally recurrent unresectable metastatic breast cancer TNBC and especially for people who cannot have atezolizumab in combination with nab-paclitaxel. Within the ACD it is stated that the Committee concluded that the relevant comparators for this appraisal should be paclitaxel, docetaxel and atezolizumab + nab-paclitaxel. MSD understands that conclusion was reached on the basis of post-hoc clinical trial data from Rugo et al 2020 [3] which demonstrated a limited overlap between the IMpassion-130 and KEYNOTE-355 study populations (36% based on the Rugo et al 2020 publication). Considering the updated positioning for pembrolizumab + taxanes for the distinct subgroup of people who cannot have atezolizumab combination (whose tumour is PD-L1 <1% with SP-142 but PD-L1 +ve CPS ≥10 by Dako 22C3 Assay), MSD considers that atezolizumab + nab-paclitaxel is no longer a relevant comparator for this STA. We therefore focus our response specifically to the relevance of paclitaxel and docetaxel comparators for the purpose of the HTA and quantify the impact of the cost effectiveness comparisons for each of these. Weekly paclitaxel was chosen as the preferred regimen over Q3W in KEYNOTE-355 as the former is better tolerated and superior in efficacy [4]. In 2020 TA639 the Committee concluded that paclitaxel was the most relevant chemotherapy comparator at that time. However, during ID1546, based on clinical opinion and due to capacity issues faced by the NHS during COVID, docetaxel utilisation was noted to have increased, followed by some limited use of nab-paclitaxel. These agents (docetaxel and nab-paclitaxel) can be administered Q3W compared with paclitaxel (QW). It was also noted that docetaxel utilisation was likely to remain in NHS chemotherapy units post-COVID-19 due to its capacity benefit. The clinical expert noted that docetaxel would not be used if a patient had had it before in the curative setting, but a proportion of patients would access it as a treatment option (Page 7 of the ACD).

	At the time of submitting this appraisal to NICE (November 2020), the primary chemotherapy comparator and this is also reflected in KEYNOTE-355. Even with the capacity benefits described above, clinical experts have stated docetaxel would not be the chemotherapy of choice due to the lower tolerability profile. COVID interim guidelines for the delivery of systemic anticancer treatments (NG161) provide NHS Trusts the option of using nab-paclitaxel for mTNBC instead of paclitaxel which is better tolerated and therefore reduces the toxicities and potential for admission [5]. This can be procured at a commercial in confidence discount by the NHS. Since docetaxel is used primarily in earlier disease stages and in fit patients, experts commented that it is very likely paclitaxel (or nab-paclitaxel which can be accessed as a result of COVD interim guidelines) would be used instead due to their superior safety profiles. Patients with de-novo metastatic disease, who therefore have not received treatment in the early setting, may receive docetaxel if the clinician feels it is appropriate. After consulting with clinicians during the ACD response period, MSD understands the use of docetaxel in TNBC patients varies by hospital and some centres do not use it at all for mTNBC (**Table 1**). This feedback is consistent with our original positioning of docetaxel as a secondary chemotherapy comparator. Assuming that docetaxel is the most relevant comparator for has a detrimental impact on the cost-effectiveness which is part due to the lower acquisition and administration costs versus paclitaxel. MSD is concerned with the likely inconsistencies arising in future HTA evaluations by a precedent being set up, whereby alternative secondary comparators which is not extensively used in the NHS (as is the case for docetaxel based on clinical expert opinion) could be used to estimate the C/E of a technology against in future appraisals. Considering the above, MSD considers pembrolizumab is disadvantaged by being assessed versus docetaxel when the Committee previously concluded that paclitaxel was the most relevant comparator for TA639. Due to the lack of docetaxel data from the literature or the trial, a simplifying assumption was made that the efficacy of all taxanes is equivalent and can be proxied using the taxane comparator arm data from KEYNOTE-355. This assumption may bias against pembrolizumab + taxanes since the safety profile for docetaxel is informed by data from paclitaxel or nab-paclitaxel. It is accepted that these agents are better tolerated compared with docetaxel, which may lead to some element of under-estimation in the cost of managing adverse events (AEs). Due to its safety profile, docetaxel is used to treat earlier stages of disease, with the exception of the de novo metastatic patients mentioned above. In

	KEYNOTE-355 within the CPS ≥ 10 score subgroup the percentage of de-novo metastatic patients was 31.6%. Based on the clinical expert opinion gathered by MSD and to address the Committee's concerns around the impact of docetaxel use in the C/E estimates, we present a 70:30 paclitaxel to docetaxel ratio. This assumes that 30% of the patients presenting with advanced/metastatic disease have not been previously treated at an earlier setting with docetaxel and therefore the first chemotherapy option could be that of docetaxel. This scenario is exploratory in nature but supported by the clinical expert input sought during the consultation period (Table 1). These analyses adjust the drug regimen comparator and drug administration costs of the model accordingly (all other cost and effect inputs remain unchanged; Table 2 presents detailed calculations). These analyses may reflect closer the true ICER for this intervention by accounting for some docetaxel. This increases the ICER to £37,137 per QALY (vs £34,887 with 100% paclitaxel use) However, it is important to note that the impact on the C/E is lower versus when 100% docetaxel is used as a comparator. Table 3 presents the C/E results assuming a mix of paclitaxel 70% and 30% docetaxel. The ICERs remain below £50,000 QALY across a number of alternative scenarios. Finally, since pembrolizumab can be used in combination with nab-paclitaxel which is a branded medicine, the 70:30 chemotherapy mix (paclitaxel/nab-paclitaxel 70%: docetaxel 30%) ICERs should be interpreted as a pessimistic and upper C/E estimate for this technology.
2	**Uncertainty in the long term benefit of pembrolizumab + taxanes (§ 3.5 of ACD).** MSD understands that the question around the uncertainty of long-term benefit for pembrolizumab + taxanes is raised with regards to long term survivorship trajectory beyond the KEYNOTE-355 trial follow up. We would like to take the opportunity to correct a typographical error in our part which is contained within the technical engagement response (page 4). Nonetheless, the arguments around the long term benefit of the intervention remain valid considering the substantial follow up which is observed alongside a very aggressive cancer such as mTNBC. We would like to clarify that the median follow up of KEYNOTE-355 as the median OS time ([redacted] for Pembrolizumab + taxanes vs taxanes alone). The values above refer to the CPS ≥ 10 population all chemotherapy patients and is "actual =follow-up duration" which is defined from randomization until earliest of the date of death or the database cutoff date if the subject is still alive.

	We offer the corrected values specifically to the CPS ≥ 10 taxane subgroup below. The final analysis (FA) in KEYNOTE-355 which took place on the 15th of June 2021, the follow up CPS≥10 taxane subgroup was [redacted] months for pembrolizumab + taxanes and taxanes alone respectively (see Table 7). The median theoretical follow up of the study with regards to the PD-L1 CPS ≥ 10 taxane subgroup at the final analysis was reported elsewhere exceeds 4 months (Table 8). This uses a definition from randomization to database-cut off date regardless of survival status with maximum follow up is approximately ~[redacted]. Throughout the follow up period we see a clear and sustained separation of the OS Kaplan-Meier (KM) curves throughout the follow up period (although we acknowledge some censoring in the tail of the KM curves). This is reflected in the favorable and statistically significant OS HR (0.54, 95% CI: 0.36, 0.82). Considering the aggressiveness of mTNBC, the follow up of KEYNOTE-355 is very robust and indicative of a long term benefit for these patients. Further, the OS of KEYNOTE-355 CPS≥10 population has been formally tested for and has met statistical significance. The magnitude of OS benefit is consistent for the pembrolizumab + taxanes versus taxanes alone in this population. MSD sought clinical expert opinion to inform the submission development process. Clinical experts noted that the aggressiveness of metastatic TNBC means that most patients would not survive beyond the first 3 years given the aggressiveness of mTNBC. This has been observed across a number of RWE publications 14, 40, 43]. The small percentage of long survivors (those beyond 3 years) with current chemotherapy would be expected to have a lower risk of death of a result of mTNBC (but an increased risk of death due to all-cause mortality as the cohort ages over time). Clinical studies clearly demonstrate the short life expectancy of mTNBC patients this since only a very small percentage survive beyond 2 years ([redacted] from KEYNOTE-355 PD-L1 CPS ≥ 10 taxane subgroup (34% across all PD-L1 CPS ≥ 10 or 36.65% of IMpassion 130 IC 1% population) [6]. Based on their prior experience with IOs in solid tumors, clinical experts noted that a stabilisation and subsequent plateau in would OS be expected to be observed from around year 3 onwards. This is due to the unique mode of action of IO therapies such as pembrolizumab which is widely recognised to contribute towards an immunotherapeutic effect. This has been observed across a number of metastatic trials and tumors (including Non-Small Cell Lung Cancer, Melanoma and Head & Neck), whereby a percentage of patients achieves long term survival due to the unique mode of action of IO agents [7-9]. Since pembrolizumab + taxanes is associated with significant

OS benefit, a higher percentage of patients would be expected to be long-term survivors.

Within the current model [redacted] patients alive at year 3 for pembrolizumab + taxanes versus [redacted] in the taxane arm (observed survivorship from KEYNOTE-355). Survival estimates for the current standard of care chemotherapies at year 3 extracted from the literature range between 6.7% (TA639 estimate for nab-paclitaxel) to 22.6% (Battisti et al 2018 DFI > 12months). Clinical experts advised MSD that Battisti et al 2018 with some long term adjustments at year 5 and year 10 survivorship is a good proxy of long term OS survival with current chemotherapies. For taxanes, estimates obtained were [redacted] at year 5 and [redacted] at year 10 which are in line with the RWE sources included in the submission. Specific to metastatic TNBC and considering the unique mode of action of IO therapies, clinical experts suggested a [redacted] survival at year 5 and a [redacted] of long term survivors at 10 year when patients were treated with pembrolizumab + taxanes [10].

The survival analyses and parametric curve selection for OS used in the base-case followed the NICE TSD DSU 14 to identify the most appropriate parametric models for OS extrapolations. In brief, the process included visual inspections, the assessment of goodness of fit statistics (AIC/BIC), clinical plausibility and validity of long term projections of long term survival projections.

MSD has previously raised concerns on the ERG's preference to model the long term OS for pembrolizumab + taxanes using the exponential curve due to its overly simplistic in nature due its reliance in constant hazards which may not adequately capture the long term survivors with IO agents.

We have explored the impact of alternative long term OS projections and in the C/E. Keeping all of the other company base-case assumptions unchanged; the ICER using exponential to model pembrolizumab + taxanes OS increases to £49,426/QALY.

Figure 1: Use of exponential distribution to model OS for Pembro + taxanes, using log-logistic alongside chemotherapy OS from real world evidence (no waning)

[redacted]

Table 9: Overall Survival estimates from model validation tab with RWE versus predicted SoC survival linked to Figure 1

Source & Overall Survival	Years								
	0.5	1	1.5	2	3	5	8	10	20
Aly 2018	76.95%	51.17%	37.95%	28.73%	17.72%	-	-	-	-

Battisi 2018 (DFI after 12 months)	89.88%	69.82%	57.22%	36.58%	22.66%	13.51%	3.49%	3.49%	-
Battisi *2018 (DFI within 12 months)*	74.39%	37.70%	18.40%	12.11%	6.01%	5.86%	-	-	-
Deluche 2020 (HR-/HER2-)	81.07%	59.85%	43.22%	33.25%	20.72%	11.76%	6.91%	6.65%	-
Modelled OS: Pembrolizumab + taxane (**exponential**)	[redacted]								
Observed OS: Pembrolizumab + taxane	[redacted]								
Modelled OS: Taxane (log-logistic)	[redacted]								
Observed OS: Taxane	[redacted]								

Figure 2 below shows the impact of the exponential curve versus the company's preferred log-normal distribution in terms of long term predications. Overall, using the exponential function~ [redacted]% of patients are expected to be alive at year 10 for pembrolizumab +taxanes versus [redacted]% in taxane arm. Considering that Battisti et al reports a 10 year survival of 3.49%, the exponential distribution is highly conservative with regards to the cost-effectiveness itself when used in isolation to model pembrolizumab + taxanes alone.

Alternative scenarios with more optimistic estimates of survival are presented below based on the current clinical data from KEYNOTE-355 and their impact on the C/E estimates. MSD's current base-case using log-normal to model OS results in an ICER of £34,887/QALY and a 10 year survival of ~[redacted]% (2nd best curve based on AIC/BIC, visual inspection, and clinical opinion and assessment versus RWE). Using a log-logistic distribution to model P+T OS (3rd best based on AIC/BIC, visual inspection and clinical opinion and assessment versus RWE) results in an ICER of £34,597/QALY and [redacted]% survivorship at year 10.
Using Generalised Gamma (worst ranked model based on AIC/BIC but only 5.73 points difference vs exponential which is preferred by the ERG) results in an ICER of £41,558/QALY and ~[redacted]% survivorship at year [redacted].
Figure **3** below includes all OS curves discussed above (exponential, log-normal, log-logistic, gen-gamma). Table 3 presents the impact on the C/E results using alternative OS extrapolations. The ICERs remain below £50,000 QALY, even when a chemotherapy mix (paclitaxel 70% : docetaxel

	to 30%) is assumed alongside alternative plausible extrapolations with or without treatment waning. The conservatism of using exponential to model for pembrolizumab + taxanes, is even more apparent when compared with long term survivorship estimates by Deluche et al 2020. Clinical experts noted that this source contained overly optimistic long term OS projections with SoC chemotherapies; 10 year survivorship at 6.65% (Figure 4 and Table **10**), which could only probably be explained if clinical trial participants were included in this retrospective study. Nonetheless, using the exponential to model the long term OS for pembrolizumab + taxanes results in a 10 year OS which is [redacted] and less than the [redacted] that could be long term survivors based on expert opinion and prior experience with IO agents. MSD urges the NICE AC to consider the C/E analyses results using the exponential survival model as high conservative for the purposes of decision making.
3	**Uncertainty in the indirect treatment comparison results between pembrolizumab + taxanes versus atezolizumab + nab-paclitaxel.** Considering the updated positioning for pembrolizumab + taxanes proposed for the distinct subgroup of people who cannot have atezolizumab combination (whose tumour is PD-L1 <1% with SP-142 but PD-L1 +ve CPS ≥10 by Dako 22C3 Assay), atezolizumab + nab-paclitaxel is no longer a relevant comparator for this STA. However, we would like to take the opportunity to comment on the uncertainties associated with the indirect treatment comparison. MSD raised at multiple occasions during the HTA process some key differences between the two studies informing the ITC (including trial recruitment criteria, PFS assessment), trial populations (baseline characteristics and differences in PD-L1 ascertainment) and the limited data reported concerning the subgroup of interest for this indication (CPS score ≥ 10). We did this proactively because we wanted to be transparent on the challenges that could be encountered later on during decision making. Considering these limitations, we positioned atezolizumab +nab-paclitaxel as a secondary alternative IO comparator since we understand that these two agents are not directly interchangeable for patients which are diagnosed with mTNBC. This is due to the limited overall overlap between study populations which is estimated to be ~36% based on a single post-hoc analysis from Impassion-130 by Rugo et al 2020.

	Nonetheless, the analyses were conducted by following the NICE DSU methodology and the updated NMA presented, were based upon the final database lock from KEYNOTE-355 leveraging the statistically significant OS results. The updated NMA results remain consistent with the earlier NMA results presented in the main submission (with the IA2 OS) and continue [redacted] pembrolizumab + taxanes versus Atezo + nab-paclitaxel for OS and PFS across the selected base-case and sensitivity analyses conducted. In brief, the selected base-case NMA results for OS HR = [redacted] and for the base case PFS by Investigator HR = [redacted]. We were unable to provide the updated NMA results using Random Effects, but we do agree with the conclusions reached that RE analysis would not likely influence the point estimates of the results provided. Whilst we understand that the ITC results are no longer relevant for decision making purposes given the new positioning proposed for this technology, we would like to take the opportunity and thank both the Appraisal Committee and the ERG for their time critiquing this element of the submission.
4	**Choice of parametric extrapolation curves used to model pembrolizumab + taxanes (§ 3.9 of ACD).** Within the ACD it is noted that; *"The ERG agreed with the company's choice of log-logistic extrapolation for paclitaxel but preferred an exponential model for pembrolizumab combination. It explained that the goodness of fit statistics between the exponential and log-normal models both corresponded with the observed data. However, it noted that the log-normal distribution showed a turning point within the first year whereas the smoothed hazard plot of the observed data did not show a turning point in the underlying hazard.* ***The exponential distribution did not have a turning point."*** MSD has already cautioned against over-interpreting smooth hazard plots in isolation when it comes to parametric model selection. We have discussed extensively in Comment 2 above why we disagree with the choice to model OS using an exponential distribution. We consider it overly simplistic to assume a constant hazard for an IO agent given the prior experience in treating solid tumors with IO therapies. It also results in overly pessimistic OS predictions over time based upon clinical opinion and based on long-term validity of OS projections versus RWE data. We would like to opportunity to position the exponential curve as highly conservative and as potentially biasing the C/E results against pembrolizumab + taxanes. This is especially the case when the ERG has accepted that the taxane chemotherapy arm which uses a log-logistic and

	assumes a decreasing hazard of death over time, has indeed been appropriately modelled. The conservatism of exponential distribution to model the OS for Pembrolizumab + taxanes is even more apparent when treatment waning is applied, which improves the ICER (due to the lower level of model adjustments introduced in the model). This is counterintuitive to how treatment waning normally work and adds further evidence to the conservatism of the exponential function used in the base-case. Regarding the lack of turning point to the hazard of OS for pembrolizumab + taxanes, this could be due to the method used to generate the "smoothed" hazard plots, or due to the sample size which is not big enough to show it. Goodness-of-fit should not be measured by the hazard plots but instead be evaluated versus the survival curves – this is according to NICE DSU guidelines (NICE DSU 14) and with clinical plausibility in mind regarding the validity of long-term projections [11]. Based on experience with IOs in other solid tumors, we expect the OS stabilisation and subsequent plateau to become more apparent as the data mature further. This is due to the unique mode of action of IO therapies such as pembrolizumab which is widely recognised to contribute towards an immunotherapeutic effect that has been observed across a number of tumours (including NSCLS, Melanoma and Head & Neck), whereby a percentage of patients achieves long term survival due to the unique mode of action of IO agents [7-9]. This immunotherapeutic effect cannot be captured using simple constant hazards assumptions for OS extrapolations. An example of modelled long term outcomes using the exponential function is presented below in Figure 1 depicts a 10 year survivorship with an IO agent siting well below the real world chemotherapy projections presented. This means that the Committee should consider the C/E results using an exponential function as highly conservative in nature. Other more plausible parametric survival options and their impact on the C/E have been described in comment 2 above and C/E results are presented in Table 3 below. These are appropriate to inform the Committee's decision for mTNBC patients whose tumour is PD-L1 <1% with SP-142 but PD-L1 +ve CPS ≥10 score by Dako 22C3 Assay.
5	**Assumptions on time to treatment discontinuation (TTD) for atezolizumab + nab-paclitaxel (§ 3.10 of ACD).** Considering the updated positioning for pembrolizumab + taxanes proposed for the distinct subgroup of people who cannot have atezolizumab

	combination (whose tumour is PD-L1 <1% with SP-142 but PD-L1 +ve CPS ≥10 by Dako 22C3 Assay), atezolizumab + nab-paclitaxel is no longer a relevant comparator for this STA. However, we would like to take the opportunity to comment on the most robust way used to inform assumptions around atezolizumab + nab-paclitaxel TTD. MSD considers the ERG's preferred assumptions around TTD modelling for atezolizumab + nab-paclitaxel, is very likely introducing bias against pembrolizumab + taxanes in the associated analyses. Evidence of this can be sourced from the TTD for atezolizumab + nab-paclitaxel reported in the TA639 Company submission documents (Table 48 for atezolizumab and Table 49 for nab-paclitaxel and company Technical Engagement Response for more information). Within each submission the company estimates a % of patients continuing treatment with atezolizumab between 9.0%-11.0% at year 2 dropping to 2.8%-4.6% at year 3. For nab-paclitaxel this was 2.8%-6.5% at year 2 dropping to 0.3%-3.0% at year 3. Our updated base-case assumption for TTD (equal to TTD from pembrolizumab + taxanes) results in 10.2% at year 2 and 4.3% at year 3. This demonstrates that assuming TTD being equal to that of pembrolizumab + taxanes is more robust to inform these comparisons (although we acknowledge that TTD data may not be directly transferable between studies. In contrast, the ERG's approach would result towards a lower TTD for atezolizumab + nab-paclitaxel. This demonstrates that assuming TTD being equal to that of pembrolizumab + taxanes is more robust to inform these comparisons (although we acknowledge that TTD data may not be directly fully transferable between studies). We would like to re-iterate that KEYNOTE-355 including a stopping rule (pembrolizumab + taxanes) for pembrolizumab but this is not the case for IMpassion-130. Therefore, assumptions which result in lower TTD (as the one employed by the ERG) are methodologically inconsistent. Whilst we understand that this issue is no longer relevant for decision making purposes given the new positioning proposed for this technology, we wanted to leverage this opportunity to briefly re-iterate the methodological inconsistencies, and to take the opportunity thank both the Appraisal Committee and the ERG for their time critiquing this element of the submission.
6	**Duration of treatment effect benefit over time for pembrolizumab + taxanes (§ 3.11 of ACD).**

	MSD retains its position that the clinical data from KEYNOTE-355 does not show any evidence of treatment effect waning for pembrolizumab + taxanes during the follow up period which is approximately [redacted] in the taxane arm. Whilst KEYNOTE-355 included a maximum treatment with pembrolizumab for 35 cycles (or ~ 2 years; taxane treatment can be continued beyond this point), the unique mode of action of pembrolizumab means that patients continue to experience benefit beyond pembrolizumab cessation as demonstrated by the updated clinical data from KEYNOTE-355. Continued treatment benefit has also consistently been observed across a number of tumours whereby a small subset of patients experiences long term survival benefit. Due to lack of relevant clinical data to data from KEYNOTE-355 which can be used to inform robust modelling around this assumption, we do not agree with the application of treatment waning into the base-case assumptions. We caution against over-interpreting these results and the impact of waning for decision making given the level of conservatism that is associated with methods used to model treatment waning. Despite our concerns around the modelling of treatment waning, we have explored its impact in scenario analysis within the original submission using two alternative options for the modelling of treatment waning (described below). Option one which assumes an abrupt treatment effect stop at a specific time point (implies a HR = 1 for OS from that time point onwards which is not clinically plausible; similar to the preferences of Committee C). In this submission the ERG preferred a maximum treatment benefit of 5 years. This implies that the treatment benefit is only maintained for 3 years after pembrolizumab cessation and diminishes instantaneously thereafter which should be considered as a highly conservative for the purposes of decision making. An alternative pragmatic methodology of gradual treatment waning has also been explored. This was based upon a SEER dataset analysis. This applies a constant hazard rate after 4 years across both treatment arms which results in a gradual treatment waning adjustments being made from that timepoint onwards. In contrast to the methodology preferred by the ERG which functions by setting the OS hazard rate of pembrolizumab + taxanes equal to the OS hazard rate of the taxanes arm after year 5 (clinically implausible), the treatment waning analyses using SEER are more pragmatic and reflective of the real word setting since it applies a gradual treatment benefit decrease over time. Given this evidence we ask that the AC consider the 5Y treatment waning ICERs generated as highly conservative in nature for decision making. It further demonstrates the

	conservatism of the ERG's preferred choice of OS extrapolations using the exponential curve since treatment waning in fact improves the cost-effectiveness when applied. Table 3 presents different waning scenarios discussed above and their associated impact on the ICER. All of these scenarios (including the ERG's preferred assumptions, and a mix chemotherapy comparator result in ICERs of less than £50,000 per QALY gained. MSD believes that the additional analyses presented mitigate against any further concerns around the C/E of this technology.
7	**Application of end-of-life criteria within this submission focusing on evidence for short life expectancy criterion for taxanes, comparisons of life expectancy versus TA639 and validity of modeled life years (§ 3.14 of ACD).** The Guide to the methods of technology appraisal 2013 by NICE discussed in section 6.2.10 specifies: "*In the case of a 'life-extending treatment at the end of life', the Appraisal Committee will satisfy itself that all of the following criteria have been met:[12]* • the treatment is indicated for patients with a short life expectancy, normally less than 24 months and • there is sufficient evidence to indicate that the treatment has the prospect of offering an extension to life, normally of a mean value of at least an additional 3 months, compared with current NHS treatment. **Below we summarise the end-of-life relevant data and we discuss these versus TA639. We also provide evidence from the literature which support the short-life-expectancy criterion taking into account the updated positioning proposed for this technology.** Within the ACD document particular focus is given as to whether the short life expectancy criterion is fulfilled for patients treated with taxanes. MSD considers that end of life criteria and in particular, short life expectancy (normally less than 24 months), are met for this appraisal for the distinct subgroup whose tumour is PD-L1 <1% with SP-142 IC but PD-L1 +ve CPS ≥10 by Dako 22C3 Assay. To ensure a compelling case for End of Life has been put forward for consideration we explored the median, mean and 2-year survivorship across this submission and from TA639. Assessment of life years (LYs) and median survival reported from TA339 demonstrates a high level of

	consistency in modelled short-term predictions in. In TA639, trial design and population differences alongside alternative assumptions employed around the choice of parametric functions in the taxane OS extrapolation, all impact to a degree the mean taxane LYs reported within that submission. However, the minor differences in mean modelled LYs reported within TA639 versus this submission do not preclude the relevance of end-of-life criteria for taxane treated patients in this submission since patients treated with taxanes also have a short survival (as we demonstrate below). Understanding these inherent differences is fundamental to enable a robust decision whilst avoiding any equity issues in the final recommendation, in particular for a subgroup of patients which is currently underserved with access only to standard chemotherapies. ***Short life expectancy:*** TNBC is known to be an aggressive cancer that disproportionately impacts younger women (mean age of diagnosis 53.0 years) and black women are nearly three times more likely to be diagnosed with the subtype than white women [2, 13]. MSD is aware that the application of end-of-life criteria is discussed by Appraisal Committees with regards to median and mean survival estimates in context to the disease severity and the current treatment options available within the NHS. For the updated positioning and population now under consideration for this submission (tumour is PD-L1 <1% with SP-142 but PD-L1 positive CPS ≥10 by Dako 22C3 Assay) the only treatment option currently available is chemotherapy. The table below offers a top line summary of trial-reported outcomes where available (median survival and 2 year survival) with standard chemotherapies. It also reports the mean life years across mTNBC TA639 and ID1546. However, as noted above, some factors (trial design, populations and assumptions on extrapolations) can impact upon the mean LY estimates generated from health economic modelling (more information in Table 5 below). It is currently estimated approximately 17% of patients with metastatic TNBC would have a tumour that would be IC <1% (SP142 assay; ineligible for atezolizumab + nab-paclitaxel) but be CPS ≥10 (22C3 Dako Assay). These patients could therefore benefit from pembrolizumab + taxanes and could be disadvantaged if the current technology was not assessed with end-of-life criteria in consideration. The estimates presented below (also Table 5) clearly demonstrate that the short life expectancy criterion (normally less than 24 months) is met for patients who are currently treated with taxanes (such as those whose

tumour is PD-L1 <1% with SP-142 IC but PD-L1 +ve CPS ≥10 by Dako 22C3 Assay).

Study		Mean (months)	Median (months)	% alive at 24 months
KEYNOTE-355 Taxanes	Observed	NA	[redacted]	[redacted]
	Modelled	[redacted]	[redacted]	[redacted]
IMpassion130 nab-paclitaxel	Observed	N/A	17.9±	36.65%≠
	Modelled	1.6 LYs or 19.2 months updated to 1.797 LYs or 21.5 months[3≠]	13.8 to 14.3 updated to 18.6 - 21.6 by ERG[3]	Paclitaxel[1]: 21% to 22.7% Docetaxel[2:] 26% to 26.8%

Notes: extracted from TA639 Committee Documents: [1]; Table 40 CS, [2]; Table 41 CS, [3]; Table 33 ERG (we assume LY estimates are undiscounted). ± Medians extracted from latest IM-130 publication by Emens et al 2020 [14]; PD-L1 +ve, ≠ 2Y OS extracted from earlier IMpassion-130 publication by Schmid et al 2019 [6]; PD-L1 +ve.

We have also responded to the Committee's queries around the validity of the modelled LYs in this submission versus the estimates reported in TA639, although as noted above, we recognise that the extent to which we can make robust comparisons across HTAs is hindered by a number of reasons.

End-of-Life assessment discussion within TA639:
The following information was extracted from TA639 (Page 17 of 114 of ID1522 ERG report (sections 1.7 and 1.8).

"*A technology meets NICE End of Life criteria if (i) life expectancy with standard of care treatments for the target population is under 24 months and (ii) the increase in life expectancy with the technology being appraised is at least 3 months. The estimates generated by the company model are that* ***median life expectancy is 13.8 months for patients treated with paclitaxel and 14.3 months for patients treated with docetaxel.*** *Results from the company model also show that, compared to treatment with paclitaxel and docetaxel, t****reatment with A+nabPx offers a median extension to life of 12.6 months and 11.6 months respectively****.*

After applying the ERG amendment of using data from the P+nabPx arm of the IMpassion130 trial to model OS for patients treated with paclitaxel and docetaxel, results showed that ***treatment with paclitaxel or docetaxel offered a median life expectancy of 18.6 months and a mean life expectancy of 21.6 months."***

Based on the above information, both the ERG and the NICE AC were satisfied at the time that mTNBC patients treated with standard chemotherapy (paclitaxel or docetaxel) experienced a short life expectancy of less than 2 years.

Comparison of median, mean and 2 year survivorship with the current submission (taxanes from KN-355):

As further evidence towards the short life expectancy criterion being met for this indication for the patients treated currently with taxanes, we have extracted the taxane chemotherapy OS mean, median and the 2 year survivorship from the current economic model (Table 4). The taxane arm modelled median ranges from [redacted] months (log-logistic OS company preferred base-case which is also preferred by the ERG) to [redacted] (using the exponential function). These estimates are very close to the observed OS median ([redacted]) from KEYNOTE-355.

The mean undiscounted life-months from the deterministic analysis range from [redacted] months (with alternative OS extrapolation using exponential) to 27.09 months (log-logistic OS for extrapolation of taxanes which is preferred by company and ERG for the base-case). This demonstrates that the subtle differences in mean survival are primarily driven by the choice of parametric extrapolations which is based upon the clinical data itself which warrant the log-logistic as most suitable for OS extrapolation in the taxane arm of KEYNOTE-355. The fact that mean survival exceeds slightly 24 months should not lead to the conclusion that the short life criterion is not met for this indication. Based on the median, 50% of patients survive on average less than [redacted] and therefore "the normal expected survival" is less than 24 months.

Further evidence to this is the 2 year survivorship from parametric models ranges from [redacted] (log-logistic OS company preferred base-case which is also preferred by the ERG) to [redacted] (with alternative OS extrapolation using exponential). These estimates are very close to the observed 2 year OS estimate from KEYNOTE-355 which is [redacted].

The median survival estimates for the taxanes arm within this submission can be considered broadly aligned with those reported in TA639 (range between 13.8 and 18.6 for paclitaxel after the ERG updates). Any minor differences can be attributed to alternative assumptions arising from the data itself and long term survival extrapolations. Subsequent final OS analysis results have been reported from IMpassion-130 (median OS estimate for placebo + nab-paclitaxel: 17.9 months)[14]. The 2-year survivorship modelled in TA639, the Impassion-130 (median OS estimate for placebo + nab-paclitaxel: 17.9 months) and 3 year OS at 22 months) [14]. The 2-year survivorship estimates modelled in TA639 ranged from 21% to 22.7% for paclitaxel (CS Table 40) or from 26% to 26.8% for docetaxel (CS Table 41), whereas the observed placebo + nab-paclitaxel OS estimate in the primary analysis was 36.65% (CS: Table 40). These

	estimates are not dissimilar to the 2 year survivorship estimates with taxanes generated from the current economic model (see Table 5). Table 33 of the ERG report from TA639 includes the life year estimates for paclitaxel (1.6 LYs [or 19.2 months] using the Company's preferred assumptions, subsequently updated to 1.797 LYs [or 21.5 months] by the ERG). The above predictions are consistent with the lower estimate of mean life months alive from this submission using alternative and worse fitting parametric distributions to the taxane arm (see Table 6; range of life months; [redacted] to 27.09). The current model also diverges from TA639 in the sense that it employs a longer time horizon which may potentially skew the mean life expectancy further. Using a 15 year time horizon results in a mean life expectancy for taxanes of [redacted] months. MSD has followed a rigorous process with regards to OS parametric survival curve selection and is confident with the robustness of its modeling. Whilst the log-logistic curve leads to an upper estimate of [redacted] mean life months of survivorship in this patient population, the selection of this parametric model is justified by the data from KEYNOTE-355. Although we understand the limitations associated with small sample sizes when looking at specific subgroups, it is also worth noting that differences in performance between nab-paclitaxel and paclitaxel in KEYNOTE-355 (see Table 6) were observed. When paclitaxel is selected as a comparator (+log-logistic distribution and rationale as per current base-case) and mean life years are outputted, the mean life months of expected survival is [redacted]; the economic model contains the option to run C/E with paclitaxel only). Given these considerations, the mean survivorship of 27.07 months should therefore be considered as an upper estimate of mean survival for this very aggressive type of cancer for patients treated with chemotherapy. **The comparison between mean life years, medians and 2 year survivorship estimates demonstrates that the model produces robust estimates of life expectancy for taxane treated patients.** ***Scientific literature support:*** Within our submission we have included an extensive list of Real World Evidence (RWE) publications that consistently demonstrate the short life expectancy criterion associated with chemotherapies for patients with mTNBC. A number of sources were available at the time of developing the original submission and were used for validation of the chemotherapy modelled OS [6, 13, 15-18]. Clinical experts were consulted to identify those that were more generalizable and could be used to validate the SoC chemotherapy arm model projections. Based on the advice received, the SoC OS chemotherapy arm was primarily validated using Battisti et al 2018 study, which was a UK audit

publication reporting OS outcomes for advanced TNBC by Disease Free Interval (DFI) status (DFI ≤ 12 months or DFI > 12months) over an 11 year period [16]. The Aly et al 2018 publication for patients receiving 1 line of therapy for advanced disease was also used to validate short to medium term model projections for the OS of SoC chemotherapies (US SEER database analysis) as this source fits the line of therapy for this indication [15]. Deluche et al 2020 which offers 10 year follow up was not used for validation since clinical experts noted that it predicted an OS plateau of ~6.65% at year 10 which was not deemed as reflective of UK survival estimates (considered too optimistic and experts noted that most patients would be dead at year 10 if treated with standard chemotherapies) [13].

Exploration of RWE sources demonstrates that median OS ranged from 14.3 months (Battisti DFI within 12 months) to 21.3 months (Battisti DFI after 12 months) and the 2 year % survivorship ranged from 12.1% (Battisti DFI within 12 months) to 36.58% (Battisti DFI after 12 months) [16]. Deluche et al 2020 and all other RWE median and 2 year estimates fell within the range noted above.
Figure 4 present these RWE versus long term taxane OS validations.

Clinicians note that the survival profile for patients treated with chemotherapies has not changed (i.e. survival remains very limited).
Figure 4 and

Table **10** present the modelled SoC chemotherapy OS versus OS estimates reported in various RWE sources including Battisti 2018, Aly et al 2019 and Deluche et al 2020 [13, 15, 16]. It is clear that the model predicts accurately the short to medium term taxane OS projections as well as the longer term OS estimates for up to 12 years for which RWE is available. This adds more supportive evidence and clearly demonstrates the poor survival profile associated with mTNBC patients treated with taxanes. This is indicative of the short life expectancy criterion being met especially for the 17% of patients with mTNBC with a tumour that is IC <1% (SP142 assay) but CPS ≥10 (22C3 Dako Assay) which are still treated with taxanes.

We understand that there was extensive discussion of the end-of-life criteria in the recent ID3735 for Avelumab in Metastatic Urothelial Carcer.
The contextualization, interpretation, and application of the end-of-life criteria was recently discussed very extensively during ID3735 [19]. A few key discussion points are presented from that document in context to the current HTA:

- Point 87: It would be "*unreasonable to state that life-expectancy was not "normally less than 24 months", even if the mean life expectancy was greater than 24 months, …if the significant majority, in the*

	modelled cohort had died prior to 24 months". This is the case in the current submission. • Point 89: "*The panel understood the concern about using means in one context and medians in another, but the end of life criteria are a stand-alone test that have to be considered on their own terms*." • Point 90: The need for flexibility "*The panel also agreed that "normally" allowed a committee a discretion to apply end of life criteria even if it felt on some measures of life expectancy might be somewhat over 24 months. Even if it had been correct to use the mean as the main driver of a decision in this case, given that the median and clinical expert opinion was all significantly below 24 months, and the mean was not substantially above 24 months, this was a case where that discretion would have needed to have been discussed."* This is the case in the current submission. Considering the above points, the Appeal Panel concluded that in the context of the ID3735 end of life criteria appear to have been met and therefore would be relevant for consideration by the Committee. For patients whose tumor expresses IC <1% using the SP142 assay but CPS ≥10 by 22C3 Dako Assay, the only treatment option is currently taxane chemotherapy. It is estimated that ~17% of patients with mTNBC do not currently have access to IO therapies and could benefit from approving this indication for use in the NHS. **MSD strongly believes that the end-of-life criteria, and in particular the short life expectancy for patients treated with taxane chemotherapies, are met for this appraisal. We have demonstrated this by showing consistency between the clinical data and model projections presented across submissions (mean, median and 2 year survival) and our understanding of the end-of-life criteria discussion to date from ID3735. We therefore urge the Committee to apply these fully when making a final recommendation in this subgroup of patients to ensure that these patients with a significant unmet need are not disadvantaged from gaining access to an effective treatment option.**
8	**Size of PD-L1 +ve CPS ≥10 score population versus PD-L1 +ve IC 1% population** Within the ACD in page 6, it is stated that *"The clinical expert and Cancer Drugs Fund clinical lead agreed that there is an overlap between the 2 measurements. However, they explained that the population with a CPS of 10 or more would be larger than the population with an IC of 1% or more."*

	MSD would like to take the opportunity to offer some additional clarifications around this statement as we do not consider to be fully reflective the prevalence of this biomarker. In KEYNOTE-355 38.1% of patients had tumours that expressed CPS≥10 and for IMpassion130 40.9% had IC≥1% [20, 21]. Rugo et al (2020) reports a post-hoc analysis of a sub population within IMpassion130 (68% of the ITT population). The percentage identified as CPS≥10 with 22C3, 52.9%, are a sub-group of a sub-population. This is inferior to prospective PD-L1 testing in registrational studies and we do not agree with using Rugo (2020) to conclude the population with a CPS≥10 would be larger than the population with IC≥ 1%. The paper was presented as evidence for the suboptimal overall percentage agreement between the two assays of 22C3 and SP142. Also, to demonstrate a proportion of patients would be IC<1% but CPS≥10 and therefore able to benefit from pembrolizumab. The updated positioning proposed for pembrolizumab + taxanes would mean that 17% of the mTNBC cohort would belikely eligible for treatment under this indication.

Appendix 1: Clinical feedback on chemotherapy use and estimation of blended chemotherapy comparator costs explored in the ACD

Table 1 summarises the clinical expert insights MSD collected during the ACD consultation process. Responses from consultant oncologists and pharmacists from nine English hospitals were gathered. With the exception of one site, docetaxel usage is fairly limited in this patient population. If taxanes are used to treat metastatic TNBC, weekly paclitaxel is preferred due to the tolerability profile compared to Q3W docetaxel or Q3W paclitaxel. Most docetaxel treated patients are likely to be fit de-novo presenting patients. Based upon this information and the percentage de-novo patients from KEYNOTE-355, a taxane mix chemotherapy comparator has been explored in the C/E, assuming 70% paclitaxel and 30% docetaxel.

Table 1: Clinical expert input sought around the usage of docetaxel to paclitaxel in the NHS

Hospital	**Q1:** What % patients in the metastatic setting that receive docetaxel today and how is this anticipated to change in the future? If changing, why?	**Q2:** Would a CPS test be carried out after a IC test if the IC score was <1%. Or would both tests be ordered at the same time?
A	Very low numbers of patients receive docetaxel.	No comment
B	Use Q3W carboplatin in the first line setting. If a taxane is used would estimate 60% docetaxel and 40% weekly paclitaxel.	No comment
C	Weekly paclitaxel is the treatment of choice for PD-L1 negative patients. Q3W paclitaxel or docetaxel isn't used as weekly paclitaxel is better tolerated.	Would prefer to test for both CPS types but would depend on pathology capacity
D	Weekly paclitaxel is standard of care for all patients. Docetaxel isn't used as it is more toxic.	Would prefer to test both CPS types concurrently but would need to discuss with pathologist.
E	For PD-L1 negative patients, only use weekly paclitaxel.	If had access to both CPS tests would want to conduct both at the same time, which would aid decision making.
F	Weekly paclitaxel is used for patients who are PD-L1 negative due to tolerability.	If pathologist had capacity, would test for both
G	Weekly paclitaxel is the treatment of choice for PD-L1 negative patients, better tolerated than Q3W and Q3W docetaxel	No comment
H	In PD-L1 negative patients, weekly paclitaxel is the choice for patients. It is better tolerated than Q3W paclitaxel or docetaxel. The aim of treatment is to keep the patient on paclitaxel for as long as possible.	No comment
I	0% use of docetaxel and not expected to change	Would perform both tests and there wouldn't be an issue in doing so.

Table 2: Calculation of costs for the mix of taxane chemotherapies; 70% paclitaxel, 30% docetaxel, with Pembrolizumab CAA discount

100% Paclitaxel as comparator	**Pembrolizumab + taxanes**	**Paclitaxel**	**Pembrolizumab + taxane vs. paclitaxel**
Total Costs	[redacted]	[redacted]	[redacted]
Regimen Related Costs	[redacted]	[redacted]	[redacted]
Drug acquisition costs	[redacted]	[redacted]	[redacted]
Drug administration costs	[redacted]	[redacted]	[redacted]
Testing costs	[redacted]	[redacted]	[redacted]
Subsequent Therapy Costs	[redacted]	[redacted]	[redacted]
Adverse Event Management Costs	[redacted]	[redacted]	[redacted]
Disease Management Costs	[redacted]	[redacted]	[redacted]
Terminal Care Cost	[redacted]	[redacted]	[redacted]
Total QALYs	[redacted]	[redacted]	[redacted]
Total LYs	**3.715**	**2.012**	**1.703**
ICER per QALY Gained			**£34,887**
100% Docetaxel as comparator	**Pembrolizumab + taxanes**	**Docetaxel**	**Pembrolizumab + taxane vs. Docetaxel**
Total Costs	[redacted]	[redacted]	[redacted]
Regimen Related Costs	[redacted]	[redacted]	[redacted]
Drug acquisition costs	[redacted]	[redacted]	[redacted]
Drug administration costs	[redacted]	[redacted]	[redacted]
Testing costs	[redacted]	[redacted]	[redacted]
Subsequent Therapy Costs	[redacted]	[redacted]	[redacted]
Adverse Event Management Costs	[redacted]	[redacted]	[redacted]
Disease Management Costs	[redacted]	[redacted]	[redacted]
Terminal Care Cost	[redacted]	[redacted]	[redacted]
Total QALYs	[redacted]	[redacted]	[redacted]
Total LYs	**3.715**	**2.012**	**1.703**
ICER per QALY Gained			**£42,415**
Taxane mix: 70% paclitaxel, 30% docetaxel (cost adjustments)	**Pembrolizumab + taxanes**	**Mix of taxanes (70% paclitaxel, 30% docetaxel)**	**Pembrolizumab + taxane vs. Mix of taxanes (70% paclitaxel, 30% docetaxel)**
Total Costs	[redacted]	[redacted]	[redacted]
Regimen Related Costs	[redacted]	[redacted]	[redacted]
Drug acquisition costs	[redacted]	[redacted]	[redacted]
Drug administration costs	[redacted]	[redacted]	[redacted]
Testing costs	[redacted]	[redacted]	[redacted]
Subsequent Therapy Costs	[redacted]	[redacted]	[redacted]
Adverse Event Management Costs	[redacted]	[redacted]	[redacted]
Disease Management Costs	[redacted]	[redacted]	[redacted]
Terminal Care Cost	[redacted]	[redacted]	[redacted]
Total QALYs	[redacted]	[redacted]	[redacted]
Total LYs	**3.715**	**2.012**	**1.703**
ICER per QALY Gained			**£37,137**
Notes: Docetaxel cost comments differ due to lower drug acquisition costs and differences in concomitant treatments necessary, dexamethasone only, in contrast to paclitaxel which requires Dexamethasone,			

Chlorpheniramide, Cimetidine (the last two require IV infusion). This leads to differences in overall administration costs since nurse time is assumed for paclitaxel for Chlorpheniramide, Cimetidine in line with the methodology used in TA639. The analyses assuming a weighted chemotherapy comparator re-weight these cost components to calculate the new ICER – see table below.

Appendix 2: Alternative extrapolations OS and comparators alongside treatment waning scenarios

Table 3: Table of scenarios explored and ICERs reported within the ACD response; using list price for branded technologies (nab-paclitaxel and subsequent therapies for 2L+ if applicable).

Alternative OS curves for pembrolizumab + taxanes and chemotherapy comparator scenarios						
Scenario for Pembro + Taxanes OS	**ICER**					
	vs paclitaxel	**vs taxane mix[1]**	**vs paclitaxel + 5 year waning**	**vs paclitaxel & SEER waning**	**vs taxane mix + 5 year waning**	**MSD assessment**
Current Company base-case	£34,887	£37,137	£39,531 (as per TE)	£31,605	£42,138	Original ICER + alternative C/E scenarios to account for some docetaxel use
Log-Logistic	£34,597	£36,836	£40,596	£32,388	£44,123	3rd best fitting alternative choice for pembrolizumab +taxanes extrapolation
Gen-gamma	£41,559	£44,319	£41,179	£32,430	£43,910	6th ranked AIC/BIC curve resulting in some longer term survivorship vs exponential projections which sits above Deluche et al 2020
Exponential *(ERG exploratory analysis 1)*	£49,426	£52,786	£41,813	£32,167	£44,597	Overly simplistic and therefore highly conservative; assumes constant hazards for pembrolizumab +taxanes when in chemotherapy arm this is not the case
ERG preferred analysis≠	£53,167±	£56,731	£44,930≠	£34,468	£47,782	Full replication of the ERGs preferred base-case; as above, overly pessimistic against pembrolizumab

Notes:

[1] Assumes 70% paclitaxel :30 docetaxel% as per clinical opinion sought by MSD at ACD stage considering the % of patients presenting with de-novo mTNBC based on KEYNOTE-355 clinical data. Blue: new scenarios not included in original submission. Underlined ICER: for clarity these are discussed within the ACD response letter.

≠ Comprises of ERG exploratory analyses 1-6 and replication of Table 7 of ERG report post Technical Engagement response. ±Replicated from Table 9 of ERG report. Some of these exploratory analyses do not impact the C/E comparisons for pembrolizumab + taxanes. **Bold notes the updates carried forward by the ERG formulating their preferred base-case.** Exploratory 1; Use of alternative OS survival functions **exponential** for pembrolizumab + taxanes (vs log-normal), Exploratory 2; **full piece** PFS models (vs two-piece 9 Kaplan-Meier and **Weibull (**vs log-normal for pembrolizumab + taxanes used in updated base-case), Exploratory 3; Alternative TTD for Atezo +nab-pacl per ERG's preference (does not impact the analyses vs taxanes), Exploratory 4; Capped **treatment duration of 5 years** (vs life time benefit), Exploratory 5; **Vial sharing** (vs no vial sharing for chemotherapies as discussed in the ACM), Exploratory 6; Use of **log-logistic** (vs Weibull) to model TTD for pembrolizumab + taxanes vs **log-normal** (vs log-logistic) for taxanes.

Appendix 3: Modelled estimates demonstrating short life expectancy for taxanes regardless of the choice of parametric curves to model chemotherapy.

The table below presents extracted mean, median survivorship and % alive at 2 years for all parametric options available within the model. It also contains extracted information extracted from TA639 although MSD cautions against direct economic model comparisons due to trial differences and lack of access to depth of data required for more robust comparisons. For taxane chemotherapy treated patients, the median OS is well below 24 months and the vast majority of patients do not survive beyond two years. The mean survival estimated from the current log-logistic model in the current submission is only ~27 months (range of 22 to 27 months). This assessment demonstrates that the short life expectancy criterion for Taxanes is met for patients whose tumours express IC <1% and CPS >=10, those patients who are ineligible for atezolizumab combination.

Table 4: Survival outputs from the current economic model demonstrating the case for short life expectancy for taxanes

Submission	Treatment	OS curve selection	Mean undiscounted months alive	Median Survival (months)	% alive at 24 months
ID1546	Pembrolizumab + taxanes	KN-355 observed	NA	[redacted]	[redacted]
		Log-normal	[redacted]	[redacted]	[redacted]
		Exponential	[redacted]	[redacted]	[redacted]
		Log-logistic	[redacted]	[redacted]	[redacted]
		Gen-Gamm	[redacted]	[redacted]	[redacted]
		Weibull	[redacted]	[redacted]	[redacted]
		Gompertz	[redacted]	[redacted]	[redacted]
	Taxanes alone	KN-355 observed	NA	[redacted]	[redacted]
		Log-logistic	[redacted]	[redacted]	[redacted]
		Log-normal	[redacted]	[redacted]	[redacted]
		Gen-Gamm	[redacted]	[redacted]	[redacted]
		Exponential	[redacted]	[redacted]	[redacted]
		Weibull	[redacted]	[redacted]	[redacted]
		Gompertz	[redacted]	[redacted]	[redacted]
	Paclitaxel only	KN-355 observed	NA	[redacted]	[redacted]
		Log-logistic	[redacted]	[redacted]	[redacted]
TA639 extracted; populations differ based on PD-L1 status	Atezo + nab-pacl	IMpassion-130 observed	NA	25.4 ±	51%≠
		Modelled; Weibull	2.433 LYs or 29.2 months#	NR	49.9%[4]

Notes: extracted from TA639 Committee Documents: [1]; Table 40 CS, [2]; Table 41 CS, [3]; Table 33 ERG (#we assume LY estimates are undiscounted). ± Medians extracted from latest IM-130 publication by Emens et al 2020 [14]; PD-L1 +ve, ≠ 2Y OS extracted from earlier IMpassion-130 publication by Schmid et al 2019 [6]; PD-L1 +ve.

Table 5: Direct comparison of modelled and observed outcomes for chemotherapies (taxanes or nab-paclitaxel) between KEYNOTE-355 and IMpassion-130 (embedded in ACD response comment 7).

Study		Mean (months)	Median (months)	% alive at 24 months
KEYNOTE-355 Taxanes	Observed	NA	[redacted]	[redacted]
	Modelled	[redacted]	[redacted]	[redacted]
IMpassion130 nab-paclitaxel	Observed	N/A	17.9±	36.65%≠
	Modelled	1.6 LYs or 19.2 months updated to 1.797 LYs or 21.5 months[3≠]	13.8 to 14.3 updated to 18.6 - 21.6 by ERG[3]	Paclitaxel[1]: 21% to 22.7% Docetaxel[2:] 26% to 26.8%

Notes: extracted from TA639 Committee Documents: [1]; Table 40 CS, [2]; Table 41 CS, [3]; Table 33 ERG (we assume LY estimates are undiscounted). ± Medians extracted from latest IM-130 publication by Emens et al 2020; PD-L1 +ve, ≠ 2Y OS extracted from earlier IMpassion-130 publication by Schmid et al 2019 [6]; PD-L1 +ve.

Table 6: Subgroup Analysis of Overall Survival (Subjects with PD-L1 CPS ≥10) (ITT Population) – Final DBL

	Pembrolizumab + Chemotherapy (N=220)			Placebo + Chemotherapy (N=103)			Pembrolizumab + Chemotherapy vs. Placebo + Chemotherapy
	N	Number of Events	(%)	N	Number of Events	(%)	Hazard Ratio (95% CI)[†]
Overall	220	155	(70.5)	103	84	(81.6)	0.73 (0.55, 0.95)
Chemotherapy on study (IVRS)							
Nab-Paclitaxel	63	[redacted]		36	[redacted]		0.63 (0.39, 1.03)
Paclitaxel	33	[redacted]		11	[redacted]		0.34 (0.16, 0.72)
Gemcitabine/Carboplatin	124	[redacted]		56	[redacted]		0.88 (0.61, 1.25)
Chemotherapy on study (taxane vs. gemcitabine/carboplatin) (IVRS)							
Taxane	96	[redacted]		47	[redacted]		0.54 (0.36, 0.82)
Gemcitabine/Carboplatin	124	[redacted]		56	[redacted]		0.88 (0.61, 1.25)

[†] Analysis (HR and 95% CI) in the overall population is based on Cox regression model with Efron´s method of tie handling with treatment as a covariate stratified by chemotherapy on study (taxane vs gemcitabine/carboplatin), prior treatment with same class of chemotherapy in the (neo)adjuvant setting (yes vs no); analysis in the subgroups is based on the unstratified Cox model.

If any level of a subgroup variable has fewer than 30 subjects, subgroup analysis is not performed in that level of the subgroup variable.

Database Cutoff Date: 15JUN2021

Table 7: Summary of Follow-up Duration Subpopulation of Participants with PD-L1 CPS ≥ 10 and Pre-assigned to Taxane Chemotherapy

	Study: KEYNOTE 355[a]	
	Pembrolizumab + Chemotherapy[b] N[c]=96	**Placebo + Chemotherapy[b]** N[c]=47
Follow-up Time (Months)[c]		
Mean (SD)	[redacted]	[redacted]
Median (Q1; Q3)	[redacted]	[redacted]
Min; Max	[redacted]	[redacted]

a: Database Cutoff Date: 15JUN2021

b: Chemotherapy: paclitaxel or nab-paclitaxel

c: Calculated from the date of randomization until earliest of the date of death or the database cutoff date if the subject is still alive

Max: Maximum; Min: Minimum; Q1: First Quartile; Q3: Third Quartile; SD: Standard Deviation

Table 8: Summary of Theoretical Follow-Up Time Subpopulation of Participants with PD-L1 CPS ≥10 and Pre-assigned to Taxane Chemotherapy

	Study: KEYNOTE 355[a]	
	Pembrolizumab + Chemotherapy N[b]=96	Placebo + Chemotherapy N[b]=47
Theoretical Follow-Up Time (Months)[c]		
Mean (SD)	[redacted]	[redacted]
Median (Q1; Q3)	[redacted]	[redacted]
Min; Max	[redacted]	[redacted]

a: Database Cutoff Date: 15JUN2021

b: Number of participants: intention-to-treat population with PD-L1 CPS ≥10 and pre-assigned to taxane chemotherapy

c: Theoretical follow-up duration is defined as the time from randomization to the database cutoff date regardless of whether the participant is still alive or not.

Max: Maximum; Min: Minimum; Q1: First Quartile; Q3: Third Quartile; SD: Standard Deviation

Figure 1: Use of exponential distribution to model OS for Pembro + taxanes, using log-logistic alongside chemotherapy OS from real world evidence (no waning)

[redacted]

Table 9: Overall Survival estimates from model validation tab with RWE versus predicted SoC survival linked to Figure 1

Source & Overall Survival	Years								
	0.5	1	1.5	2	3	5	8	10	20
Aly 2018	76.95%	51.17%	37.95%	28.73%	17.72%	-	-	-	-
Battisi 2018 (DFI after 12 months)	89.88%	69.82%	57.22%	36.58%	22.66%	13.51%	3.49%	3.49%	-
Battisi *2018 (DFI within 12 months)*	74.39%	37.70%	18.40%	12.11%	6.01%	5.86%	-	-	-
Deluche 2020 (HR-/HER2-)	81.07%	59.85%	43.22%	33.25%	20.72%	11.76%	6.91%	6.65%	-
Modelled OS: Pembrolizumab + taxane (**exponential**)	[redacted]								
Observed OS: Pembrolizumab + taxane	[redacted]								
Modelled OS: Taxane (log-logistic)	[redacted]								
Observed OS: Taxane	[redacted]								

Figure 2: Comparison between log-normal and exponential to model OS for pembrolizumab + taxanes (no waning)

[redacted]

Figure 3: Comparison between log-normal, log-logistic, gen-gamma and exponential to model OS for pembrolizumab + taxanes (no waning)

[redacted]

Figure 4: Long term model validations versus RWE sources included in the submission

[redacted]

Table 10: Overall Survival estimates from model validation tab with RWE versus predicted SoC survival linked to Figure 4

Source & Overall Survival	Years								
	0.5	**1**	**1.5**	**2**	**3**	**5**	**8**	**10**	**20**
Aly 2018	76.95%	51.17%	37.95%	28.73%	17.72%	-	-	-	-
Battisi 2018 (DFI after 12 months)	89.88%	69.82%	57.22%	36.58%	22.66%	13.51%	3.49%	3.49%	-
Battisi *2018 (DFI within 12 months)*	74.39%	37.70%	18.40%	12.11%	6.01%	5.86%	-	-	-
Deluche 2020 (HR-/HER2-)	81.07%	59.85%	43.22%	33.25%	20.72%	11.76%	6.91%	6.65%	-
Modelled OS: Pembrolizumab + taxane (**log-normal**)	[redacted]								
Observed OS: Pembrolizumab + taxane	[redacted]								
Modelled OS: Taxane (log-logistic)	[redacted]								
Observed OS: Taxane	[redacted]								

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Pembrolizumab plus chemotherapy for untreated, triple-negative, locally recurrent unresectable or metastatic breast cancer [ID1546]

Consultation on the appraisal consultation document – deadline for comments 5pm on Tuesday 29 March 2022. Please submit via NICE Docs.

	Please read the checklist for submitting comments at the end of this form. We cannot accept forms that are not filled in correctly. The Appraisal Committee is interested in receiving comments on the following: • has all of the relevant evidence been taken into account? • are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence? • are the provisional recommendations sound and a suitable basis for guidance to the NHS? NICE is committed to promoting equality of opportunity, eliminating unlawful discrimination and fostering good relations between people with particular protected characteristics and others. Please let us know if you think that the preliminary recommendations may need changing in order to meet these aims. In particular, please tell us if the preliminary recommendations: • could have a different impact on people protected by the equality legislation than on the wider population, for example by making it more difficult in practice for a specific group to access the technology; • could have any adverse impact on people with a particular disability or disabilities. Please provide any relevant information or data you have regarding such impacts and how they could be avoided or reduced**.**
Organisation name – Stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder please leave blank):	Breast Cancer Now
Disclosure Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	N/A

Comment number	**Comments** Insert each comment in a new row. Do not paste other tables into this table, because your comments could get lost – type directly into this table.

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Pembrolizumab plus chemotherapy for untreated, triple-negative, locally recurrent unresectable or metastatic breast cancer [ID1546]

Consultation on the appraisal consultation document – deadline for comments 5pm on Tuesday 29 March 2022. Please submit via NICE Docs.

1	It is disappointing that NICE has provisionally been unable to recommend this pembrolizumab combination as it would have improved the options available for this group of patients. There is currently a group of patients who may be ineligible for the atezolizumab combination that is available on the NHS but could be eligible for pembrolizumab as a result of the different tools used to measure PD-L1 expression. We are pleased that the committee has recognised the unmet need for this group of patients. We urge the company, MSD and NICE to work together during this consultation period to consider every possible solution, with a focus on the end of life criteria, so that the drug can be recommended for routine use on the NHS.
2	The poor life expectancy of this group of patients and the urgent need for new effective treatments is well documented and we reiterate the unmet need as per our initial patient organisation submission and comments made during the appraisal meeting. The mean versus median approach regarding the end of life criteria was raised by the clinical expert in the committee meeting and whilst we appreciate that the committee did not want to discuss this further as they are well aware of the issues, we do want to raise the fact that we can't be left in a situation where dependent on how the criteria is applied in this situation that a group of patients are potentially disadvantaged. We hope that flexibility and discretion will be used in this situation as it has been for other appraisals regarding the end of life criteria.
3	To highlight the unmet need we have an example from a patient with secondary triple negative breast cancer. It is unclear why the patient may have been tested with a non-Roche PDL1 assay initially when currently only the atezolizumab combination is available, however, it illustrates that different tests can provide different results opening up the doors to important treatment options. *A patient told us "I received atezolizumab with nab-paclitaxel which was effective for me for around 8-9 months. When I was originally tested to see if I was PDL1 positive at the hospital, the test showed up negative. My clinician then said Roche had a specific test for atezolizumab and that I should be re-tested. This showed that I was PDL1 positive and I then started on atezolizumab. This shows different tests can pick up PDL1 differently which is why it's important that pembrolizumab and the test associated with it are made available alongside atezolizumab to ensure no patients are missed and that everyone has the chance to benefit from an effective immunotherapy"*

Insert extra rows as needed

Checklist for submitting comments

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- 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.
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- 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

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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.

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

Name	

Comments on the ACD:
Are the recommendations sound and a suitable basis for guidance to the NHS?

No, the recommendations are not sound guidance for the NHS. Pembrolizumab plus chemotherapy is proven to increase overall survival in patients with PD-L1 metastatic triple negative breast cancer. While questions remain over the effectiveness of atezolizumab plus chemotherapy following the publication of the IMpassion131 trial, we believe that NHS patients should have access to the current best standard of care which is pembrolizumab plus chemotherapy. Furthermore, as the NICE committee has noted, differences in ascertainment of PD-L1 status mean that some patients who would benefit from pembrolizumab plus chemotherapy will be denied the chance to access any immunotherapy regimen. Therefore these patients have an unmet need which will not be addressed until pembrolizumab plus chemotherapy is approved.

A subset of patients with a PD-L1 positive mTNBC are either unable to take taxane chemotherapy because of intolerance or are unlikely benefit from taxane chemotherapy because they have received it within the last 12 months after treatment for early stage breast cancer. The marketing authorisation for pembrolizumab allows patients to receive treatment with an alternative chemotherapy backbone, whereas atezolizumab must be administered alongside nab-paclitaxel. There is a strong argument that for patients who cannot receive a taxane, pembrolizumab addresses an unmet need and therefore should be made available.

We also want to reiterate the importance to patients of rapid tumour testing. Triple negative breast cancer is an aggressive subtype, and long waits for biopsy results cause patients considerable anxiety. As pembrolizumab has to be given in the first line, patients must wait for results without receiving any systemic treatment and without knowing if this delay will cause progression.

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

At METUPUK, we were dismayed to that the NICE committee did not consider that pembrolizumab plus chemotherapy met the end of life criteria. As we still do not have accurate data on metastatic breast cancer, we cannot give an exact life expectancy for metastatic triple negative breast cancer, but we know that 12-18 months median is often quoted. Moreover, because triple negative breast cancer often affects younger patients, this disease is responsible for many decades of life lost. We therefore strongly argue that any treatment for metastatic triple negative breast cancer qualifies under the end of life criteria, and note the atezolizumab plus nab-paclitaxel was accepted under the end of life criteria for first line treatment of PD-L1 positive mTNBC. We support the committee asking the company to re-examine their survival data because their estimates of survival in both the pembrolizumab group and the control group are much higher than has been reported in official updates to the KEYNOTE-355 trial.

The redactions in the committee papers to make it difficult to make meaningful comments about cost effectiveness because of confidential discounts.

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?

Breast cancer predominantly affects women. Although men can get breast cancer, 99% of cases occur in women. Therefore women will be disproportionately affected by this ruling. Triple negative breast cancer disproportionately affects younger people and people of colour. In addition, younger people, particularly those in their 20s and 30s are most likely to have a delayed, missed or late stage diagnosis, and are most likely to be pregnant or post pregnancy. These groups are also most likely to have the poorest outcomes and shortest disease free survival. Access pembrolizumab and access to rapid PD-L1 testing is key to increasing survival times in these groups.

Has all of the relevant evidence been taken into account?

No, we believe important evidence has not been taken into account regarding the comparator treatment atezolizumab. In the United States, the FDA currently only recommends pembrolizumab plus chemotherapy for PD-L1 positive metastatic triple negative breast cancer. The treatment recommended by NICE of atezolizumab plus chemotherapy was withdrawn in the USA by Roche in August 2021 after the IMpassion131 trial failed to meet its primary endpoint. We note the differences in the chemotherapy backbone in the IMpassion130 trial upon which the NICE guidance is based and the IMpassion131 trial which failed to show a benefit, meaning the two studies are not directly comparable. However, most UK patients would prefer for their oncologist to be given the freedom to select the most appropriate treatment for them, and many patients are aware that the treatment offered by NICE is no longer recommended in the USA. We realise that the remit of this consultation is only pembrolizumab plus chemotherapy, but it is important also to consider the wider context of alternative drugs available to patients.

A related issue which is of importance to patients is the need for rapid PD-L1 testing. Most patients with metastatic triple negative breast cancer have aggressive fast growing disease. Patients tell us that delays in getting biopsy results cause significant anguish at a very difficult time, and many patients fear progression because commencing treatment is delayed waiting for biopsy results.

Confidential until published

Pembrolizumab in combination for untreated, locally recurrent inoperable or metastatic, triple negative breast cancer [ID1546]. A Single Technology Appraisal

Addendum: ERG comments on the company's response to the Appraisal Consultation Document

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Declared competing interests of the authors

None of the authors has any conflicts of interest to declare.

1 Introduction

The NICE Appraisal Committee met to discuss pembrolizumab in combination with paclitaxel/nab-paclitaxel for untreated, locally recurrent inoperable or metastatic, triple negative breast cancer (TNBC) in February 2022. Following this meeting, NICE issued an Appraisal Consultation Document (ACD) that did not recommend the intervention.[1]

The company submitted its response to the ACD in March 2022. The company's response was structured around eight comments, with no updated version of the executable model. Importantly, the positioning of pembrolizumab plus paclitaxel/nab-paclitaxel was changed from that proposed in the CS, such that it was for a subgroup of people who cannot have atezolizumab with nab-paclitaxel. These would be patients whose tumour is PD-L1 <1% with SP-142 but PD-L1 positive CPS ≥10 score by Dako 22C3 Assay. The company estimates that 17% of TNBC patients would meet these criteria. The company has assumed that the efficacy data from the CPS ≥10 score by Dako 22C3 Assay is generalisable to the new positioning of pembrolizumab plus taxanes although no additional analyses were provided to support this assumption.

This document provides a commentary on the company's ACD response and should be read in conjunction with the ERG report,[2] and the ERG's response to technical engagement (TE).[3] Section 2 provides a summary of the company's response to the ACD and the ERG's critique of these points. Section 3 presents the results of the company's updated base case and additional analyses undertaken by the ERG. Overall conclusions are presented in Section 4.

All results presented in this document use the time-to-death approach for utility as preferred by the NICE Appraisal Committee. The Patient Access Scheme (PAS) discount for pembrolizumab has been included, but confidential comparator PAS discounts are excluded. Results which include confidential comparator PAS discounts are presented in a separate confidential addendum.

2 Summary of the company's response to the ACD and ERG critique

This ERG addendum is also structured around the eight comments in the company's response to the ACD which are detailed in Sections 2.1 to 2.8. Each section summarises the company's position and also includes the ERG's opinion of the new data / assumptions.

2.1 Comment 1: Choice of the relevant comparator

As stated in Section 1, the positioning of pembrolizumab plus paclitaxel/nab-paclitaxel has been changed such that atezolizumab plus nab-paclitaxel is no longer a comparator. The company's response to the ACD therefore focuses on paclitaxel and docetaxel as comparators.

The company contends that paclitaxel is the most appropriate comparator, citing Section 3.4 of the Final Appraisal Determination (FAD)[4] for TA639,[5] (atezolizumab plus nab-paclitaxel) which stated that '*weekly paclitaxel is the most relevant comparator*' …. '*because it has a more favourable toxicity profile than docetaxel so people are able tolerate treatment, and maintain a treatment response, for longer*'. However, the company notes that docetaxel utilisation had increased during the COVID-19 pandemic as docetaxel could be administered every three weeks, rather than weekly, and that in the Appraisal Committee meeting for pembrolizumab plus taxanes, a clinical expert noted that docetaxel use is likely to remain due to pressures post-COVID-19.

The company sought advice and received responses from consultant oncologists and pharmacists working in nine English hospitals which is detailed in Appendix 1 of the company's response to the ACD. The responses obtained suggested that the use of docetaxel was low and that weekly paclitaxel was preferred, although some specified this for PD-L1 negative patients, although Hospital B was an outlier with 60% docetaxel use and 40% paclitaxel use. The company concluded that the use of docetaxel varies by hospital and explored a comparator that consisted of 70% paclitaxel and 30% docetaxel, based on the fact that '*due to its safety profile, docetaxel is used to treat earlier stages of disease, with the exception of the de novo metastatic patients' and that in the CPS ≥ 10 subgroup in KEYNOTE-355 the percentage of de-novo metastatic patients was 31.6%.*' This change increased the company's base case ICER from £34,887 to £37,137, and to £42,138 when a 5-year waning period is considered. The 70% paclitaxel and 30% docetaxel mix changed the ERG's deterministic preferred analysis, which did not include vial sharing, from £44,930 (against paclitaxel) and £54,771 (against docetaxel) to £47,782 against blended taxanes. See Table 3 of the company's response to the ACD for further details and additional analyses.

The ERG has two key issues relating to Comment 1 from the company:

1) The ERG prefers full incremental analyses to be presented rather than blended ICERs as this can improve the efficient allocation of resources. The ERG would have preferred that the toxicity and potentially shorter treatment response of docetaxel referred to in TA639[5] be explicitly included within the model. The ERG believes that if these were included, the ICER for pembrolizumab against docetaxel would decrease and become more favourable to pembrolizumab plus taxanes.
2) The ERG believes that it is likely that the testing costs associated with pembrolizumab are now underestimated in the company's model. In the CS, 38.1% of patients were assumed to be PD-L1 positive CPS ≥10 score by Dako 22C3 Assay who would be treated with pembrolizumab plus taxanes, if recommended. However, a proportion of these patients would be eligible for atezolizumab plus nab-paclitaxel and would receive this treatment instead. The company states that 16.9% of TNBC patients would be patients who are CPS≥10 by Dako 22C3 Assay, but would be negative by SP142 test.[6] This implies that for every 1000 tests performed approximately 169 patients would be treated in the new positioning compared with approximately 381 in the positioning in the CS assuming that the SP142 test and the Dako 22C3 Assay were performed simultaneously. The responses obtained by the company from consultant oncologists and pharmacists suggested that this would be the preferred approach if there was sufficient pathology capacity.

2.2 Comment 2: Uncertainty in the long-term benefits of pembrolizumab plus paclitaxel/nab-paclitaxel

The thrust of this comment is similar to the company's responses to key issue 1 and key issue 2 in the ERG report.[2] This was addressed in detail in the ERG's response to the company's TE response.[3] Key details have been provided, although extensive repetition has been avoided. The ERG notes that the company assumes that the efficacy data from the CPS ≥10 score by Dako 22C3 Assay is generalisable to the new positioning of pembrolizumab plus taxanes, which adds additional uncertainty to the relative efficacy of pembrolizumab plus taxanes.

The company sought clinical expert opinion that stated that '*most patients would not survive beyond the first 3 years given the aggressiveness of mTNBC*' and that after this period those treated with current chemotherapy '*would be expected to have a lower risk of death of a result of mTNBC (but an increased risk of death due to all-cause mortality as the cohort ages over time)*'. For patients treated with pembrolizumab plus taxanes, the clinical experts '*noted that a stabilisation and subsequent plateau in would OS be expected to be observed from around year 3 onwards*' stating that this has been observed in studies, albeit in different diseases.[7-9] As such, the company has concerns with the ERG's use of an exponential distribution for pembrolizumab plus taxanes, '*which may not adequately capture the long*

term survivors with IO agents'. The company has explored the use of different distributions for pembrolizumab plus taxanes, all of which reduce the ICERs and favour pembrolizumab treatment.

The ERG assumes that the company is satisfied with the ERG's choice of distribution (log-normal) for the taxanes arm as it is the one chosen by the company and focuses only on the distribution for the pembrolizumab plus taxanes arm in this document.

Figure 1 shows the hazard plot for pembrolizumab plus taxanes (replicated from Figure 1 of the company's TE response). This figure shows that (i) the hazards observed in the first 200 weeks did not exhibit a turning point as would be expected if the company's preferred log-logistic distribution was appropriate and (ii) that the hazards did not match that anticipated by the clinicians who advised the company (which would have been initially high, then decreased and stabilising. As such, the ERG maintains its preference for the exponential distribution.

Figure 1: The hazard plot for death for pembrolizumab plus taxanes (reproduced from Figure 1 of the company's TE response)

In its response to the ACD, the company provide a plot of the difference in OS when using the exponential and the log-normal distributions when waning of treatment effect is not assumed (Figure 2). As expected, the log-normal distribution has a longer tail, and in later years a greater proportion of patients are alive than when an exponential distribution is used and produces a more favourable ICER for pembrolizumab plus taxanes.

Figure 2: Comparison between log-normal and exponential to model OS for pembrolizumab + taxanes (no waning) (reproduced from Figure 2 of the company's response to the ACD)

2.3 Comment 3: Uncertainty in the indirect treatment comparison results between pembrolizumab plus taxanes versus atezolizumab plus nab-paclitaxel.

Given the new proposed positioning of pembrolizumab plus taxanes this issue is no longer relevant to the decision problem. The ERG has not critiqued this comment apart from referring interested readers to previous discussions on this issue[3] and confirming that the view of the ERG is unchanged.

2.4 Comment 4: Choice of parametric extrapolation curves used to model pembrolizumab and taxanes

This point is very similar to issues raised in Comment 2, and the reader is also referred to the ERG's response to that comment. The company comment that the exponential distribution is '*overly simplistic*' as it assumes a constant hazard; however, this is largely in keeping with the observed hazards from KEYNOTE-355 (Figure 1). The company states that the lack of observed turning point '*could be due to the method used to generate the "smoothed" hazard plots, or due to the sample size which is not big enough to show it.*' The ERG also notes that it could be because there is not a turning point in the true distribution.

The company provides data on the extrapolation of the exponential distribution to model overall survival (OS) for pembrolizumab plus taxanes which the company states '*depicts a 10 year survivorship with an IO agent siting well below the real world chemotherapy projections presented*'. Figure 1 from the company's response to the ACD is reproduced in Figure 3. The ERG notes that at 10 years the extrapolated OS for pembrolizumab plus taxanes is greater than all other sources apart from Deluche *et al*.[10] which the company states '*was not used for validation since clinical experts noted that it predicted an OS plateau of ~6.65% at year 10 which was not deemed as reflective of UK survival estimates (considered too optimistic and experts noted that most patients would be dead at year 10 if treated with standard chemotherapies)'*. As such, the point being made by the company is unclear.

Figure 3: Extrapolation of OS data compared with other data sources

The ERG notes that the use of external information can be informative in choosing distributions to fit immature data; however, this should not override the observed data unless there are strong prior beliefs that experiences in different disease areas are generalisable to how pembrolizumab plus taxanes would perform in TNBC. The ERG maintains that based on current data the exponential appears to be the most appropriate distribution for OS, but acknowledges that it is possible that the long-term hazard of death could change as data mature.

2.5 Comment 5: Assumption on time to treatment discontinuation for atezolizumab plus nab-paclitaxel.

Given the new proposed positioning of pembrolizumab plus taxanes this issue is no longer relevant to the decision problem. The ERG has not critiqued this comment apart from referring interested readers back to previous discussions on this issue[3] and confirming that the view of the ERG is unchanged.

2.6 Comment 6: Duration of treatment effect benefit over time for pembrolizumab plus taxanes

The company reiterates that it believes the method used by the ERG that was preferred by the Appraisal Committee was '*highly conservative*'. The company comments that this approach has a sudden change in the hazard ratio at 5 years (which is correct) and explored an alternative method which uses data from the Surveillance, Epidemiology and End Results (SEER) program (a USA database that likely does not include a large proportion of patients treated with pembrolizumab) to assume waning happens in both arms at four years. This reduces the ICER compared with the approach preferred by the committee.

The ERG maintains its view that it would not expect a treatment benefit to persist at the levels observed in the initial periods of KEYNOTE-355 for a long period of time when patients are progressing and receiving subsequent lines of treatment. Text from the ERG response to TE[3] states that '*Table 58 of the CS indicates that for people receiving pembrolizumab plus paclitaxel/nab-paclitaxel treatment, with a median follow up of* [redacted] *months, that* [redacted] *of patients received second-line treatments,* [redacted] *received third-line treatments and that* [redacted] *received fourth-line treatments. Such levels of subsequent treatment use, appear to indicate that pembrolizumab plus paclitaxel/nab-paclitaxel had not been sufficiently efficacious in a large proportion of patients. The company has not provided in their TE response updated data on subsequent treatments based on the FA data-cut (15th June 2021); however, based on the model it is inferred that that* [redacted] *of patients received second-line treatments,* [redacted] *received third-line treatments and that* [redacted] *received fourth-line treatments. The ERG believes it implausible that the any relative survival benefit associated with pembrolizumab treatment compared with taxane treatment in the initial period of KEYNOTE-355 would be maintained many years after cessation of pembrolizumab treatment, and after the use of subsequent treatments."*

2.7 Comment 7: Application of the end-of-life criteria

Within this comment the company: (i) summarises data for this appraisal considered relevant to the end-of-life criteria, (ii) contrasts the Appraisal Committee's decision with that made in TA639[5] and (iii) supplies additional data to support the short-life expectancy criterion being met, when atezolizumab plus nab-paclitaxel is no longer a comparator. The decision on whether the end-of-life criteria is met is a judgement for the Appraisal Committee although the ERG attempts to provide salient information in this section.

The company states that the observed median survival for people receiving treatment with taxanes in KEYNOTE-355 was [redacted] months and that at 2 years less than [redacted] of patients were alive. For the modelled distribution these values became [redacted] months and [redacted] respectively; the model also provided an estimate of mean survival, which was [redacted] months. The median estimate of survival falls below 24 months, whereas the mean estimate is above this value.

The company additionally states that using an exponential distribution for OS in the taxanes group reduces OS to [redacted] months, although this argument is weakened as the hazards appear to show a clear turning point as seen in Figure 4. Further, the company states that the life expectancy in the taxanes group would reduce to [redacted] months if the time horizon is reduced to 15 years as in TA639, although the ERG is unclear why this change would be supported.

Figure 4: The hazard plot for death for taxanes (reproduced from Figure 2 of the company's TE response)

[redacted]

The company provides information from the ERG report for TA639 related to the life expectancy for patients treated with taxanes, although the ERG prefers to use the NICE FAD for TA639,[4] which reports median overall survival of 25.0 months for patients receiving atezolizumab plus nab-paclitaxel and 15.4 months for patients receiving nab-paclitaxel and states that the Appraisal Committee believed that the end-of-life criteria were met. No reference to mean life expectancy was made in the FAD for TA639.

The company cites real-world evidence sources to support the case that life expectancy for patients receiving taxes is less than 2 years. The company states that the OS for the taxanes arm was primarily validated using Battisti et al.,[11] which was a UK audit reporting OS outcomes over an eleven year period. Sources and OS estimates were provided by the company in Table 9 of its response to the ACD, with this table reproduced in Table 1.

Table 1: OS estimates for people receiving taxanes

Source & Overall Survival	Years								
	0.5	**1**	**1.5**	**2**	**3**	**5**	**8**	**10**	**20**
Aly 2018[12]	76.95%	51.17%	37.95%	28.73%	17.72%	-	-	-	-
Battisi 2018[11] (DFI after 12 months)	89.88%	69.82%	57.22%	36.58%	22.66%	13.51%	3.49%	3.49%	-
Battisi *2018[11] (DFI within 12 months)*	74.39%	37.70%	18.40%	12.11%	6.01%	5.86%	-	-	-
Deluche 2020[10] (HR-/HER2-)	81.07%	59.85%	43.22%	33.25%	20.72%	11.76%	6.91%	6.65%	-
Modelled OS: Pembrolizumab + taxane (**exponential**)	[redacted]								
Observed OS: Pembrolizumab + taxane	[redacted]								
Modelled OS: Taxane (log-logistic)	[redacted]								
Observed OS: Taxane	[redacted]								

The company states that when Deluche *et al.*[10] is excluded, as it was considered too optimistic, the median OS ranged from 14.3 months (Battisti *et al.*[11] disease-free interval (DFI) within 12 months) to 21.3 months (Battisti *et al.* [11] DFI after 12 months). The ERG cautions that the longer life expectancy shown in KEYNOTE-355 may be due to studies recruiting healthier patients, which may mean that the additional QALYs provided by pembrolizumab treatment are greater in KEYNOTE-355 than would be observed in clinical practice. If time on pembrolizumab treatment duration is unchanged this would increase the ICER and be more unfavourable to pembrolizumab plus taxanes treatment.

The company also reports discussion from ID3735[13] (avelumab in metastatic urothelial cancer) where the appeal panel decided that it would be "*unreasonable to state that life-expectancy was not "normally less than 24 months", even if the mean life expectancy was greater than 24 months, …if the significant majority, in the modelled cohort had died prior to 24 months*" and that "*The panel understood the concern about using means in one context and medians in another, but the end of life criteria are a stand-alone test that have to be considered on their own terms*" and that "*The panel also agreed that "normally" allowed a committee a discretion to apply end of life criteria even if it felt on some measures of life expectancy might be somewhat over 24 months. Even if it had been correct to use the mean as the main driver of a decision in this case, given that the median and clinical expert opinion was all*

significantly below 24 months, and the mean was not substantially above 24 months, this was a case where that discretion would have needed to have been discussed". The company states that these points are relevant in this appraisal.

The ERG believes that this is a judgement decision for the Appraisal Committee; in this appraisal [redacted] of patients in the taxanes arm modelled to be alive at 2 years ([redacted] observed), and the median survival was [redacted] months (mean [redacted] months).

2.8 Comment 8: The respective sizes of the populations that could be treated with pembrolizumab plus taxanes and atezolizumab plus nab-paclitaxel.

The company highlights sentences in the ACD that state "*The clinical expert and Cancer Drugs Fund clinical lead agreed that there is an overlap between the 2 measurements. However, they explained that the population with a CPS of 10 or more would be larger than the population with an IC of 1% or more*". The company believes that these sentences are incorrect and states that "*in KEYNOTE-355 38.1% of patients had tumours that expressed CPS≥10 and for IMpassion130 40.9% had IC≥1%*".

3 Additional undertaken by the company and the ERG

3.1 Results of the analyses presented by the company

In Table 3 of the company's response to the ACD, multiple deterministic ICERs are presented. The company's base case is an ICER of £37,137 which compares paclitaxel and taxanes to a mixture of paclitaxel (70%) and docetaxel (30%). The company also explores the impact of the waning assumptions as assumed by the Appraisal Committee, which increases the ICER to £42,138 compared with the mixture of paclitaxel and docetaxel. The company also explored the ICERs compared with paclitaxel alone when using treatment waning estimated from the SEER database; this decreased the ICER in all scenarios compared with no waning, and in some cases, considerably, which appears to lack face validity.

3.2 Description of additional exploratory analyses undertaken by the ERG

The ERG has maintained its base case apart from two aspects. The first is to assume that vial sharing will occur as this was the Appraisal Committee's preference; the second is to increase the costs of testing by Dako 22C3 Assay per treated person (see Section 2.1). Only the time-to-death approach for utility has been used in accordance with the Appraisal Committee's preferred assumption, and atezolizumab plus nab-paclitaxel is no longer a comparator based on the company's new positioning of pembrolizumab plus taxanes.

ERG exploratory analysis 1: Allowing vial sharing

The ERG allowed vials to be shared for all IV drugs, except for pembrolizumab and atezolizumab where vial sharing was assumed not to occur, in accordance with the Appraisal Committee's preference. This decreased the ERG's preferred ICER.

ERG exploratory analysis 2: Increasing the costs of Dako 22C3 testing per treated patient

As the company has changed the proposed positioning of pembrolizumab plus taxanes, more tests are undertaken per treated patient (see Section 2.1). It was estimated that the Dako 22C3 Assay testing costs would increase from £108.65 per treated patient to £244.94 per treated patient. This change increased the ERG's preferred ICER.

The ERG has not used a blended comparator approach but instead estimated the ICER compared with paclitaxel and docetaxel individually. Table 2 provides the result of fully incremental analyses, whereas Table 3 provides the ICER when only paclitaxel is a comparator. As stated, the ICER compared with docetaxel may be unfavourable to pembrolizumab plus taxanes treatment as the toxicity of docetaxel, and the potentially worse outcome measures have not been included in the company model.

3.3 Results of exploratory analyses undertaken by the ERG

Table 2: Results of the ERG exploratory analyses, pembrolizumab plus paclitaxel/nab-paclitaxel versus paclitaxel, docetaxel and atezolizumab plus nab-paclitaxel, time-to-death approach for modelling HRQoL

Option	LYGs*	QALYs	Costs	Inc. LYGs*	Inc. QALYs	Inc. costs	ICER (per QALY gained)
1) ERG preferred analysis after Technical Engagement (deterministic)							
Docetaxel	2.26	[redacted]	[redacted]	-	[redacted]	[redacted]	**-**
Paclitaxel	2.26	[redacted]	[redacted]	-	[redacted]	[redacted]	**Dominated**
Pembrolizumab plus paclitaxel/nab-paclitaxel	3.99	[redacted]	[redacted]	1.73	[redacted]	[redacted]	**£54,771**
2) 1) plus allowing vial sharing (deterministic) †							
Docetaxel	2.26	[redacted]	[redacted]	-	[redacted]	[redacted]	-
Paclitaxel	2.26	[redacted]	[redacted]	-	[redacted]	[redacted]	**Dominated**
Pembrolizumab plus paclitaxel/nab-paclitaxel	3.99	[redacted]	[redacted]	1.73	[redacted]	[redacted]	**£52,958**
3) 1) plus additional Daka 22C3 assay testing costs per treated patient (deterministic)							
Docetaxel	2.26	[redacted]	[redacted]	-	[redacted]	[redacted]	-
Paclitaxel	2.26	[redacted]	[redacted]	-	[redacted]	[redacted]	**Dominated**
Pembrolizumab plus paclitaxel/nab-paclitaxel	3.99	[redacted]	[redacted]	1.73	[redacted]	[redacted]	**£54,901**
ERG preferred analysis: combining 2) and 3) – (deterministic)							
Docetaxel	2.26	[redacted]	[redacted]	-	[redacted]	[redacted]	-
Paclitaxel	2.26	[redacted]	[redacted]	-	[redacted]	[redacted]	**Dominated**
Pembrolizumab plus paclitaxel/nab-paclitaxel	3.99	[redacted]	[redacted]	1.73	[redacted]	[redacted]	**£53,088**
ERG preferred analysis: combining 2) and 3) – (probabilistic)							
Docetaxel	2.31	[redacted]	[redacted]	-	[redacted]	[redacted]	-
Paclitaxel	2.31	[redacted]	[redacted]	-	[redacted]	[redacted]	**Dominated**
Pembrolizumab plus paclitaxel/nab-paclitaxel	4.02	[redacted]	[redacted]	1.72	[redacted]	[redacted]	**£53,197**

Inc. - incremental; ICER - incremental cost-effectiveness ratio; LYG - life year gained; QALY - quality-adjusted life year
** undiscounted; †For all IV drugs except for pembrolizumab and atezolizumab*

Table 3: Results of the ERG exploratory analyses, pembrolizumab plus paclitaxel/nab-paclitaxel versus paclitaxel, time-to-death approach for modelling HRQoL

Option	LYGs*	QALYs	Costs	Inc. LYGs*	Inc. QALYs	Inc. costs	ICER (per QALY gained)
1) ERG preferred analysis after Technical Engagement (deterministic)							
Paclitaxel	2.26	[redacted]	[redacted]	-	-	-	-
Pembrolizumab plus paclitaxel/nab-paclitaxel	3.99	[redacted]	[redacted]	1.73	[redacted]	[redacted]	**£44,930**
2) 1) plus allowing vial sharing (deterministic)†							
Paclitaxel	2.26	[redacted]	[redacted]	-	-	-	-
Pembrolizumab plus paclitaxel/nab-paclitaxel	3.99	[redacted]	[redacted]	1.73	[redacted]	[redacted]	**£43,111**
3) 1) plus additional Daka 22C3 assay testing costs per treated patient (deterministic)							
Paclitaxel	2.26	[redacted]	[redacted]	-	-	-	-
Pembrolizumab plus paclitaxel/nab-paclitaxel	3.99	[redacted]	[redacted]	1.73	[redacted]	[redacted]	**£45,060**
ERG preferred analysis: combining 2) and 3) – (deterministic)							
Paclitaxel	2.26	[redacted]	[redacted]	-	-	-	-
Pembrolizumab plus paclitaxel/nab-paclitaxel	3.99	[redacted]	[redacted]	1.73	[redacted]	[redacted]	**£43,242**
ERG preferred analysis: combining 2) and 3) – (probabilistic)							
Paclitaxel	2.31	[redacted]	[redacted]	-	-	-	-
Pembrolizumab plus paclitaxel/nab-paclitaxel	4.02	[redacted]	[redacted]	1.72	[redacted]	[redacted]	**£42,936**

Inc. - incremental; ICER - incremental cost-effectiveness ratio; LYG - life year gained; QALY - quality-adjusted life year
** undiscounted; †For all IV drugs except for pembrolizumab and atezolizumab*

4 Overall conclusions

Incorporating changes in the assumptions related vial sharing and Dako 22C3 Assay testing costs resulted in the ERG's preferred ICER becoming more favourable to pembrolizumab plus paclitaxel / nab-paclitaxel. The deterministic ICER compared with docetaxel decreased from £54,771 (£54,893 probabilistic) in the ERG's previous base case to £53,088 (£53,197 probabilistic). The deterministic ICER of pembrolizumab plus paclitaxel/nab-paclitaxel compared with paclitaxel decreased from £44,930 (£44,637 probabilistic) in the ERG's previous base case to £43,242 (£42,936). The ICER compared to docetaxel may be unfavourable to pembrolizumab plus paclitaxel / nab-paclitaxel as the toxicity profile of docetaxel and the potentially shorter treatment response cited in TA639 has not been incorporated in the analyses.

A confidential appendix contains the results incorporating confidential PASs, and prices from the Drugs and pharmaceutical electronic market information tool (eMIT), and Commercial Medicines Unit (CMU) for other interventions.

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